

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

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

**MEDICAL REVIEW(S)**

## MEMORANDUM

DATE: August 12, 2009

FROM: Russell Katz, M.D.  
Director  
Division of Neurology Products/HFD-120

TO: File, NDA 22-421

SUBJECT: Action Memo for NDA 22-421, for the use of Mirapex ER (Pramipexole Dihydrochloride) Extended-release Tablets in the treatment of patients with early Parkinson's Disease (PD)

NDA 22-421, for the use of Mirapex ER (Pramipexole Dihydrochloride) Extended-release Tablets in the treatment of patients with early Parkinson's Disease (PD), was submitted by Boehringer Ingelheim on 10/24/08. Mirapex ER is to be given once a day. Mirapex immediate release tablets (Mirapex IR) are currently approved for the treatment of patients with PD (both early and late, in a three times a day regimen) and Restless Legs Syndrome (RLS). The current application contains the results of a single controlled trial in patients with early PD, as well as other pharmacokinetic (Phase 1) studies and safety data from various sources, including a controlled trial in patients with late PD and open-label extensions of various studies. The application also contains the results of a trial in which patients stable on immediate release pramipexole were crossed-over to continue to receive Mirapex IR or the same daily dose of Mirapex ER. The application also contains results of genotoxicity studies of several impurities, and the requisite chemistry and manufacturing (CMC) data.

The application has been reviewed by Dr. Kenneth Bergmann, medical officer, Dr. Jingyu Luan, statistician, Dr. John Duan, Office of New Drug Quality Assessment, Carol Noory and Dr. Fang Li, Office of Clinical Pharmacology, Dr. Wendy Wilson, chemist, Dr. Antoine El-Hage, Division of Scientific Investigation, Dr. Terry Peters, pharmacologist, Dr. Lois Freed, pharmacology team leader, Dr. LaToya Shenee' Toombs, Division of Medication Error Prevention and Analysis, Dr. Sharon Watson, DDMAC, and Dr. Gerald Podskalny, neurology team leader.

In this memo, I will very briefly review the relevant data and offer the rationale for the division's action.

As noted above, the sponsor submitted the results of a single controlled trial in patients with early PD. The study has been described and reviewed in detail by Drs. Luan and Bergmann.

In brief, patients were enrolled in a randomized, double-blind, double-dummy, multi-center study in which they were randomized to receive either Mirapex ER (once a day), Mirapex IR (three times a day), or placebo. The study was to be of 33 weeks duration, but by agreement with the Agency, the primary outcome was to be assessed at Week 18. An analysis of a subset of patients who completed 33 weeks was to be assessed at that time point to establish the persistence of any effect seen at Week 18. The trial consisted of a 7 week titration phase, followed by a maintenance phase. Patients were to be titrated to their “best” dose, with a maximum allowable dose of 4.5 mg/day, given either once/day with the ER formulation, or in a TID regimen with the IR formulation.

The primary endpoint was the UPDRS II and III subscales, and was to be assessed when approximately 250 patients had completed 18 weeks. The 33 week analysis was to be performed when approximately the first 100 patients completed this duration of treatment. The primary comparison was to be between Mirapex ER and placebo. Numerous secondary outcomes were also assessed.

Analyses of essentially all outcomes reached statistical significance for both the ER and IR formulations at Week 18, and the results for the ER and IR groups were very similar (see, for example, Dr. Luan’s review, pages 16-18 and 19-20). In addition, the drug-placebo differences seen at the Week 33 analyses were essentially the same as the differences seen at Week 18 (see Tables 9 and 10, Dr. Luan’s review, page19).

There were no safety issues of particular concern, or that were essentially different from those known to be associated with Mirapex IR. Of particular interest, however, was the fact that this was one of the few trials done with a dopamine agonist in which systematic collection of data on impulsive and compulsive behavior occurred; there was no difference in the incidence of these behaviors between Mirapex ER and placebo (for example, the frequency of positive responses to any question on the mMIDI, a measure of compulsive sexual behavior, buying, and gambling, was 6%, 5%, and 7% for placebo, ER, and IR, respectively).

## Toxicology

Because of questions raised about the potential genotoxicity of two impurities (Z and V) in the marketed IR tablets, the sponsor performed several genotoxicity studies. These impurities were shown to be genotoxic, but the genotoxicity is considered likely to be an artifact related to the presence of catechol (known to be genotoxic), which forms as a result of the degradation of these impurities. The projected quantities of catechol that will be formed under the proposed specifications for the two impurities are trivial, and therefore the proposed specifications for these impurities are acceptable. However, a study of the mixture of these two (and two other) impurities performed in the presence of

metabolic activation revealed an accentuated response. The question arose as to whether these two other impurities (b) (4) present in the final drug product; we are assured that they are not.

A new degradation product (CD 10503) was also identified. The proposed specification limit for this degradant (b) (4) is above the level of qualification, so the sponsor performed a 13 week toxicity study (that demonstrated no new toxicities), but CD was found to be mutagenic.

CD was found to be positive in the Ames assay. It was also positive in the in vitro chromosomal aberration assay and negative in the in vivo micronucleus assay, although low doses were used, and there was no positive control. According to Dr. Freed, the overall evidence suggests that formaldehyde is responsible for the positive genotoxicity results (b) (4) (b) (4) (b) (4). The amount of formaldehyde presumably present in the final drug product is considered acceptable, and supports the proposed specification of (b) (4) for CD 10503).

An additional issue raises concerns about the safety of the proposed product.

As noted earlier, immediate release Mirapex (referred to in this memo as Mirapex IR) is already marketed. Mirapex IR comes in the following strengths: 0.125 mg, 0.25 mg, 0.5 mg, 0.75 mg, 1 mg, and 1.5 mg. Mirapex ER is proposed for 0.375 mg, 0.75 mg, 1.5 mg, 3 mg, and 4.5 mg. The IR tablet is taken three times a day; the ER tablet once a day.

As can be seen, there are 2 strengths (0.75 and 1.5 mg) that exist in common in both products. In addition, all tablets in both IR and ER formulations are white. In addition, there are 5 IR strengths that, when given TID (the appropriate regimen), result in a daily dose of pramipexole that is represented by each of the ER strengths. That is:

IR strengths	ER strengths
0.125 mg TID	= 0.375 mg
0.25 mg TID	= 0.75 mg
0.5 mg TID	= 1.5 mg
1 mg TID	= 3 mg
1.5 mg TID	= 4.5 mg

In addition, the IR strengths are available in round (0.125 mg, 1, and 1.5 mg) and flattened oval (0.25, 0.5, and 0.75 mg) shapes. The ER strengths are proposed as round (0.375 and 0.75 mg) and spheroidal oval (1.5, 3, and 4.5 mg) shapes. There is not a consistent shape for each line of products. The ER tablets are

debossed with a symbol on one side (presumably a Boehringer Ingelheim-related symbol) and an identification code on the other side (see Dr. Bergmann's review, page 161 for a clear picture of the IR and ER tablets).

The review team is concerned that the similarity in appearance (shape, color) as well as overlapping strengths, will result in medication errors. Further, DMEPA is concerned that the carton and container labels for the IR and ER formulations are similar enough to raise the real possibility of dispensing errors.

Specifically, there are numerous potential error scenarios. DMEPA notes that it is common for the suffix "ER" to be left off prescriptions. In this case, were this to happen, the most likely errors would involve the overlapping strengths. That is, a prescription for 0.75 mg TID (intended to be filled with the IR) could result in 0.75 of the ER given TID, an error that would result in a significant overdose. A similar error could result with the 1.5 mg tablets, and the errors could, of course, occur in the other direction as well (that is, a prescription for the 1.5 mg (ER) once a day could be filled with the 1.5 mg IR tablet, resulting in significant under-dosing). Militating against this possibility, though, is the fact that the overlapping strengths are not particularly similar in appearance (for example, the shapes are different). However, as noted in the DMEPA review, the container and carton labels of the ER and IR formulations are somewhat similar in appearance, sharing some similar colors and design (b) (4)

To the extent that this similarity might result in the wrong product being taken off the pharmacy shelf, this dispensing error could occur.

As Drs. Podskalny and Bergmann also note, the 3 largest strengths of the ER formulation (1.5, 3, and 4.5 mg) are all very similar in appearance, especially the 1.5 mg and 3 mg strengths. If a patient was supposed to be prescribed one of these strengths, but received the other by mistake, it would be almost impossible to distinguish one of these strengths from the other.

How could it happen that a patient could receive the wrong strength of an ER formulation?

One way would be if, for example, the patient was prescribed ER 4.5 mg, once a day. If the pharmacy did not stock the 4.5 mg strength, they might dispense the 3 mg and the 1.5 mg strengths. In this case, patients would have 2 strengths with almost identical appearance. If they were to confuse the pills (that is, take 2, 3 mg tablets instead of one of each, or take 2, 1.5 mg tablets instead of one of each) errors would occur.

Another way this could occur would be if the wrong strength was taken off the shelf by a pharmacy technician, and a pill bottle filled with the wrong strength.

Given the similarity in appearance of these tablets, inspection by the pharmacist could easily miss the fact that the wrong strength was dispensed.

The potential for all of these errors to occur is increased by the fact that there are no identifiable markings on the ER tablets. As I noted above, the markings on either side of the ER tablets are idiosyncratic, and not identifiable by the patient or pharmacist. Should the wrong tablet be dispensed, it would be impossible for the patient to identify an ER tablet as an ER tablet, or what the strength was. If the tablets were debossed with “ER” on one side, and the strength on the other, this could help prevent such errors. Further, the fact that there is no consistent shape for each formulation is also likely, in my view, to predispose to confusion between formulations.

I also note that Dr. Toombs of DMEPA states in her review that their analysis of the carton and container labels as well as of the tablets themselves, “...noted areas of needed improvement in order to minimize the potential for medication errors.”. She further notes that, given the sponsor’s choice to employ “product characteristics” that are similar between the formulations, they have “...eliminated a potentially valuable error reduction strategy...”, and that surveys of pharmacists have revealed that, although physician handwriting, similar product names and package labeling are the most common causes of dispensing errors, “tablet similarity” is also a frequent contributing factor. Finally, Dr. Toombs states: “DMEPA notes that confusion between Mirapex and Mirapex ER is likely to occur, and that collective measures to ensure product differentiation are necessary to help to minimize these potential errors.”

I agree that the similarities in tablet appearance (both between IR and ER formulations and among the ER formulation tablets themselves), overlapping strengths between the IR and ER formulations, and similarities in carton and container labels, combined with the common practice of prescribers leaving the “ER” suffix off of prescriptions, are likely to result in medication errors. It is difficult to predict exactly the sorts of errors that might occur (some examples are given above), but this does not materially lessen my concerns. I believe the factors described, on face, are likely to result in errors; clearly the clinical team and DMEPA agree.

I further believe that should errors occur (either under-or overdosing), the clinical consequences could possibly be significant. Underdosing PD patients could result in stability problems, including falls, and overdosing could result in needless and potentially serious adverse reactions (e.g., blood pressure changes, cognitive changes [e.g., hallucinations], nausea/vomiting, etc.). Importantly, I believe that, where changes can reasonably be made that might minimize the risk of errors that are likely to occur, those changes should be made prior to the introduction of a product into the marketplace. I note that Dr. Toombs in her review concludes that errors are likely to occur, and that measures to “ensure product differentiation are necessary...”. I agree that when errors are

predictable and likely, all reasonable efforts should be made to prevent them prior to marketing. For this reason, I believe we should ask the sponsor to address our concerns prior to marketing.

One alternative to this approach is to approve the product without requiring changes, and rely on post-marketing reports of errors to inform us whether or not predicted errors are, in fact, occurring. My view is that post-marketing reports cannot reliably provide adequate information on this point, and, beyond this, if we believe (as we do) that errors are likely, it is our responsibility to make all reasonable efforts to prevent them, and not merely record them if they occur.

As the review team notes, it would be useful for the sponsor to make changes to their carton and container labels, as well as possibly to the shape and color of the tablets. At the least, there is general internal agreement that the ER tablets should be embossed with information that could help the pharmacists and patients to tell 1) whether the tablet they are holding/looking at is an ER tablet, and 2) what the dose is. A relatively simple way to effect this change is for the sponsor to deboss the ER tablets with "ER" on one side, and with the strength on the other side. I believe we should ask the sponsor to employ this debossing approach, as well as make them consider the other possible changes to the labeling and tablets to further minimize the possibility of errors.

(b) (4)

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(b) (4)

For the reasons that I have described above, then, I will issue a Complete Response letter, with attached draft labeling.

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/s/  
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RUSSELL G KATZ

08/24/2009

## CLINICAL REVIEW

Application Type	NDA
Application Number(s)	22421
Priority or Standard	Standard
Submit Date(s)	24 October 2008
Received Date(s)	24 October 2008
PDUFA Goal Date	24 August 2009
Reviewer Name(s)	Kenneth Bergmann, MD
Review Completion Date	5 August 2009
Established Name	Pramipexole Dihydrochloride Extended-Release Tablets
(Proposed) Trade Name	MIRAPEX ER
Therapeutic Class	Dopamine agonist
Applicant	Boehringer Ingelheim
Formulation(s)	Extended Release 0.375, 0.75, 1.5, 3.0, and 4.5 mg
Dosing Regimen	Once daily
Indication(s)	Parkinson's Disease
Intended Population(s)	Adults with PD

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## 1 Recommendations/Risk Benefit Assessment

Following assessment of the clinical data, it is the opinion of this review that Pramipexole Extended Release (PPX ER, Mirapex ER®) is effective for the treatment of the motor signs and symptoms of early Parkinson's disease. It has a side effect profile consistent with its class (dopamine agonist) and its overall risk to benefit ratio is therapeutically acceptable.

However, the appearance of the pills (multiple sizes and shapes all of which are white, including doses which overlap the mg strength of the immediate release formulation) is likely to result in an unacceptable level of risk for medication error due to confusion among the dosage forms and their strengths. For this reason, the reviewer suggests a Complete Response be given to the Sponsor, requiring a change in the appearance in the ER formulation in order to more fully identify dosages and to differentiate it from the immediate release (IR) formulation.

### 1.1 Recommendation on Regulatory Action

As indicated above, a Complete Response is suggested due to the potential for medication error resulting from the similar appearance of the ER and IR formulations. Information supporting this conclusion is presented in Section 7.6.5 Potential for Medication Error. Outside of this consideration, the reviewer finds that Mirapex ER fulfils the requirements for approval.

Review of clinical data finds sufficient evidence for Mirapex ER's use in the treatment of early Parkinson's disease only. In this submission, the basis of approval is a single efficacy trial of 18 weeks duration in early Parkinson's disease using a well-accepted motor rating scale. The primary endpoint was the change from baseline of the sum of Parts II (Activities of Daily Living) and Part III (Motor Function) score of the UPDRS (Unified Parkinson's Disease Rating Scale) assessed at the week 18 visit.

Courtesy of the primary statistical review, the mean change in UPDRS from baseline was -5.1, -8.1 and -8.6 for placebo, PPX ER and PPX IR, respectively. The p-value is 0.0330 (PPX ER vs. placebo) and 0.0018 (PPX IR vs. placebo). The improvement in the placebo group is largely due to the need for rescue medication (carbidopa / levodopa) in a small number of patients during the trial, which had a potent effect in this group. Primary review of pharmacokinetic parameters is courtesy of Clinical Pharmacology and provides support of pharmacokinetic equivalence to the immediate release product. This clinical review endorses these findings.

No clinical evidence to support treatment of advanced disease was submitted for consideration and the safety concern is that adverse events may be more prevalent in patients with advanced disease.

## **1.2 Risk Benefit Assessment**

No new or unexpected adverse events were discovered in the course of the development program for this extended release formulation of a drug that has been marketed in the United States since 1997. Safety data was obtained from the placebo controlled efficacy trial in early Parkinson's disease as well as a trial in advanced Parkinson's disease still in progress.

## **1.3 Recommendations for Postmarket Risk Management Activities**

Because a Complete Response is suggested on the basis of the potential for medication error, no recommendations for postmarket risk related activities are made. Putting this issue aside, however, the reviewer sees no other need for post-approval action.

## **1.4 Recommendations for Postmarket Studies/Clinical Trials**

No recommendations for postmarket studies are made.

## **2 Introduction and Regulatory Background**

Parkinson's disease (PD) is a chronic progressive degenerative disorder of the central nervous system, with slowly progressive degeneration of the nigrostriatal dopamine system. The predominant motor symptoms are tremor, increased muscle tone and bradykinesia, but non-motor symptoms also cause considerable disability. The underlying pathophysiology of the motor symptoms is a deficiency of dopamine in neuronal terminals in the striatum.

The estimated incidence of PD is 4.5 to 16 per 100,000 persons/year. The prevalence of PD is between 175 to 350 / 100,000 population in the US. Parkinson's disease is associated with eventual disability or death. Untreated PD had a mortality rate of 80 % within 10 years of diagnosis, but even successfully treated PD patients without dementia still experience a shortened life span.

Levodopa (L-dihydroxyphenylalanine or L-dopa) is a dopamine precursor which is decarboxylated in the brain to become dopamine. It is combined with carbidopa, a dopa-decarboxylase (DDC) inhibitor, so that this conversion takes place mostly within the central nervous system. This remains an effective symptomatic therapy of PD four decades following its introduction. However, with each passing year of levodopa treatment, more fluctuations in motor control occur. These often become disabling. Motor complications involve fluctuations, erratic or unstable responses to medications (e.g. wearing-off phenomena) and dyskinesia or involuntary movements.

Pramipexole is a member of the class of drugs known as dopamine agonists. Dopamine agonists (DAs) are synthetic agents which directly stimulate dopamine receptors.

These are used either in monotherapy for the treatment of the motor symptoms of PD in the early stage of the disease or in the later phase of the disease to lessen motor complications associated with levodopa therapy. Early DAs were ergot derivatives and associated with significant adverse events related to their chemical structure. Pergolide, a semi synthetic ergoline derivative has been associated with myxomatous heart valve degeneration, and is no longer marketed.

## 2.1 Product Information

Pramipexole immediate release (PPX IR) tablets were initially approved for the treatment of signs and symptoms of idiopathic Parkinson's disease (PD), as monotherapy or in combination with levodopa in 1997. It is registered in more than 80 countries.

Pramipexole Extended Release (PPX ER) tablets have been investigated by the Sponsor under IND 75,961 and this current NDA seeks approval for use in adults with Parkinson's disease. Pramipexole immediate release tablets (PPX IR) are approved for the treatment of Parkinson's disease and restless legs syndrome: NDA 20-667: Parkinson's disease (7/1/1997); RLS (11/7/2006).

The Sponsor has the following applications for PPX IR tablets:

IND 34,850 Parkinson's disease

(b) (4)

IND 67,465 RLS

IND 76,936 Tourette's Syndrome in pediatric patients

(b) (4)

Fibromyalgia

(b) (4)

## 2.2 Tables of Currently Available Treatments for Proposed Indications

Agents currently indicated in the US for the treatment of PD act by exerting their primary pharmacological effect at or near dopamine neuron terminals in the striatum. Their dopamine related adverse events may result from this site and / or from stimulation of one of the other dopamine tracts found in the human central nervous system such as mesolimbic dopamine system. Dopaminergic agents also exert physiological effects upon the juxtaglomerular apparatus in the kidney resulting in increased renal blood flow.

**Table 1 Currently available anti-Parkinson medication**

Dopamine precursor	levodopa		Catabolic inhibitors:	
			DOPA decarboxylase	carbidopa
Dopamine agonist	apomorphine			
	bromocriptine		COMT	entacapone
	pramipexole			tolcapone
	ropinirole			
			MAO-B	selegiline
Anticholinergic	amantadine			rasagiline
	trihexyphenidyl			
	benztropine		Antiglutamatergic	amantadine

### 2.3 Availability of Proposed Active Ingredient in the United States

Pramipexole, the active ingredient in this extended release formulation, is marketed in the US as an immediate release medication, Mirapex®.

### 2.4 Important Safety Issues With Consideration to Related Drugs

Dopaminergic agents in general and DAs in particular, are associated with a particular constellation of adverse events. These include sleep disturbances, worsening of levodopa related dyskinesia, orthostatic hypotension, hallucinations, delusions, compulsions, impulsiveness, and other behavioral complaints. While the severity of some events is related to the stage of underlying Parkinson's disease, others are not.

In addition, some medication associated behavioral abnormalities may be induced in patients without PD, as has been seen in patients with Restless Legs Syndrome treated with DAs.

These are addressed in Section 7, Review of Safety.

### 2.5 Summary of Presubmission Regulatory Activity Related to Submission

The substance of five regulatory meetings leading to this NDA submission is summarized below. FDA comments and discussion regarding NDA Modules 3 and 4 are omitted here due to their review in non-clinical sections of the NDA. Requests concerning the physical structure of the electronic submission and datasets are also omitted.

### 2.5.1 Pre-IND Meeting

A meeting prior to the filing of IND 63897 was held with then Sponsor Pharmacia, as well as current Sponsor Boehringer Ingelheim, on 30 August 2002.

FDA agreed with the Sponsor's suggestion that two 6 month clinical trials are acceptable to support pramipexole XR (as it was then named).

FDA agreed to the Sponsor's plan which intended to use superiority of pramipexole XR versus placebo to support approval of the NDA. The primary efficacy endpoint was to be based on the LOCF change from baseline to the end of the maintenance visit in the sum of Unified Parkinson's Disease Rating Scale (UPDRS) Part II + Part III scores compared with placebo based on an analysis of variance adjusting for baseline sum of UPDRS Part II + Part III scores, baseline selegiline use, and investigator effect. FDA agreed to accept a 3 and 6 month studying support of this indication. While it was felt that the analysis was acceptable it would be subject to review when the complete plan was made available.

(b) (4)

FDA agreed to consider a statistical analysis plan having regional endpoints for both US and European registration.

FDA agreed to consider the current PPX IR safety database sufficient to assess the long-term safety of pramipexole XR in accordance with ICH Guidelines. However, it was suggested that QTc data be collected as it was not in the original PPX IR NDA.

(b) (4)

FDA told the sponsor that they would need a bioequivalence trial comparing the highest strength of the XR product (once daily dosing) to the approved IR product (t.i.d. dosing). Since doses would have to be titrated upwards, single dose and multiple dose information on dose proportionality covering the various XR strengths, as well as equivalency between the highest XR strength and the IR product could be gathered from this trial as various strengths from the lowest to the highest are used in this trial. Further, with one extra day of dosing for the highest strength toward the end of the trial, food information could be obtained on the highest strength of the XR product that they plan to market, by giving the highest XR strength with food.

FDA agreed that the XR peak-trough ratios could be comparable or less than the IR formulation. The Sponsor had proposed to select the total daily XR dose based upon data for an XR formulation that, when given once daily, provided a comparable extent of absorption (AUC) and comparable peak-trough ratios relative to the same daily dose for the IR formulation given three times daily.

[REDACTED] (b) (4)

### 2.5.2 Pre-IND Meeting

A meeting prior to the filing of IND 75961 was held with the sponsor on 11 January 2007.

FDA agreed that it find acceptable if the Sponsor refers in the IND for the new PPX ER tablets to the existing IND 34,850 and NDA 20-667 (for immediate release PPX tablets in Parkinson's disease) for available information regarding drug pharmacology and toxicology to support the conduct of a 6-month Phase 3 trial in patients with early Parkinson's disease.

Given the extensive clinical safety database for PPX IR tablets, FDA also found acceptable that the Sponsor refer to the previous human experience with PPX IR already submitted to the Division under IND 34,850 and NDA 20-667, and to submit the final trial reports from three Phase I clinical pharmacology studies with PPX ER tablets to support the conduct of a 6-month Phase 3 trial in early Parkinson's disease patients.

[REDACTED] (b) (4)

FDA responded that only a synopsis had been provided and data were not presented to clearly show that PPX is evenly absorbed throughout the intestinal tract, since the  $t_{max}$  values for the individual formulations as well as  $C_{max}$  and AUC had not been provided. FDA found the Sponsor's proposal to be generally reasonable. It was recommended that dose dumping with alcohol be evaluated. First in vitro dissolution studies in various concentrations of alcohol (e. g. 5, 10, 20 and 40%) were to be conducted. Once results were available, it was recommended that the Sponsor discuss this with the Office of Clinical Pharmacology in order to assess the need for in vivo study. FDA indicated the alcohol study can be performed by adding the alcohol to the selected dissolution media

using the selected dissolution method previously discussed. As a post-meeting note, the in-vitro alcohol studies can be done with the highest strength ER tablet since the % of hypromellose (b) (4) and the dissolution using the proposed method appears to be similar across all strengths in an exploratory stability study.

The Sponsor indicated that all pharmacokinetic (PK) studies with PPX ER tablets had been conducted only in males, with the intention to evaluate PK in females within the Phase 3 trial 248.524 in early PD patients by means of population PK analyses. The Sponsor wished to know whether FDA agreed that the Sponsor's proposal would provide sufficient gender-specific pharmacokinetic information to support the NDA for the ER tablets. FDA responded that it seemed reasonable based on what is known about the pharmacokinetics in females based on the approved Mirapex labeling. However, the Sponsor was directed to justify this when the NDA is submitted.

The Sponsor proposed conducting three Phase I studies using the PPX ER tablets. Study 248.530 assessed the PK performance of the ER tablets at all dose levels (0.375 - 4.5 mg) and compared the ER tablets to IR tablets at the highest ER dose strength of 4.5 mg daily and compared the bioavailability of this highest dose strength in the fasted and fed state. Food effect was additionally assessed in Study 248.560 after a single dose of the lowest dose strength of 0.375 mg. No further PK studies were planned aside from Study 248.524, the population PK planned for the Phase III trial in early PD. The FDA indicated that the Phase 1 studies, if adequately performed, would adequately characterize the PK of the ER tablets for an NDA, but also indicated that the final evaluation is dependent on review of the NDA.

The FDA was queried about the design, duration, primary endpoint (change from baseline in the sum of UPDRS Parts II and III) and statistical analysis plan (primary analysis = superiority of PPX ER tablets to placebo) for Study 248.524 which was to demonstrate the efficacy and safety of PPX ER tablets for the treatment of early Parkinson's disease and which was to be the only trial with the ER tablets planned to be conducted, in part, in the US.

FDA indicated that the duration (6 months) of the trial, the primary endpoint, and the demonstration of superiority of ER to placebo were acceptable. It was not clear from the synopsis provide whether there were plans to investigate the effects of concomitant use of selegiline, anticholinergic, and other anti-Parkinson medications. FDA requested that the Sponsor specify the acquisition of the primary outcome measures (UPDRS II & III) in relation to 'on time'. The Sponsor responded that 'off time' comparison between the IR and ER was now a key secondary outcome measure.

The FDA agreed that Phase III Studies 248.524 and 248.525 were adequate to characterize the efficacy of PPX ER tablets for the treatment of the signs and symptoms of idiopathic early and advanced Parkinson's disease, respectively. It was also agreed

that proposed size and duration of exposure in these studies would be sufficient to evaluate the safety of PPX ER tablets in early and late PD.

The Sponsor asked for guidance concerning the pharmacokinetic data linking the new dosage form to the previously studied IR formulation, proposing to rely upon:

- A pharmacokinetic package (with Study 248.530 as the basis) linking the PPX ER tablets to the PPX IR tablets for treatment of Parkinson's disease (for demonstration of efficacy).
- Interim (approximately 3-month) safety results from Phase III Studies 248.524 and 248.525 (for demonstration of safety).
- Updated (6-month) safety data from Phase III Studies 248.524 and 248.525 submitted in the 4-month safety update]
- Safety data with the ER formation from the Phase I healthy volunteer studies.

FDA responded that, if bioequivalence based on both  $C_{max}$  and AUC were demonstrated between the IR and the ER formulations, it may be possible to support approval of the ER formulation without submitting controlled trial data. However, before taking that approach, FDA indicated that the Sponsor would need to provide PK/PD evidence supporting the fact that the same effect is achieved with PPX, whether the levels are continuous or fluctuate over the course of the day. The effect of differences in  $t_{max}$  and shape of the PK profile for the ER vs. IR should be evaluated. Such evidence may come from either clinical or nonclinical studies.

FDA added that in the absence of this information on the PK-PD relationship for PPX, Phase III trials may be required to provide efficacy information to support approval. Even if approval could be supported based on the PK/PD approach for efficacy, FDA voiced reservations that the occurrence of neuropsychiatric adverse events (such as compulsive behaviors) will not be the same with long term treatment with an ER formulation versus an IR formulation. In addition, since an ER formulation presumably provides continuous dopaminergic exposure to post-synaptic dopamine receptors as opposed to fluctuating levels provided by IR, this may have a bearing on the natural history of the disease (such as time to development of motor complications in early PD patients). Controlled studies of 6 month duration (or even longer) may be necessary to assess some of these issues.

The Sponsor stated that, having established bioequivalence between the IR and ER formulations based on  $C_{max}$  and AUC, they now propose to submit an NDA based mainly on this bioequivalence and supplementing it with a 3 month interim comparable efficacy data between IR and ER in the 6 month trial on patients with early Parkinson's disease. There was discussion regarding the use of this 3 month data showing comparability of effectiveness between the IR and ER formulations based on single (outcome) measurements per day versus the information obtained from multiple assessments done over a 24 hour period in a PK-PD study assessing the effect with continuous versus fluctuating plasma levels over the course of the day and the effect of differences in the  $T_{max}$  and shape of PK profile between the two formulations. The Sponsor indicated that based on statistical consideration, logistics involving recruitment

of subjects and other considerations, they prefer to submit the above 3 month interim efficacy data from the trial in early Parkinson's disease rather than from the trial in advanced Parkinson's disease.

FDA acknowledged that it was willing to accept the Sponsor's above proposal; however, the Sponsor was reminded that using data from the early Parkinson's disease trial may lead to approval for ER formulation use only in early Parkinson's disease population, and that the decision to review advanced Parkinson's disease data in relation to the proposed NDA cycle may be discretionary. Further, FDA asked the Sponsor to justify the basis for the assumption that the efficacy seen at 3 month interim analysis will be maintained out to 6 months. The Sponsor replied that the assumption will be based, in part, on the analysis of an estimated 40 - 50% of total enrolled subjects who will have had their 6 month data available during the interim analysis. The sponsor also commits to submit available safety data along with the 3 month interim efficacy data, and submit all the updated safety with the 4 month safety update.

FDA indicated that any controlled trials should include active surveillance for neuropsychiatric adverse events (such as compulsive behaviors) and recommend the inclusion of a rating scale for evaluating predisposition to these abnormal behaviors. The Sponsor stated that they plan to screen for compulsive behaviors potential using modified Minnesota Impulsive Disorders Interview (MIDI) scale at the baseline and at the end of the 6 month trial. FDA requested that the Sponsor include another modified MIDI evaluation in all patients around 2-3 months (about the time that these adverse events begin to emerge early during trials) as well as in individual cases when suggestion of compulsive behaviors is detected during questioning at each visit. FDA also suggested that the protocol include mechanisms to actively solicit information regarding whether subjects are experiencing these adverse events during every visit.

Discussion was held concerning the format of a through QT trial. The Sponsor referenced a designed submitted to IND 67465 for Restless Legs Syndrome. FDA noted that the dose used in this trial, 1.5 mg q.d. is smaller than the planned exposure of 4.5 mg q.d for ER formulation. The Sponsor was asked to provide justification for not studying higher doses and was told that, assuming no safety problems with the above QT trial, ECG (linked to  $T_{max}$ ) data may provide adequate safety information of ER formulation effect on QT interval. The Sponsor was also told that they should provide justification for not studying higher doses.

FDA noted that, according to the current PPX IR labeling, clearance of PPX is 60-75% lower in patients with moderate and severe renal impairment compared with healthy volunteers. FDA raised the question whether the renal function study for PPX IR would have had some QT data with higher than usual exposures that the sponsor could use to support their QT proposal.

FDA indicated that the QT trial could use the maximum tolerated dose and could be performed in Parkinson's disease patients instead of healthy subjects if tolerability is an

issue. Using the IR tablet (with a more discrete  $t_{max}$  than the ER tablet) is reasonable. The Sponsor should justify the dose that is selected with respect to ensuring that exposure after the IR dose will cover the exposures that would occur after accumulation of the ER tablet at steady state, any extrinsic or intrinsic factors that could result in increased  $C_{max}$ , and justify that the proposed dose is the maximum tolerated dose and why a supra therapeutic dose can't be used. The proposal for the QT trial protocol is to be submitted for review by the Interdisciplinary Review Team for QT.

### **2.5.3 Comments on proposed thorough QT trial.**

Correspondence was sent to the Sponsor on 27 June 2007 in connection with IND 67465 to comment upon requirements for the study of the effects of PPX on the QT interval. See below Section 7.4.4 Electrocardiograms.

### **2.5.4 End of Phase II Meeting**

An End of Phase II Meeting was held with the Sponsor on 22 August 2007 in order to clarify the safety and efficacy data needed to support an NDA for PPX in extended release formulation for the treatment of Parkinson's disease in the same population as the currently approved immediate release formulation.

Comments and points of agreement relevant to the clinical and safety review are summarized below, taken from the FDA minutes of that meeting, found in DARRTS under IND 75961.

Study 248.524 is a 33-week flexible-dose trial intended to demonstrate the efficacy and safety of PPX ER tablets for the treatment of early Parkinson's disease. An interim efficacy analysis was planned once approximately 250 randomized patients had completed at least 18 weeks of therapy or had discontinued treatment prior to week 18. The interim efficacy analysis was to test the primary efficacy endpoint (UPDRS II+III score) in a confirmatory way for the comparison of PPX ER versus placebo for patients who have completed at least 18 weeks or have discontinued treatment prior to week 18. The Sponsor proposed that the results of this interim efficacy analysis be a key component of the demonstration of efficacy of PPX ER tablets for the treatment of Parkinson's disease.

FDA was concerned about the potential situation wherein this trial achieves significance during interim analysis but fails at the final analysis. After discussion, it was agreed that once this trial achieves statistical significance at the interim analysis at an alpha of 0.05, all further efficacy assessments and efficacy analysis would stop, and that collection of blinded safety data would continue for the full 6 month duration. Further, it was agreed that the interim data analysis will include 6 month data from at least 100 subjects who have completed the trial in order to assess maintenance of efficacy out to 6 months.

FDA was concerned that in this trial, modified MIDI scores ( a scale for behavior aberrations that are potentially related to DAs) are evaluated using descriptive statistics without a confirmatory mechanism to check that subjects identified by this scale do indeed have those behaviors. The sponsor agreed to require that all subjects identified via modified MIDI undergo formal psychiatric evaluation using standardized interview such as the Structured Clinical Interview for DSM-IV Axis II Personality Disorders (SCID-II) to confirm impulse control disorders.

The FDA indicated a need for the following statistical requirements:

- The exact rule of pooling the small centers in Protocol 248.524 & 248.525 needed to be stated.
- The interaction term [REDACTED] (b) (4) should be excluded from the primary ANCOVA model.
- As secondary analysis, significance of the interaction term should be explored, and if it is significant, further exploratory analysis needs to be done to find the specific centers for which treatment has differential effects.
- The findings of all exploratory analyses must be reported.
- With use of LOCF ANCOVA analysis as the primary method, longitudinal analysis (MMRM) needs to be done as a sensitivity analysis (i.e., as secondary analysis) on the primary outcome measure.

Study 248.636 is a 9-week trial intended to demonstrate the safety and efficacy of switching (overnight switch) from PPX IR to PPX ER in early PD patients. The sponsor indicated that they wished to test the difference in proportions of patients who successfully switched from IR to IR or ER at the end of 9 weeks of maintenance (primary endpoint) with a one-sided non-inferiority statistical test at the 5% level of significance.

FDA expressed reservations about using non-inferiority statistical tests to compare the efficacy of the two formulations following switching because we do not know the appropriate non-inferiority margin. FDA acknowledged that a trial intended to compare safety and efficacy of PPX IR versus ER after switching from PPX IR using descriptive statistics may provide useful information which potentially can be included in the Dosage and Administration section of the label.

FDA also indicated that Full Analyses Set with Last Observation Carried Forward would be preferable to Per Protocol Set for the primary efficacy analyses and noted that inclusion of drop outs (particularly due to lack of efficacy) would be important.

For Study 248.524, Study 248.636 and Study 248.525, FDA required active solicitation of significant daytime sleepiness or episodes of falling asleep at every visit/telephone encounter, and an open-ended question to capture other treatment-emergent compulsive behaviors (in addition to gambling, sexual and buying).

FDA indicated that efficacy data from the trial in early PD patients may lead to approval of PPX ER for use only in an early PD population. Whether the early PD trial can support a claim of efficacy in advanced PD would be a matter of review. The concern was that there was the possibility that after approval for both indications on the basis of the early PD trial results, the ongoing advanced PD trial could be negative (the results will not be available for timely review during the review cycle. (PPX IR is approved for treatment of both early and advanced PD).

The Sponsor wished to include efficacy and unblinded safety data, in the form of individual trial reports from trials 248.524 and 248.636, at the time of the 4-month safety update. It also wished to be able to provide instructions to physicians for safely switching patients treated with PPX IR tablets to PPX ER tablets in the Prescribing Information for PPX ER tablets based on results from Study 248.636. FDA indicated that data submitted at the 4 month safety update will leave little time for review, insufficient to include such results in the labeling.

FDA agreed to review pharmacokinetic data from 100 patients treated with PPX ER in addition to Study 248.530. PK sampling points were to be before, and 1, 2, and 4 hours after drug administration at a single visit. FDA agreed that to quantitate the effect of renal function, data from 100 subjects treated with ER will be sufficient in combination with those subjects taking IR, along with the rich PK data from Phase 1, and the Sponsor's prior knowledge of IR. Rich PK data from Phase 1 in the population PK analysis was to be included in this submission. The Sponsor was to explore exposure-response relationships for both efficacy and safety endpoints.

FDA indicated that any clinical data from NDA 20,667 that will be needed to support an action (e.g. labeling changes), should be resubmitted with the new application. An example of this is renal impairment study U96-0093 since it will form the basis of modeling the data for dose recommendations in renal impairment.

### **2.5.5 Pre-NDA Submission Meeting**

A second meeting to further clarify the safety and efficacy data required in the NDA for PPX ER for the idiopathic Parkinson's disease indication as discussed at the End of Phase 2 meeting above was held on 15 April 2008.

The FDA agreed that a number of study reports previously submitted to NDA 20-667 for PPX IR and referred to in the Summary sections of this NDA do not need to be resubmitted.

The FDA agreed that Modules 2.4 and 2.6 will summarize and tabulate the pre-clinical data related specifically to the ER formulation submitted in this NDA. Otherwise it may just refer to the complete pre-clinical program which was previously submitted to NDA 20-667

The FDA agreed that the organization and/or information proposed to be included in Module 2.7.2, Summary of Clinical Pharmacology Studies, Module 2.7.3, Summary of Clinical Efficacy, Module 2.7.4, Summary of Clinical Safety as specified by the sponsor in their draft was adequate. The FDA specified that the ISS be a stand alone document with hyperlinks and provided documentation concerning its structure and content.

The FDA generally agreed with endpoints for the early Parkinson's double-blind placebo-control trial, but indicated that all else remains a review issue. (b) (4)

[REDACTED]

The FDA also concurred with the defined subpopulations for analysis of efficacy in special groups and situations.

The FDA specified that it would like to have *any and all* PPX ER data available in this application for review (b) (4)

[REDACTED]

The following agreements covered Module 5 content:

The FDA agreed that the Sponsor's proposal for analysis of Study 248.524 in Early PD was consistent with what was stated at the EOP2 meeting. The Sponsor indicated that the formal statistical primary efficacy analysis was to be based on 250 patients from trial 248.524 who had completed 18 weeks of treatment (or had discontinued treatment prior to week 18). The full alpha (0.05) was to be used for this analysis, testing for superiority of PPX ER versus placebo. In addition, the efficacy analyses in the initial NDA was to include an analysis of 100 patients from Study 248.524 who had completed 33 weeks of treatment (or had discontinued treatment prior to week 33). The descriptive efficacy analysis was to compare efficacy at three and six months in these 100 completer patients, and demonstrate whether that efficacy is maintained for 6 months of treatment. The Sponsor noted that separate data cut-offs are planned for the confirmatory analysis of 250 patients treated for 18 weeks and for the descriptive analysis of 100 patients treated for 33 weeks .

(b) (4)

[REDACTED]

[REDACTED] (b) (4)

[REDACTED]

[REDACTED] (b) (4)

FDA indicated that all PPX ER data should be submitted for review, not just data related to Parkinson's disease.

FDA indicated that all CRFs which are associated with deaths, serious adverse events and discontinuations for reasons of adverse events to be submitted in a PDF or other readable graphic/ alpha-numeric format. This was in response to the Sponsor's plan to include data from electronic CRFs in CDISC format for the 248.545 QT trial and for phase III trials 248.524, 248.525 and 248.636.

For all Phase III trials in the NDA (248.524, 248.525, 248.636) the Sponsor proposed to submit narratives for all serious adverse events (including deaths), for drop-outs due to non-serious adverse events and for cases related to treatment emergent impulse control disorders (ICD). In addition the FDA indicated that narratives must be complete. Time lines must be easily gleaned. Pertinent labs should be included as well as pertinent negative signs, symptoms and labs: e.g. reports of elevated liver functions should include not only the values of the transaminases but that for bilirubin and alkaline phosphatase, even if these labs are normal. (If the labs were not available, that should

be noted.) The narrations should be hypertext linked to the CRFs. All narrations should be contained at one location in a single PDF file.

FDA found the following pharmacokinetic analysis acceptable pending review of the data submitted: the Sponsor asked if a population PK analysis based on the subset of approximately 100 patients treated with the ER formulation that were used for the 18 week efficacy analysis of Study 248.524 in the NDA submission is adequate, given the known pharmacokinetic profile of PPX IR tablets and the results of Study 248.530 which demonstrates bioequivalence between PPX IR tablets given three times a day and PPX ER tablets given once daily. FDA also agreed that the efficacy endpoints CGI-I, PGI-I, or UPDRS II (change from baseline) related to AUCs are acceptable.

FDA agreed that the Sponsor may refer to the trial reports and data from NDA 20-667(PPX IR tablets) used for PK model development but asked for renal impairment data to be submitted. FDA specified the structure of the datasets: all datasets used for model development and validation should be submitted as a SAS transport files (\*.xpt). A description of each data item should be provided in a Define.PDF file. Any concentrations and/or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.

Model codes or control streams and output listings should be provided for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. These files should be submitted as ASCII text files with \*.txt extension (e.g.:myfile\_ctl.txt, myfile\_out.txt). A model development decision tree and/or table which gives an overview of modeling steps.

For the population analysis reports FDA requested that the Sponsor submit, in addition to the standard model diagnostic plots, individual plots for a representative number of subjects. Each individual plot should include observed concentrations, the individual predication line and the population prediction line. In the report, tables should include model parameter names and units. For example, oral clearance should be presented as CL/F (L/h) and not as THETA. The Sponsor was also asked to provide in the summary of the report a description of the clinical application of modeling results.

FDA requested the Sponsor to provide the summary section as a review aid for CPB reviewer. (An outline of the summary section of the HPBIO section was provided.) At the time of NDA submission the sponsor could use this template to write the summary of the Clinical Pharmacology and Biopharmaceutics section of the NDA or provide it to the agency as a review aid. This summary section should have been submitted electronically with appropriate hyperlinks to the relevant supporting data.

## **2.6 Other Relevant Background Information**

None.

### 3 Ethics and Good Clinical Practices

#### 3.1 Submission Quality and Integrity

The Sponsor's application was well organized and generally compliant with eCTD and CDISC SDTM standards. The exceptions to this were the analysis datasets which were not ADaM compliant. For example, they did not share the same subject identifier as SDTM datasets. There were also recoding errors in the analysis datasets. These were corrected by the Sponsor when pointed out to them. The nature of this problem and more detailed descriptions of difficulties arising in the datasets and requests made to the Sponsor may be found in the **Trial Results** section of **5.3.1 Pivotal Trial in Early PD** and in **7.1 Methods** in the **Review of Safety** in this review.

The data appeared to be of good quality and initially there were no questions related to the integrity of the data submitted. However as analysis of the primary efficacy trial progressed, some discrepancies requiring clarification became evident.

The analysis datasets submitted by the Sponsor had systematic errors that likely occurred due to mistakes in coding that were not represented in the original trial datasets derived from source documents. While this is careless on the Sponsor's part, the reviewer is satisfied that they do not represent a risk to the integrity of the efficacy results. The details leading to the reviewer's conclusion are as follows:

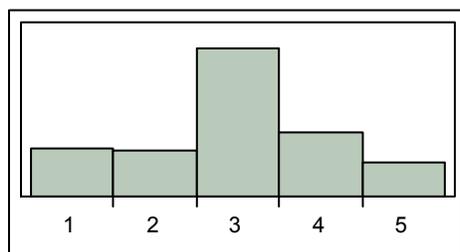
#### **Dataset Discrepancies in the Pivotal Trial in Early PD:**

The Inclusion Criteria for this trial indicates that patients may not be greater than Hoehn-Yahr Stage 3 in severity.

In Table 11.2.1:2 Selected PD-related baseline characteristics in the 248.524 Interim Analysis Study Report U08-1826-01, there are no subjects in H-Y Stages 4 and 5.

However, during the current review, it appeared that some patients are categorized as Stage 4 or 5 in the dataset. This became apparent during replication of the demographics from BASCO.xpt. The histogram below indicates the distribution of HY Stage at baseline from the TS1 dataset:

**Table 2 Miscoded PD Stages in Early PD Trial 248.524**



Hoehn-Yahr Stage Distribution of Trial 248.524 TS1: Original Dataset

Frequencies

Stage	Count	Prob
1	37	0.14286
2	35	0.13514
3	112	0.43243
<b>4</b>	<b>49</b>	<b>0.18919</b>
<b>5</b>	<b>26</b>	<b>0.10039</b>
Total	259	1.00000

It is apparent in looking at the TS3 safety cohort dataset that these advanced stages continue to accrue subjects in error at about the same rate (Stage 4 = 111 and Stage 5 = 43).

Stage 4 and 5 represent a disorder of gait and postural imbalance that would be reflected in the UPDRS. To this end, we looked at Items UPD329 (gait) and UPD330 (postural imbalance) at Visit 2 (the baseline measurement) from dataset QS.xpt. We found no item scores greater than 2 for any patient, inconsistent with a patient in Stage 4 or 5.

CRFs which had been submitted for SAEs and discontinuations were audited and we found 9 cases belonging to the advanced stage group. In each case, the HY Stage in the CRF was 3 or below. The UPDRS item analysis suggests that the CRF is likely correct, and that the problem lies in data entry and auditing. The error appears to be systematic and the distribution of stages in the safety data cohort suggests that it is present throughout the trial database. It is also of note that limits usually placed by validation criteria on the item BHOYA (i.e.: accepting only HY Stages 1, 2 and 3) in the Oracle Clinical Trial database or SAS files should have indicated that these data entries were incorrect.

**Table 3 Specific subjects miscoded in Early PD Trial 248.524**

Hoehn Yahr Stage		
PTNO	CRF	BASCO.xpt
2715	3	5
2925	2.5	4
3202	3	5
3220	2.5	4
3500	3	5
3523	3	5
4215	2.5	4

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4220	3	5
4301	3	5

These findings were presented to the Sponsor by teleconference on 19 May 2009 and an audit was requested.

Their response was as follows:

In the telecon with Drs. Podskalny and Bergmann held May 19, 2009, BI was asked to audit the analysis datasets provided in NDA 22-421. The analysis datasets were provided in the NDA and formatted according to BI standards as agreed with the Division at the preNDA meeting.

We note that the NDA also included data tabulation datasets in FDA-specified CDISC Study Data Tabulation Module (SDTM) format. These datasets were validated by the vendor (b) (4). The analysis datasets formatted according to BI standards were provided in the NDA as supplementary review information.

Although there were some findings related to decodes, the results of the audit confirm the integrity of the data in the analysis datasets. Given the findings related to the decodes, BI has identified options to ensure that the data can be correctly analyzed. More detailed description of the audit and its results are presented below.

#### **Description:**

BI audited all analysis datasets for studies 248.524, 248.525 and 248.636, namely:

- POPU (patient set assignments),
- BASCO (baseline and covariate data),
- INDER-E (individual and derived endpoint data-efficacy)
- INDER-S (individual and derived endpoint data-safety)
- IPV (important protocol violations)
- GENTRT (generic treatment file)

The following audits were carried out:

- A review to look for any missing decodes
- A review of un-coded items for valid interpretation
- Inspection of the content of coded variables for consistency across trials
- Inspection of plausibility between code and decode for all coded variables

The following findings were noted in the audit of the analysis datasets.

#### **Findings previously discussed with FDA:**

1) For trial 248.524 (cut-offs i1 and i2), the BASCO dataset contains the coded variable BHOYA but is missing the corresponding decoded variable BHOYADC that would provide the translation of the codes (1 to 7) assigned to Hoehn & Yahr stages 1, 1.5, 2, 2.5, 3, 4 and 5. For example 5 in BHOYA represents "Stage 3". Note that no patient had a code greater than 5.

2) For trial 248.524 (cut-offs i1 and i2), in the BASCO dataset the variable PRETRT, labeled as "Pre-treatment status: pre-treated" captures only discontinued PD therapy prior to baseline and not concomitant treatment for PD at baseline. The submission of the revised dataset INDER\_1 (sequence

0007, submitted March 27, 2009), clarified the disposition of patients regarding pretreatment and treatment with rescue medication.

**Additional findings:**

1) For trials 248.524 (cut-offs i1 and i2), and 248.525 (cut-offs TS1 and TS2/3), in the INDER\_S dataset, the decodes for the variable WT (weight) in the decoded variable EPTNMDC are not correct (they do not decode to "Weight (kg)").

For your information, the weight data are included in rows labeled "WT" under the column heading "EPTNM." Weight is listed three ways, in separate rows, as:

- No transformation,
- Difference from baseline, and
- Percentage change from baseline.

Analyses of any variables in INDER\_E and INDER\_S should be carried out using the coded variable under the column heading EPTNM to select data, and not the decoded variable under the column heading EPTNMDC. See screen-shot of the SAS-view showing relevant columns below (several columns are hidden for ease of viewing).

**Figure 1 Sponsor's screenshot of SAS analysis table**

	STUDY	PTNO	VISDT	STUDYDAY	VISNO	EPTNM	EPTNMDC	EPTTRS	EPTTRSDC	EPT	EPTDC
205	0248_0524	3601	04JAN08	93	70	DIA2	Standing Diastolic Blood Pr	0	No transformation	60	
206	0248_0524	3601	04JAN08	93	70	DIA2	Standing Diastolic Blood Pr	1	Difference from base	-10	
207	0248_0524	3601	04JAN08	93	70	DIA2	Standing Diastolic Blood Pr	2	Percentage change fr	-14.2857	
208	0248_0524	3601	04JAN08	93	70	HYPO	Orthostatic hypotension	0	No transformation	0	
209	0248_0524	3601	04JAN08	93	70	HYPOSYM	Symptomatic orthostatic hyp	0	No transformation	0	
210	0248_0524	3601	04JAN08	93	70	PR1	Supine Pulse Rate	0	No transformation	84	
211	0248_0524	3601	04JAN08	93	70	PR1	Supine Pulse Rate	1	Difference from base	12	
212	0248_0524	3601	04JAN08	93	70	PR1	Supine Pulse Rate	2	Percentage change fr	16.66667	
213	0248_0524	3601	04JAN08	93	70	PR2	Standing Pulse Rate	0	No transformation	84	
214	0248_0524	3601	04JAN08	93	70	PR2	Standing Pulse Rate	1	Difference from base	12	
215	0248_0524	3601	04JAN08	93	70	PR2	Standing Pulse Rate	2	Percentage change fr	16.66667	
216	0248_0524	3601	04JAN08	93	70	SLSIQ	Significant daytime sleepin	0	No transformation	0	No
217	0248_0524	3601	04JAN08	93	70	SYS1	Supine Systolic Blood Press	0	No transformation	112	
218	0248_0524	3601	04JAN08	93	70	SYS1	Supine Systolic Blood Press	1	Difference from base	-10	
219	0248_0524	3601	04JAN08	93	70	SYS1	Supine Systolic Blood Press	2	Percentage change fr	-8.19672	
220	0248_0524	3601	04JAN08	93	70	SYS2	Standing Systolic Blood Pre	0	No transformation	110	
221	0248_0524	3601	04JAN08	93	70	SYS2	Standing Systolic Blood Pre	1	Difference from base	-10	
222	0248_0524	3601	04JAN08	93	70	SYS2	Standing Systolic Blood Pre	2	Percentage change fr	-8.33333	
223	0248_0524	3601	04JAN08	93	70	WT	Standing Systolic Blood Pre	0	No transformation	55	
224	0248_0524	3601	04JAN08	93	70	WT	Standing Systolic Blood Pre	1	Difference from base	1	
225	0248_0524	3601	04JAN08	93	70	WT	Standing Systolic Blood Pre	2	Percentage change fr	1.851852	
226	0248_0524	3601	05FEB08	125	80	ABN0TH	Other abnormal behavior or	0	No transformation	0	No
227	0248_0524	3601	05FEB08	125	80	BMI	Body Mass Index	0	No transformation	24.12175	
228	0248_0524	3601	05FEB08	125	80	BMI	Body Mass Index	1	Difference from base	0.43858	
229	0248_0524	3601	05FEB08	125	80	BMI	Body Mass Index	2	Percentage change fr	1.851864	
230	0248_0524	3601	05FEB08	125	80	DIA1	Supine Diastolic Blood Pres	0	No transformation	80	
231	0248_0524	3601	05FEB08	125	80	DIA1	Supine Diastolic Blood Pres	1	Difference from base	10	
232	0248_0524	3601	05FEB08	125	80	DIA1	Supine Diastolic Blood Pres	2	Percentage change fr	14.28571	

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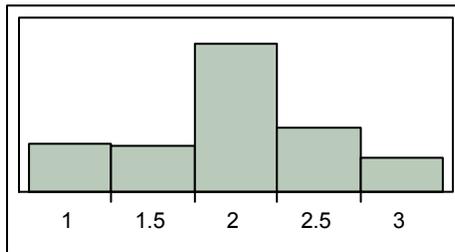
2) For trial 248.636, country name decodes were not provided for the country codes DE, F and NL. The codes DE, F, and NL represent Germany, France and The Netherlands.

### Conclusion

A thorough audit of the analysis datasets revealed the decode issues outlined above. These decoding issues do not impact the analyses carried out by BI and included in the reports. Further, they do not affect the integrity of the data and should not cause an inability to analyze or interpret the data. If requested, amended datasets with corrected decode for WT, and addition of decodes for BHOYA and COUNTRY, can be provided.

The reviewer analyzed the distribution of Hoehn and Yahr staging on entry into the trial from dataset QS.XPT for 248.524. This characterized the TS1 population for the efficacy analysis:

**Table 4 Distribution of Recoded PD Stage in Early PD Trial 248.524**



Hoehn-Yahr Stage Distribution of TS1: Recoded Dataset

#### Frequencies

Level	Count	Prob
1	37	0.14286
1.5	35	0.13514
2	112	0.43243
2.5	49	0.18919
3	26	0.10039
Total	259	1.00000

**Reviewer's Conclusion:** It appears that the Sponsor's analysis of this error is likely correct and that the source of the error was in coding from datasets into analysis sets and not at the level of data collection from source documents.

### 3.2 Compliance with Good Clinical Practices

The Sponsor certifies that it did not use any debarred investigators. Prior to the start of the trial, the protocol, the informed consent and the subject information forms were reviewed and approved by the local Institutional Review Boards (IRBs) / Independent Ethics Committees (IECs) and approval by the appropriate regulatory authorities in participating countries.

The constitution of the IRBs/ IECs met the requirements of the participating countries. A list of all IRBs/ IECs members, including their locations and the name and qualification of each committee chairperson, was provided to the reviewer. Informed consent was obtained from all subjects and the studies were performed in accordance with the Declaration of Helsinki.

One domestic and one foreign clinical trial site were selected for inspection by the Division of Scientific Investigations on the basis of having the largest number of enrolled subjects. One of the two audits revealed unexplained changes in data forms and data changes at times remote from the subjects visit when the clinic was not open. Pharmacokinetic samples were performed out of time window and were not refrigerated. Other errors were found at this site, e.g.: informed consent was not updated to reflect amendments to the trial.

This site was also one of the clinical sites selected for on-site internal audit by the Sponsor and subsequently certified. The report of that audit was not included in the NDA submission. All audit results were requested from the Sponsor when the DSI result became known. (The Sponsor stated that these were not included with the NDA because the Sponsor submitted an interim analysis, and not a final report of the pivotal efficacy trial.) Review of these summary reports indicate that the Sponsor found substantially the same deviances from GCP as did DSI, documenting an adequate audit process by the Sponsor.

As a result of the DSI inspection, the data from this clinical site were excluded from the efficacy analysis. Data relating to any adverse events were included in the safety analysis.

### **3.3 Financial Disclosures**

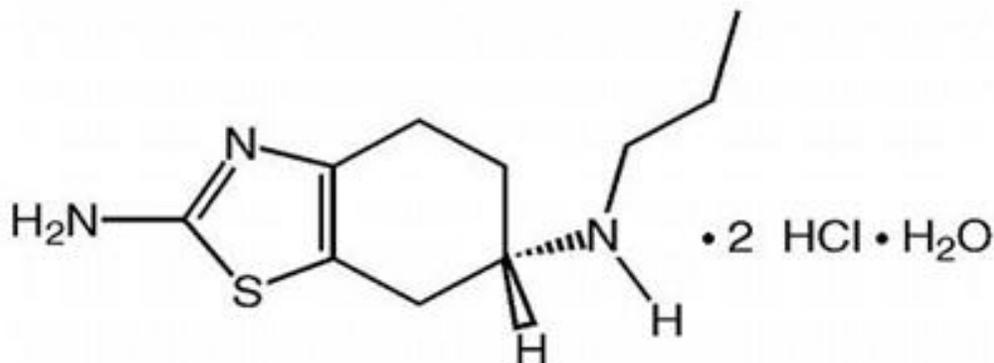
The Sponsor provided required information regarding financial disclosure. In the pivotal efficacy trial there were no conflicts of interest noted; the consultants receiving funds above the thresholds for reporting did not enter patients for the efficacy analysis.

### **4 Significant Efficacy/Safety Issues Related to Other Review Disciplines**

None were identified at the midcycle review meeting. Final reviews from related disciplines have not been incorporated into this medical review at the time of its writing.

## 4.1 Chemistry Manufacturing and Controls

Figure 2 Chemical structure of pramipexole (source: Sponsor)



No chemistry or manufacturing concerns have been identified in preliminary stages of their review. However, as of the GRMP due date for this primary clinical review, there are outstanding requests for data from the Sponsor for questions concerning drug substance, drug product, and regional packaging information.

## 4.2 Clinical Microbiology

No investigations of clinical microbiology are submitted.

## 4.3 Preclinical Pharmacology/Toxicology

No pharmacological toxicology concerns have been identified in preliminary stages of their review.

## 4.4 Clinical Pharmacology

Studies 248.560 and 248.530 constituted the clinical pharmacology program. These characterized the pharmacokinetics of single and multiple dose administration, relative bioavailability of high dose ER versus IR, food effects, and dose proportionality. Study 248.607 characterized pharmacokinetics in a Japanese population.

No studies of the pharmacokinetics of extended release pramipexole in renal failure have been performed. The use of PPX ER in patients with moderate to severe renal failure is addressed further in Section 9.2 Labeling Recommendations.

#### 4.4.1 Mechanism of Action

**Table 5 Receptor binding affinities Ki (nM)**

	D1	D2	D3	D4	$\alpha$ 1 Adreno	$\alpha$ 2 Adreno	ACH	5-HT1A	5HT2
Pramipexole	>1000	6.9	0.9	15	>1000	188	>1000	>1000	>1000

Pramipexole acts as a potent postsynaptic dopamine receptor stimulator (agonist). It is excreted renally, largely unmetabolized, and no biologically active products have been identified.

#### 4.4.2 Pharmacodynamics

Any pertinent pharmacodynamic issues are reviewed from a clinical point of view within the sections on efficacy and safety.

#### 4.4.3 Pharmacokinetics

Initial information for the ER formulation, courtesy of the Clinical Pharmacology review team, reveals that there is dose proportionality over the 0.375 – 4.5 mg dose range.  $T_{1/2}$  is about 9 h after a single dose. Inter-subject variability is <35% for AUC or  $C_{max}$ . There is low plasma protein binding (about 15%) and steady state is reached in 3-4 days. The ER formulation is equivalent to the IR formulation given TID with respect to AUC and  $C_{max}$ . The mean AUC and  $C_{max}$  is the same at steady state in Caucasians and Japanese when adjusted for body weight. It can be taken without regard to food; absorption may be slower, but the AUC is equivalent.

From IR product labeling, it also has the following characteristics: 80% renally excreted, mostly unchanged. Agents that affects renal tubule secretion (e.g.: cimetidine) increases AUC 50 %. It does not interact with CYP metabolism.

### 5 Sources of Clinical Data

All documents and datasets reviewed for this NDA submission are in electronic form. The path to this information in the CDER Electronic Document Room is:

\\CDSESUB1\EVSPROD\NDA022421\0000

## 5.1 Tables of Studies/Clinical Trials

The following are a listing of clinical studies contributing to efficacy and safety data. This is copied from Sponsor Document U08-3710, 8 October 2008. There are a total of 13 trials with PPX ER formulation in support of the PD indication. Their contributions to either safety and / or efficacy analysis are defined further in the text of the appropriate review sections below. An additional trial for the indication of fibromyalgia contributes some safety data as well:

(248.637) - A randomized, double-blind, placebo-controlled, dose titration, efficacy and safety trial of PPX ER (0.75 mg to 4.5 mg) administered orally once daily versus placebo over a 16-week maintenance phase in patients diagnosed with fibromyalgia as assessed by the American College of Rheumatology (ACR) criteria, followed by a 24-week open-label extension phase.

The review and discussion of safety data integrates the 120 day safety update provided by the Sponsor.

Abbreviations found in the tables in this section:

PPX = pramipexole dihydrochloride  
PBO = placebo  
PK = pharmacokinetic  
QD = once daily  
T.I.D. = three times daily  
DB = double-blind  
OL = open-label  
SR = sustained release  
ER = extended release  
IR = immediate release  
BA = bioavailability  
PD = Parkinson's disease  
UPDRS = Unified Parkinson Disease Rating Scale

**Table 6 Pramipexole development program (source: Sponsor)**

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

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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
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 (476)	PD patients	33 weeks, with descriptive efficacy analysis at week 18	On-going; Interim clinical safety 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	248.610	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: 61 (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: 241	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: 74	PD patients	Up to 81 weeks	Ongoing; None
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

## 5.2 Review Strategy

The review strategy focuses upon the following areas and their supporting trial(s):

- Is the ER formulation of pramipexole superior to placebo in relieving the symptoms of early PD? (*This is reviewed in Section 5.3.1*)
  - Efficacy data from the interim analysis at 18 weeks of the Phase III trial in early PD (248.524). This is the sole source of efficacy data for this application.
- Do the IR and ER formulations of pramipexole have comparable pharmacokinetic and pharmacodynamic properties? (*These are summarized in Section 4.4.3 and are covered more fully in the primary review from Clinical Pharmacology*)
  - In vitro to in vivo correlation of PPX IR to PPX ER (248.560)
  - Comparison of different dose formulations (248.529)
  - Define pharmacokinetics of PPX ER, interference from food and comparison to PPX IR (248.530)
  - Comparison of bioavailability of PPX ER to PPX IR (248.607)
  - Pharmacokinetics and tolerability of PPX IR in renal impairment (7215-96-006)
  - Population pharmacokinetics from the ongoing Phase III trial in early PD (248.524)
- Is ER formulation of pramipexole safe? (*These trials are described in Section 5.3.2 but review of their safety data is found in Section 7. The QTc safety trial may be found in Section 7.4.5*)
  - QTc trial (248.545)
  - Safety and comparability of overnight switch from PPX IR to PPX ER (248.636)
  - Safety data from the ongoing Phase III trial in early PD (248.524)
  - Safety data from the ongoing Phase III trial in advanced PD (248.525)
  - Safety data from open label extension trials (248.633 and 248.634)
  - Safety data from efficacy safety and PK trial in advanced PD (248.610)
  - Safety data from Phase II trial in fibromyalgia (248.637)

Trials contributing only safety data are briefly described in this section in order to be able to understand the participants' exposure to drug and how safety assessments were made.

Three open label trials are ongoing and are collecting long term safety data on PPX ER. Two long term extension trials (248.633 and 248.634) contain patients who completed the double blind portions of the early PD (248.524) and advanced PD (248.525) trials, respectively. The overnight switch trial in early PD (248.636) also entered patients into 248.633. Trial 248.610 is collecting open label safety data on patients who have

completed the double blind portion of this active control trial, which is ongoing, still recruiting, and still blinded.

The results of analysis of safety assessments are described. Data has been updated from the 120 day safety update provided by the Sponsor. The original cut off date for this submission was in May, 2008, with extension by the 120 day safety update to September 1, 2008 (December 1, 2008 for all SAEs).

## **5.3 Discussion of Individual Studies/Clinical Trials**

### **5.3.1 Pivotal Trial in Early PD (248.524)**

#### **Trial**

A double-blind, double-dummy, placebo-controlled, randomized, three parallel groups trial comparing the Efficacy, Safety and Tolerability of PPX ER versus placebo and versus PPX IR administered orally over a 26-week maintenance phase in patients with early Parkinson's disease (PD)

#### **Phase III**

#### **Purpose**

The objective of the trial was to determine the efficacy, safety and tolerability of PPX ER compared with placebo and with PPX IR in patients with early Parkinson's disease.

The primary objectives of the interim analyses were:

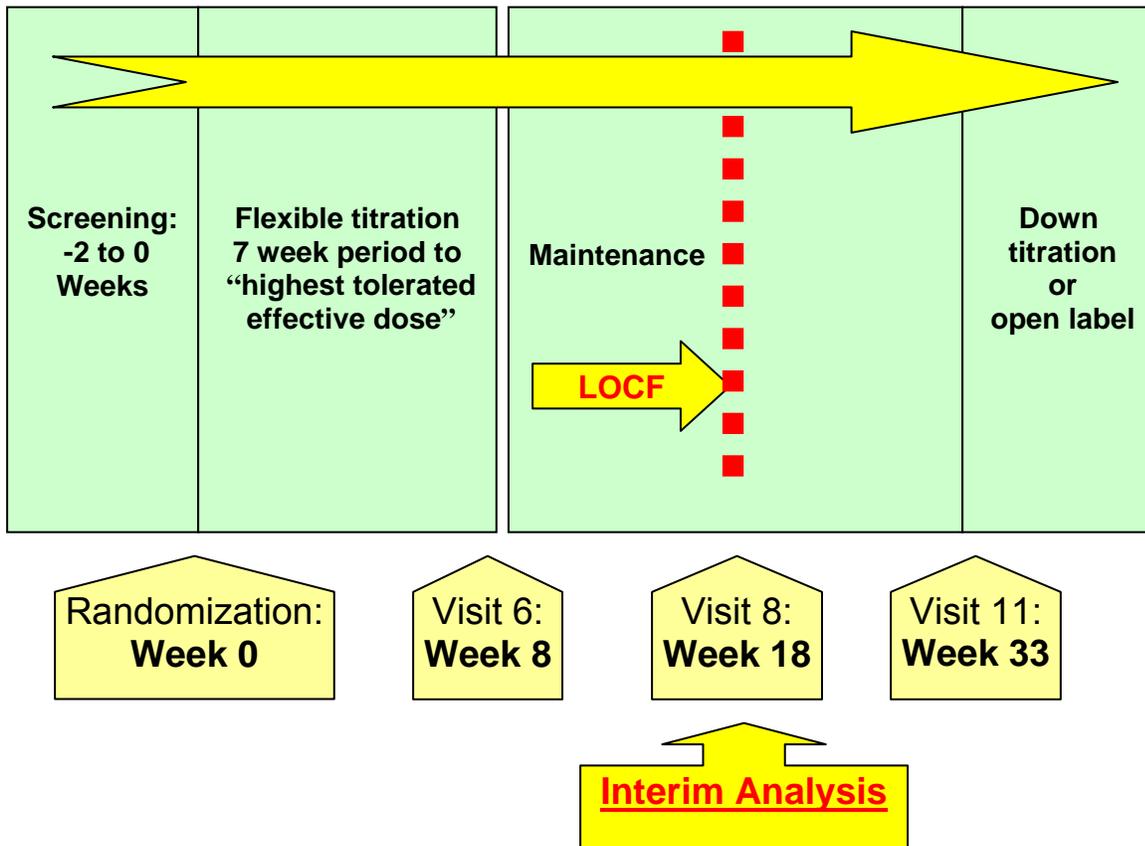
- Determine the efficacy (as measured by the change from baseline in the total score for UPDRS parts II and III combined), safety and tolerability of PPX ER compared with placebo in approximately 250 patients treated for 18 weeks (or having discontinued treatment prior to week 18)
- Confirm, in a sub-set of approximately 100 patients treated for 33 weeks (i.e. completed patients), that efficacy was maintained up to 6-month maintenance treatment.

#### **Trial design**

The trial, with a double-blind, double-dummy, placebo-controlled, randomized, parallel group design, is ongoing. The portion of the data submitted was collected from the start date May 23, 2007 up to the submission cut-off date, May 5, 2008.

The trial consists of three arms of parallel group design in outpatients with early Parkinson's disease. Patients were to be treated over 33 to 34 weeks, comprising a 7 weeks up-titration phase, 26 weeks maintenance phase and, for patients not entering the open-label extension trial, one week for down-titration. An open long term continuation is available to those completing the trial.

**Figure 3 Early PD 248.524 Trial Design**



Primary endpoint:

- The change from baseline of the sum of Parts II (Activities of Daily Living) and Part III (Motor Function) score of the UPDRS (Unified Parkinson's Disease Rating Scale) to be assessed at Visit 8, i.e.: week 18.

Key secondary criteria:

- Clinical Global Impression of Improvement (CGI-I) responder rate
- Patient Global Impression of Improvement (PGI-I) responder rate

Other secondary criteria:

- UPDRS I, II and III individual section scores (change from baseline)

- Proportion of patients with at least a 20% improvement relative to baseline in the UPDRS II+III total score
- Proportion of patients requiring L-Dopa supplementation during the trial
- Beck's Depression Inventory (BDI) version IA (change from baseline)
- Parkinson's Disease Sleep Scale (PDSS) (change from baseline)
- Likert Scale for pain related to Parkinson's disease (change from baseline)
- PDQ-39 (Parkinson Disease Questionnaire--39 item quality of life scale change from baseline)
- EQ-5D (EuroQoL quality of life scale - change from baseline)

Pharmacokinetic data:

PPX ER plasma concentrations (exposure) were assessed. Results of population pharmacokinetics and pharmacokinetic/pharmacodynamic analysis are reviewed primarily by Clinical Pharmacology.

Safety endpoints:

All 539 patients that have been entered into the trial as of the cut off dates for the 120 day Safety Amendment to the NDA are used in the safety assessment. The Sponsor specifies the following as their major safety endpoints:

- Incidence of adverse events (AEs)
- Proportion of withdrawals due to AEs
- Vital signs (blood pressure and pulse rate) and weight (change from baseline)
- Epworth Sleepiness Scale (ESS) (change from baseline)
- Modified Minnesota Impulsive Disorders Interview (MMIDI): sub-scales for compulsive sexual behavior, compulsive buying and pathological gambling
- Safety laboratory parameters

**Key Inclusion Criteria**

- Male or female patient with idiopathic Parkinson's disease (PD) confirmed by at least two of the following signs: resting tremor, bradykinesia, rigidity.
- Parkinson's disease diagnosed within 5 years.
- Patients 30 years of age or older at the time of diagnosis.
- Modified Hoehn and Yahr stage of 1 to 3.
- Patients requiring additional therapy/ introduction of therapy (for de novo patients) to treat their Parkinsonian symptoms at the time of enrolment (screening visit, V1) according to the investigator's judgment.

**Key Exclusion Criteria**

- Evidence of atypical parkinsonism
- Dementia defined as MMSE < 24 at screening
- History of psychosis but not drug induced hallucinations

Clinical Review  
Kenneth Bergmann, MD, FAAN  
NDA 22-421  
Mirapex ER / pramipexole dihydrochloride extended-release tablets

- Significant ECG abnormality, orthostatic hypotension, liver function > 2times ULN, or creatinine clearance <50 mL/min

### **Concomitant Medication**

- No dopamine agonists or levodopa allowed within 4 and 8 weeks of baseline, respectively. Amantadine, MAO-B inhibitors and anticholinergics were allowed at stable dosages
- Medication with dopaminergic activity (stimulants, blockers, neuroleptics) prohibited.

### **Trial Visits**

The timeline and procedures for Study 248.524 and the trial checklist are electronically reproduced from the Sponsor's Document. No.U08-1826-01 as are the rest of Sponsor's figures and tables in this section unless otherwise noted.

**Table 7 Early PD Trial Checklist (source: Sponsor)**

Trial period	S <sup>1</sup>	B <sup>1</sup>	Flexible up-titration phase										Maintenance phase							Down-titration phase V12 <sup>2</sup>
			TC1	V3	TC2	V4	TC3	V5	TC4	V6	V7	V8	V9	V10	V11 <sup>2</sup>	V12 <sup>2</sup>				
Visit number	V1	V2	TC1	V3	TC2	V4	TC3	V5	TC4	V6	V7	V8	V9	V10	V11 <sup>2</sup>	V12 <sup>2</sup>				
Week	-2 to -1	0	1	2	3	4	5	6	7	8	13	18	23	28	33	34				
Day	-14 to -7	0	7 ±2	14 ±2	21 ±2	28 ±2	35 ±2	42 ±2	49 ±2	56 ±3	91 ±3	126 ±3	161 ±3	196 ±3	231 ±3	238 ±3				
Written informed consent	X																			
Demographics	X																			
Baseline conditions	X																			
Inclusion/ Exclusion criteria	X	X																		
Physical exam.	X																			
Ophthalmologic monitoring	X <sup>7</sup>													X <sup>7</sup>						
BP, Pulse, Weight, Height <sup>4</sup>	X	X		X		X		X		X	X	X	X	X	X	X				
Check for abnormal behaviour <sup>5</sup>				X		X		X			X		X							
Modified MINDI		X								X		X			X	X				
MMSE	X																			
Modified Hoehn and Yahr	X																			
Randomisation		X																		
Medication fax	X	X																		
UPDRS part I, II and III	X	X		X		X		X		X	X	X	X	X	X	X				
CGI-I						X				X	X <sup>8</sup>	X	X <sup>8</sup>	X <sup>8</sup>	X	X				
PGI-I				X		X		X		X	X <sup>8</sup>	X	X <sup>8</sup>	X <sup>8</sup>	X	X				
ESS		X				X				X		X			X	X				
BDI		X				X				X		X			X	X				
PDSS		X				X				X		X			X	X				

Trial period	S <sup>1</sup>	B <sup>1</sup>	Flexible up-titration phase										Maintenance phase										Down-titration phase
			V1	V2	TC1	V3	TC2	V4	TC3	V5	TC4	V6	V7	V8	V9	V10	V11 <sup>2</sup>	V12 <sup>2</sup>					
Visit number	V1	V2	TC1	V3	TC2	V4	TC3	V5	TC4	V6	V7	V8	V9	V10	V11 <sup>2</sup>	V12 <sup>2</sup>							
Week	-2 to -1	0	1	2	3	4	5	6	7	8	13	18	23	28	33	34							
Day	-14 to -7	0	7	14	21	28	35	42	49	56	91	126	161	196	231	238							
Pain scale		X	±2	±2	±2	X				X		X			X								
PDQ-39		X										X			X								
EQ-5D		X										X			X								
Safety lab tests	X									X					X								
PK samples <sup>10</sup>	X									X	X				X	X <sup>3</sup>							
Serum pregnancy test (if applicable)	X																						
12-lead ECG	X																						
Dispense/re-dispense trial medication		X		X		X		X		X	X	X	X	X	X	X <sup>3</sup>							
Check medication compliance			X	X	X	X	X	X	X	X	X	X	X	X	X	X <sup>6</sup>							
Concomitant therapy	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X							
Adverse events <sup>11</sup>	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X							

1 Abbreviations are for "Screening" and "Baseline."  
 2 All assessments planned at Visit 11 and at Visit 12 have to be done even if a patient is prematurely withdrawn from the treatment phase  
 3 To be done at Visit 12 only if abnormal at Visit 11  
 4 Height will only be measured at Screening (Visit 1)  
 5 At Visit 11, dispense study medication for the down-titration phase if patients are not entering the open-label extension study  
 6 At Visit 12, check medication compliance during the down-titration phase  
 7 At Visit 1 and Visit 10, patients will be referred to an ophthalmologist for an ophthalmologic monitoring (vision control and funduscopy). Results should be available for Visit 2 and Visit 11, respectively  
 8 In case L-Dopa is introduced as a rescue medication at Visit 7, 9 or 10, an assessment of CGLI and PGLI should be done before starting L-Dopa.  
 9 In case the patient experiences any abnormal behaviour, then the Modified MMDS sub-scale has to be completed. In addition to the questions about pathological gambling, compulsive sexual behaviour and compulsive buying, a separate question should be addressed: "Since the last visit, have you experienced any other abnormal behaviour or urges? If yes, please specify."  
 9a In case of a newly reported positive screening at any of the MMDS sub-scales and/or at the question about any other abnormal behaviours or urges, this should be reported as an AE. These patients should be referred to a psychiatrist, to evaluate the diagnosis.  
 10 Blood samples for PK measurements of pramipexole will be taken at visit 1 (blank sample), at visit 6: before and 02:00 h after drug administration and at visit 7: before, 01:00 h, 02:00 h and 04:00 h after drug administration.  
 11 In addition to reviewing adverse events the following question should be asked at TC1, V3, TC2, TC3, V5, TC4, V7, V9, V10, V12: "Since the last visit, have you experienced significant day time sleepiness or any episodes of unexpected falling asleep?" In case of a positive answer, it should be reported as an Adverse Event.

## Treatments and other ancillary management

Doses during the 7 week up-titration phase and the 26 week maintenance phase consist of the following seven dose levels patients were titrated up if they reported that they were not “at least a little bit better”:

- PPX ER 0.375 mg, 0.75 mg, 1.5 mg, 2.25 mg (1.5 mg + 0.75 mg), 3.0 mg, 3.75 mg (3.0 mg + 0.75 mg) or 4.5 mg in the morning,
- PPX IR 0.375 mg (0.125 mg t.i.d), 0.75 mg (0.25 mg t.i.d), 1.5 mg (0.5 mg t.i.d), 2.25 mg (0.5 mg t.i.d +0.25 mg t.i.d ), 3.0 mg (1.0 mg t.i.d), 3.75 mg (1.0 mg t.i.d + 0.25 mg t.i.d), or 4.5 mg (1.5 mg t.i.d)
- Placebo tablets matching the PPX ER tablets and the PPX IR tablets

**Table 8 Early PD Trial: double dummy dosing (source: Sponsor)**

Tablets → ↓Treatment group	PPX ER morning	PPX IR morning	PPX IR midday	PPX IR evening	Placebo PPX ER morning	Placebo PPX IR morning	Placebo PPX IR midday	Placebo PPX IR evening
Pramipexole ER	X					X	X	X
Pramipexole IR		X	X	X	X			
Placebo Group					X	X	X	X

## Randomization and Controls

Trial medication was administered in double blind fashion. Not all dosage formats were identical because the final commercial formulations were used.

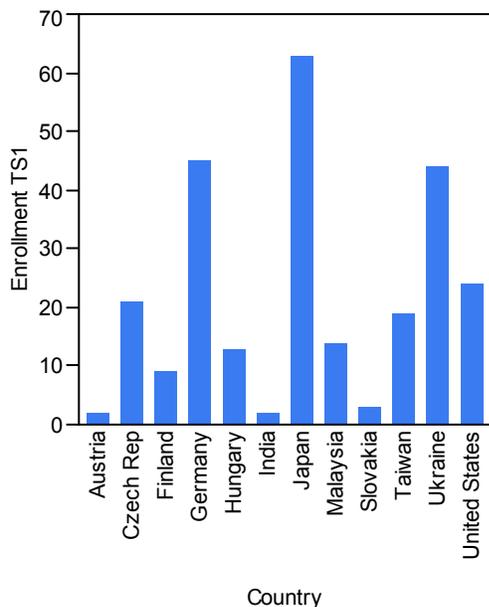
After screening, the patient was randomized and received medication at Visit Two. Assignment to treatment was in the ratio of 2:2:1 for IR, ER and placebo, respectively. Randomization was preassigned by 5 subject block design as coded by a commercial program (PMX CTM Release 3.3.0, ProPack Data GmbH). The blind has not been broken for the interim efficacy analysis in which the CRO kept treatment assignments from the Sponsor’s trial team.

## Subject Enrollment

Ninety-five multinational sites contributed to the total N of the trial; however, most of these 539 subjects did not contribute data to this interim efficacy analysis.

Sixty-one trial sites in twelve countries contributed 259 subjects (TS1, see below) to the efficacy cohort in this multicenter trial. Enrollment ranged from 1 to 11 subjects per site, the median being 4 subjects. Enrollment by country ranged between 2 and 63 subjects, median 17 and mean 22:

**Figure 4 Early PD Trial: enrollment by country**



### Protocol Amendments

The trial began on 23 May 2007. There were 5 protocol amendments:

#### Amendment 1 (May 3, 2007)

- Changed to more stringent contraceptive method at request of German Health Authority.

#### Amendment 2 (July 11, 2007)

- Breakfast was allowed before PK sample to provide a naturalistic setting for PK measurement, following FDA recommendation. Time of meal and sample recorded.
- Closer, open ended questioning added concerning daytime sleepiness and sleep attacks added to all visits and phone calls, following FDA requirement.
- Added question regarding "other abnormal behavior or urges" to questions of pathological gambling, compulsive sexual behavior and compulsive buying, following FDA recommendation.

#### Amendment 3 (July 27, 2007)

- De novo patients excluded if investigator thought treatment was needed other than allowed concomitant medication. Added by request of Slovakian Health Authority.

Amendment 4 (November 14, 2007) FDA requests from EOP2 meeting:

- Psychiatric evaluation and confirmation of a positive impulse disorders interview (MMIDI)
- PK samples at before, 1, 2, and 4 hours after trial drug administration.
- Performance start time of UPDRS standardized to link to PK samples at Visit 7.
- Patient may be sent to dermatologist for question of skin examination
- Creatinine clearance to be estimated by MDRD formula not Cockcroft and Gault formula

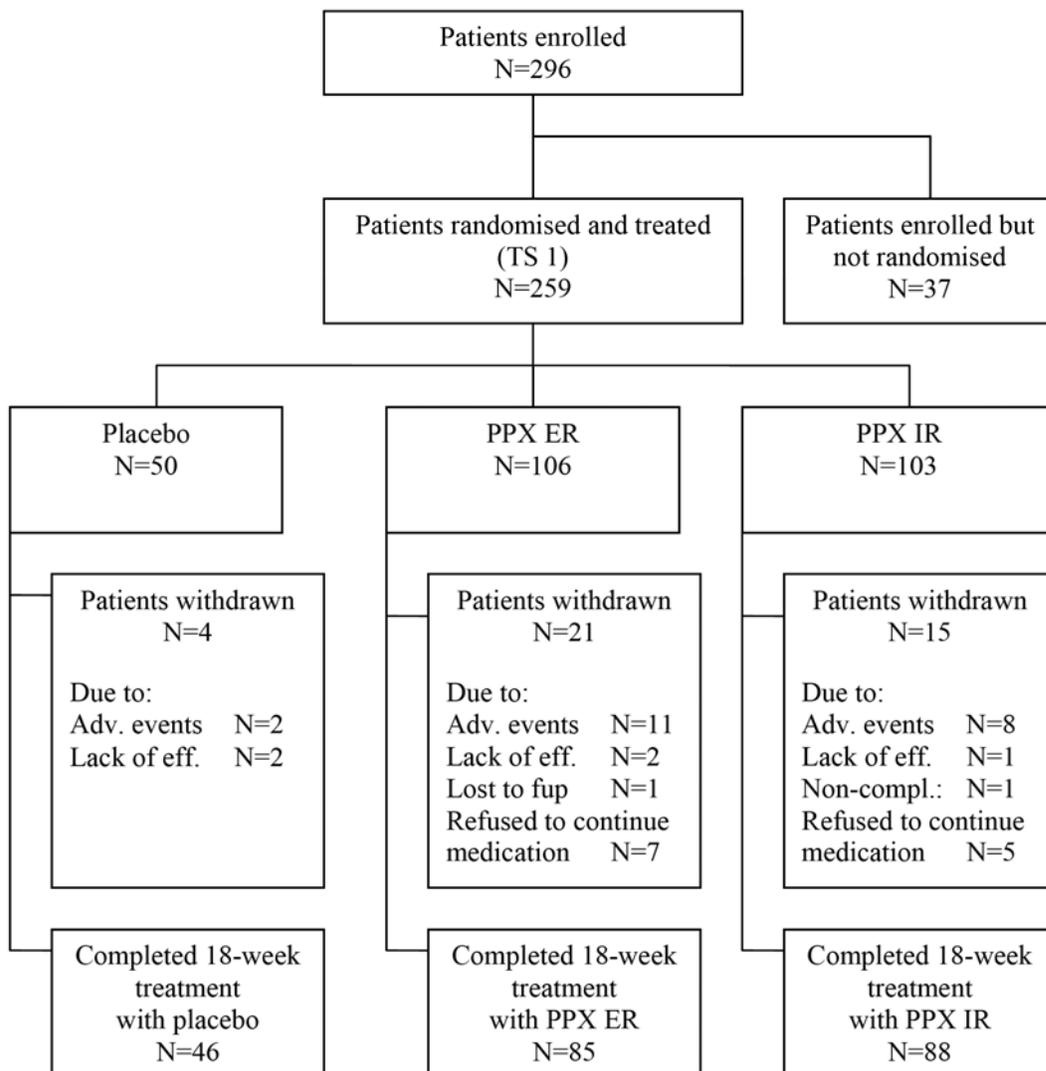
Amendment 5 (January 29, 2008)

- Interim efficacy analysis added to trial at 18 weeks for demonstration of superiority of PPX ER to placebo;
- A noninferiority analysis was added for comparison of PPX ER to PPX IR.
- "Descriptive" efficacy analysis of at least 100 patients added at 6 months to assess maintenance of treatment effect.
- Update of expected adverse reactions to PPX (hypersexuality, pruritis, rash, and other hypersensitivity).
- Recruitment period prolonged to reach enrollment
- Finland and India added as participating countries

### **Trial populations**

Sponsor's protocol flow chart of the treatment group used for the first interim analysis at 18 weeks, specifies the group which comprises the major efficacy analysis:

**Figure 5 Early PD Trial: population disposition (source: Sponsor)**



The group of patients comprised of those enrolled and treated for 18 weeks are designated Treatment Set 1 (TS 1). Those left of group TS 1 after withdrawals constituted the FAS 1 (Full Analysis Set 1) population. Patients who withdrew but had made it as far as visit 11 (week 33 of the trial) were included in the analyses of FAS 1. A subset of FAS 1 (PPS 1) was defined as patients without “important protocol violations” for efficacy.

The group constituting the second interim analysis consisted of those in the trial when approximately 100 patients had reached 33 weeks or had dropped out.

This second treated set (TS 2) consisted of those who have had at least one dose of medication and had completed Visit 11 at 33 weeks. The cut-off was defined as the time of randomization visit (Visit 2 at Week 0) of the 100<sup>th</sup> randomized patient. Those

patients who completed Visit 11 and had a post baseline efficacy assessment were designated for Full Analysis Set 2 (FAS 2), a subset of TS 2. A third treatment set (TS 3) was defined as all patients who were dispensed medication and took one dose, regardless of the treatment duration. This comprises the population used for this reviewer’s safety assessment in Section 7.

**Table 9 Early PD Trial: analysis dataset populations**

Analysis set	Placebo	PPX ER	PPX IR	Total
	N (%)	N (%)	N (%)	N (%)
TS 1	50 (100.0)	106 (100.0)	103 (100.0)	259 (100.0)
FAS 1	50 (100.0)	102 ( 96.2)	101 ( 98.1)	253 ( 97.7)
PPS 1	39 ( 78.0)	91 ( 85.8)	92 ( 89.3)	222 ( 85.7)
TS 2	19 (100.0)	42 (100.0)	40 (100.0)	101 (100.0)
FAS 2	19 (100.0)	42 (100.0)	39 ( 97.5)	100 ( 99.0)
TS 3	103 (100.0)	223 (100.0)	213 (100.0)	539 (100.0)

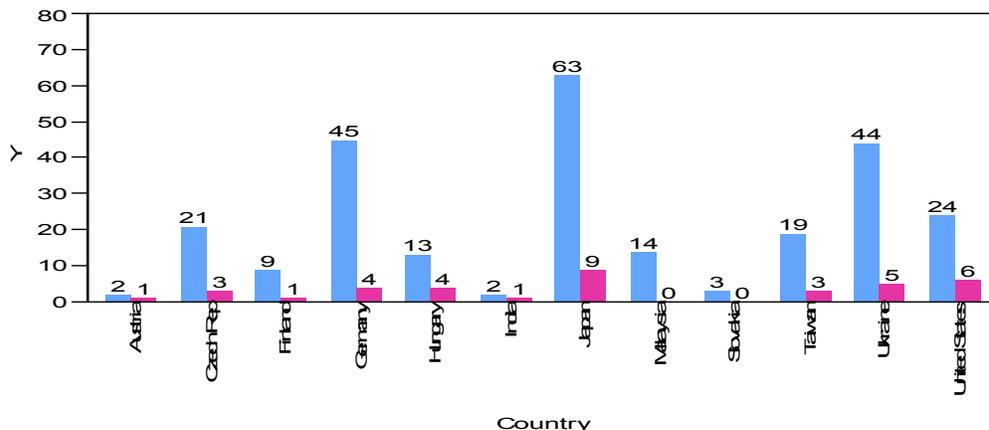
The N for these groups from Sponsor data:

Notes:

- Percentages for FAS 1 and PPS 1 based on TS 1.
- The reason for exclusion was partial values for the main outcome variable (UPDRS II+III). This resulted in exclusion of six TS 1 subjects from FAS 1 (4 from PPX ER and two from PPX IR; one PPX IR patient was excluded from TS 2 for the FAS 2 analysis.
- Six subjects were dropped from TS1 to become FAS1. They lacked UPDRS II+III outcome data. (*This constitutes this reviewer’s efficacy cohort.*)
- 31 patients were taken from FAS 1 to produce the PPS 1 cohort due to protocol violations and discontinuations. Rescue with levodopa, a prohibited medication, disproportionately affected the placebo group in this regard and reduced its size.

Thirty one subjects were dropped from FAS1 to become PPS1 with N = 222. 11 came from each of the placebo and PPX ER groups with 9 from the PPX IR group. These were fairly evenly distributed across sites (red = dropped from PPS1 in bar chart below). The reasons for exclusion are discussed below in the discussion of protocol violations. The number of dropped subjects in each arm is small, and do not appear to represent systematic effect and is actually smaller than that seen in many PD trials.

**Figure 6 Early PD Trial: full analysis population by country**



### Patient Disposition

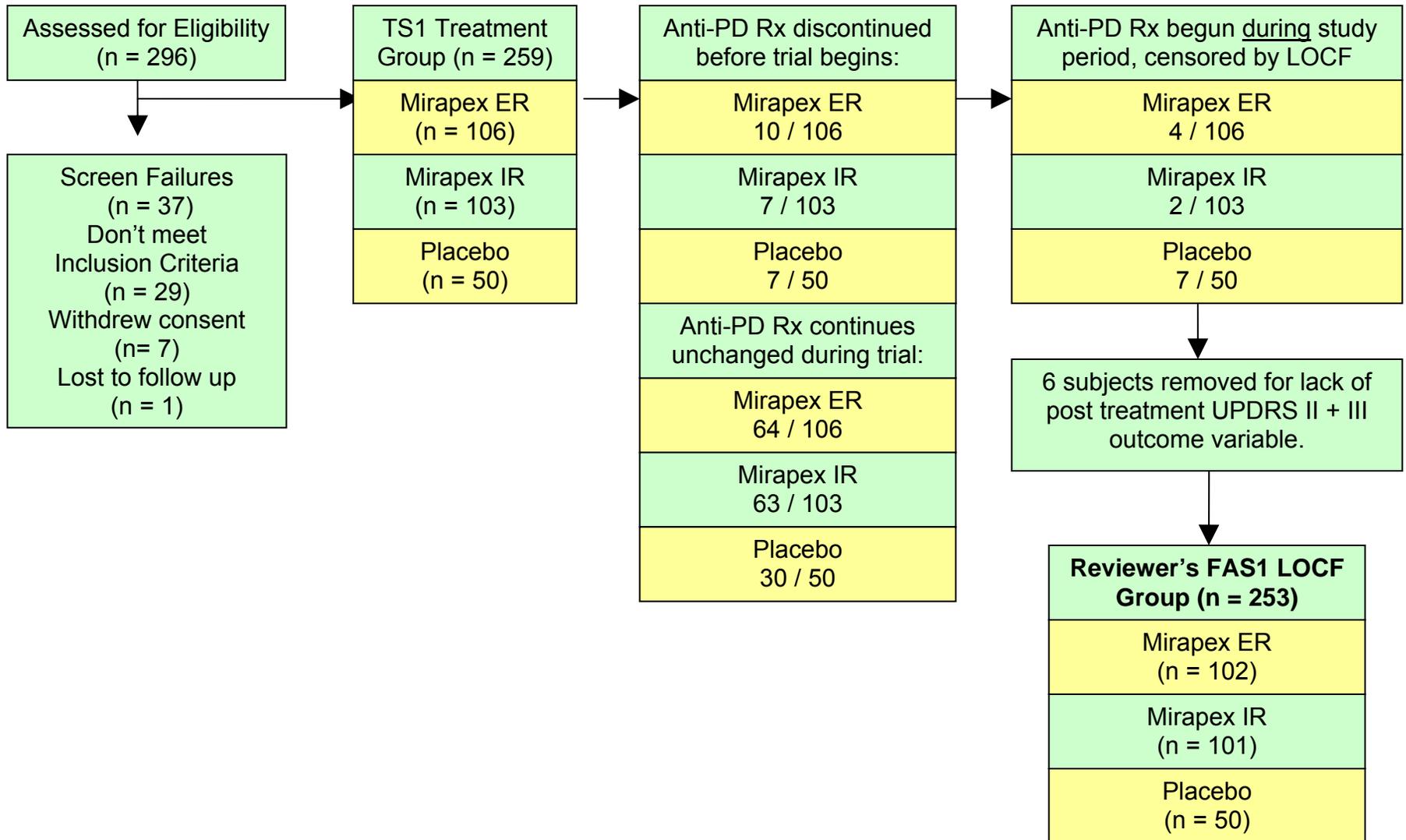
The chart below summarizes the patient flow in Trial 248.524, as derived from the datasets provided to the reviewer:

Reasons for screen failures included abnormal ECG, orthostatic hypotension, dementia as measured by MMSE, creatinine clearance below cutoff (renal insufficiency) and changes in baseline medications. Refusal to take trial medication was listed as withdrawal of consent. These screen failures occurred in eleven countries, without clustering. Demographic data on these subjects was not provided. Six subjects were dropped because of the lack of a post treatment primary efficacy outcome observation. The reasons are in the Sponsor's table below:

**Table 10 Early PD Trial: subjects without post treatment efficacy data (source: Sponsor)**

Country	Investigator	Pat. No.	Sex/ Age	Treatment	Treatment Duration (days)	UPDRS Part II+III at baseline	Reason for discontinuation
Czechia	Kanovsky	2079	M/52	PPX ER 0.375	3	22	AE-Erysipelas
	Ruzicka	2002	M/67	PPX ER 0.375	3	25	Misdiagnosed
Ukraine	Golovchenko	2563	F/31	PPX ER 0.375	5	25	AE-Nausea/ Vomiting
	Smolanka	2519	M/76	PPX ER 0.375	14	41	AE-Nausea/ Vomiting
Japan	Murata	3443	F/68	PPX IR 0.375	1	21	AE-Somnolence/ Nausea
	Yamamoto	3422	F/61	PPX IR 0.375	1	19	AE-Panic disorder

**Figure 7 Reviewer's path to Early PD Trial full analysis set**



### **Method for determining the outcome of efficacy analysis (exposure / response)**

For the primary and continuous secondary efficacy endpoints, the Sponsor proposed an analysis of covariance (ANCOVA) model for the primary efficacy analysis in order to explore the presence of center effects and treatment by center interactions. Since the number of patients per treatment in each center might be small, pooling of centers was considered, to be determined in a blinded fashion. All analyses with center as factor will be adjusted on pooled centers.

The null hypotheses was proposed to be tested using an ANCOVA model with  $\alpha=0.05$  in the Per Protocol population (PPS1), and Full Analysis Set (FAS1) population with use of last observation carried forward (LOCF). However, the Treated Set population (TS1) will be analyzed for safety.

- Full analysis set (FAS) population is defined as all patients who were randomized to treatment and received at least one dose of trial drug and provide any post-baseline efficacy assessment.
- Per protocol set (PPS) population is defined as all patients from the FAS population who completed at least 18 weeks of active treatment, and had a measurement of the primary efficacy endpoint at baseline (week 0) and after 18 weeks, and who have had no major protocol violation.
- Treated set (TS) population is defined as all patients who were dispensed trial medication and were documented to have at least one dose of investigational treatment.

Descriptive statistics were provided for all three populations.

Superiority of PPX ER to placebo (at 18 weeks) and non-inferiority of PPX ER to IR (at 33 weeks) are planned to be evaluated in a hierarchical system of hypotheses.

The objectives of the two interim analyses performed in this early PD trial were:

A. at 1st interim analysis: to determine the efficacy, safety and tolerability of PPX ER compared with placebo in approximately 250 patients treated for 18 weeks (or having discontinued treatment prior to week 18)

B. at 2nd interim analysis: to confirm, in a sub-set of approximately 100 patients treated for 33 weeks, that efficacy was maintained up to 6 month maintenance treatment.

Because this is an interim analysis, the Sponsor indicated that an independent Contract Research Organization (CRO) performed the analysis, in order to ensure that Sponsor staff directly involved in the trial has no access to the randomization list. This CRO has been involved in reporting the unblinded interim data.

## **Trial Results**

*Reviewer's note: This efficacy analysis section was completed prior to the discovery of data integrity issues from one of the audited trial sites (see Section 3.2 Compliance with GCP, above). Exclusion of the efficacy data derived from the five patients contributed by this site does not change the efficacy result. As a result, the analysis below was not changed and includes this site. The primary statistical review covers this issue more fully.*

*In brief, the statistical reviewer indicates that with the 5 subjects from SITEID = USA-s01 excluded, the LS mean change in UPDRS is changed from -5.1, -8.1, and -8.4 (Table 11.4.1.1.1:1 in sponsor's clinical trial report, page 98) to -5.1, -8.1 and -8.6 for placebo, PPX ER and PPX IR, respectively. The p-value is changed from 0.0282 (PPX ER vs. placebo) and 0.0016 (PPX IR vs. placebo) to 0.0330 (PPX ER vs. placebo) and 0.0018 (PPX IR vs. placebo).*

### **Demographics and Concomitant Medications**

TS1 cohort consisted of 259 individuals with early Parkinson's disease. The Sponsor's submitted datasets were manipulated to isolate this cohort for analysis.

The average age of onset of PD in the trial participant cohort was 61 years with a median age of 62 and range of 30 to 83. Ten percent of cases were either below 49 or above 71 years of age. There were 144 males and 115 females, a ratio of 1.3:1. (This degree of male predominance is consistently found in prevalence studies of PD.) The duration of illness as determined by time from diagnosis to consenting to participate in the trial was half a year on average and under three years for 90% of the subjects. No one had been diagnosed for more than 5 years before entering the trial. There is no data provided concerning length of time that the patient had symptoms prior to diagnosis. There were no differences in clinical features of illness related to gender.

The primary outcome variable is the sum of items in Parts II (Activities of Daily Living) and III (Motor Exam) of the UPDRS. Higher score signifies increased severity of disease. Mean baseline UPDRS II+III was 29.4; in men 30 (95% CI 28-33) and 28 in women (95% CI 26-31), was not clinically significantly. There were 161 subjects classified as "white" and 98 as "Asian" in the trial. Their average UPDRS II+III score also did not differ significantly (white: 31, 95 % CI 29-33; Asian: 27, 95% CI 24-30)

Analysis was performed to look at distribution of demographic parameters among the three treatment arms. Parametric analysis was performed for all three treatment arms looking for disparity in age at trial consent, age at onset of PD, duration of illness from time of diagnosis, baseline UPDRS II+III, BDI (depression scale), PDQ-36 (quality of life scale), nighttime psychosis, daytime sleepiness. None was found. No one region or country was overly responsible for any particular degree of illness severity.

### Concomitant medications before trial medication

As indicated in the Sponsor’s tables below, 24 of 259 subjects had some anti-Parkinson drug treatment before the trial as allowed in the exclusion criteria, with a greater proportion in the placebo group. These had a “stop date” before Visit 2 (randomization).

**Table 11 Early PD Trial: discontinued anti-PD medication (source: Sponsor)**

Previous antiparkinsonian therapy ATC4	Placebo N (%)	PPX ER N (%)	PPX IR N (%)	Total N (%)
Number of patients treated	50 (100.0)	106 (100.0)	103 (100.0)	259 (100.0)
Any anti-PD therapy	7 ( 14.0)	10 ( 9.4)	7 ( 6.8)	24 ( 9.3)
Anticholinergics	2 ( 4.0)	4 ( 3.8)	1 ( 1.0)	7 ( 2.7)
Levodopa	2 ( 4.0)	3 ( 2.8)	1 ( 1.0)	6 ( 2.3)
Amantadine	1 ( 2.0)	2 ( 1.9)	2 ( 1.9)	5 ( 1.9)
Dopamine agonists	1 ( 2.0)	4 ( 3.8)	3 ( 2.9)	8 ( 3.1)
Monoaminoxidase-B-inhibitors	2 ( 4.0)	1 ( 0.9)	2 ( 1.9)	5 ( 1.9)
Investigational drug*	0 ( 0.0)	0 ( 0.0)	1 ( 1.0)*	1 ( 0.4)

\* The patient has completed a previous study with PPX ER, PPX IR and placebo. The data of this patient are still blinded. Details will be provided once the unblinded data of this patient are available.

Source data: [Table 15.1.4.1: 7](#)

### Concomitant medications during the trial period

During the trial, 61 % of subjects (157 of 259) were taking other anti-parkinson drug treatments. This is defined as a patient who had medication either before or after Visit 2 (randomization) and a stop date after Visit 2. These subjects continued these anti PD medications unchanged into the evaluation periods. This was carefully confirmed by the reviewer through additional queries to the Sponsor.

The most common concomitant PD therapies were amantadine (32.0% of total population), MAO B-inhibitors (25.1%) and anticholinergics (21.2%). L-dopa was reported by 16.0% patients in the placebo group compared to 2.8% in the PPX ER group and 1.9% in the PPX IR group. Amantadine was reported by 20.0% patients in the placebo group, 32.1% patients in the PPX ER group and 37.9% patients in the PPX IR group. Of note, levodopa was given to 13 subjects, and it was begun within 14 days of the final efficacy assessment in 11, including 7 of 50 placebo subjects. These important confounds are discussed below in the evaluation of efficacy.

**Table 12 Early PD Trial: concomitant anti-PD medication (source: Sponsor)**

Concomitant antiparkinsonian therapy ATC4	Placebo N (%)	PPX ER N (%)	PPX IR N (%)	Total N (%)
Number of patients treated	50 (100.0)	106 (100.0)	103 (100.0)	259 (100.0)
Any concomitant PD therapy	30 ( 60.0)	64 ( 60.4)	63 ( 61.2)	157 ( 60.6)
Anticholinergics	11 ( 22.0)	26 ( 24.5)	18 ( 17.5)	55 ( 21.2)
Levodopa*	8 ( 16.0)	3 ( 2.8)	2 ( 1.9)	13 ( 5.0)
Amantadine	10 ( 20.0)	34 ( 32.1)	39 ( 37.9)	83 ( 32.0)
Dopamine agonists	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)
Monoaminoxidase-B-inhibitors	10 ( 20.0)	26 ( 24.5)	29 ( 28.2)	65 ( 25.1)

\*Levodopa with or without COMT inhibitor (NB. percentage calculated manually)

Source data: [Table 15.1.4.1: 9](#)

Categorical analysis looked at the distribution of gender, race, prior treatment of PD, and treatment with amantadine, MAO-B inhibitors or anticholinergics. These were all evenly distributed across the three treatment arms.

Other concomitant medications not related to the treatment of PD were taken by 216 (83%) of the sample. The Sponsor indicates “the most common other (non PD-related) concomitant therapies were anti-hypertensive agents acting on the renin-angiotensin system (overall, 30.1% patients), topical products for joint and muscular pain (25.5%), stomatological (oral/dental) preparations (23.9%), analgesics (23.2%), drugs for acid related disorders (21.6%), anti-thrombotic agents (20.1%) and lipid modifying agents (19.3%). The proportion of patients with other (non PD-related) concomitant therapies was similar in the 3 treatment groups.”

### Compliance with Trial Medication

Patients were instructed to bring medication to each visit and returned medication was physically counted and recorded. Percent compliance was based by dose in milligrams (not number of missed doses). Compliance had to be between 80 and 120% at every visit. Eligibility for analysis in the Sponsor’s FAS1 group was determined before the final locking of the database and 8 patients were excluded on this basis (PPX ER n=5, PPX IR n=3). In the 259 subjects of TS1, the Sponsor indicates that mean compliance at the last visit (Visit 8) was 100% placebo, 98.1% PPX ER and 99.9% PPX IR.

For the second interim analysis, compliance for 101 subjects in TS2 at Visit 11 (week 33) was comparable to that above with 1 subject excluded for poor compliance, yielding the FAS2 analysis group with n = 100.

### Dosing Information and Exposure

The final dosage level achieved in the maintenance period (mg of PPX/day) was investigated for all treatment arms.

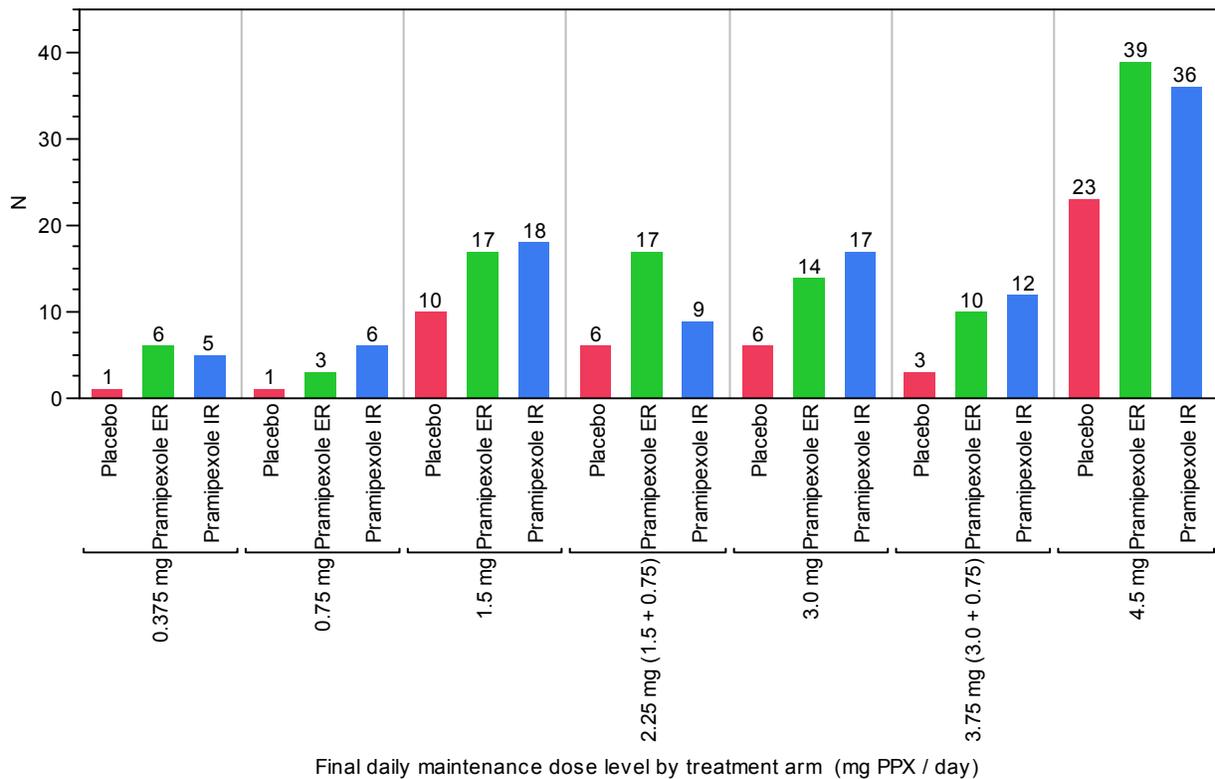
There is no evidence of excessive premature drop out of subjects in the placebo arm. (Randomization ratio was 2:2:1 active: active: placebo.) For the following factors in the contingency tables below, there were no differences in the numbers of subjects by treatment arm in TS1 LOC by categorical analysis (Chi square).

**Table 13 Early PD Trial: treatment factors by trial agent dose level**

**Numbers of subjects at a given final daily maintenance dose level of PPX.**

<b>Total mg / day</b>	<b>0.375</b>	<b>0.75</b>	<b>1.5</b>	<b>2.25</b>	<b>3.0</b>	<b>3.75</b>	<b>4.5</b>	
<b>By gender</b>								
Female	6	5	27	16	19	9	33	115
Male	6	5	18	16	18	16	65	144
Total	12	10	45	32	37	25	98	259
<b>By race</b>								
Asian	5	4	20	14	12	10	33	98
White	7	6	25	18	25	15	65	161
Total	12	10	45	32	37	25	98	259
<b>By concomitant use of amantadine</b>								
No	10	7	30	20	26	18	65	176
Yes	2	3	15	12	11	7	33	83
Total	12	10	45	32	37	25	98	259
<b>By concomitant use of MAO-B inhibitor</b>								
No	9	6	31	29	29	19	71	194
Yes	3	4	14	3	8	6	27	65
Total	12	10	45	32	37	25	98	259
<b>By concomitant use of anticholinergic</b>								
No	7	8	30	28	32	20	79	204
Yes	5	2	15	4	5	5	19	55
Total	12	10	45	32	37	25	98	259
<b>By any pre-trial treatment of PD</b>								
No	11	9	43	29	34	22	87	235
Yes	1	1	2	3	3	3	11	24
Total	12	10	45	32	37	25	98	259

**Figure 8 Early PD Trial: subjects by final daily maintenance dose**



### Protocol Deviations and Violations

Of 296 patients screened 259 were enrolled. Those screen failures are described above in **Patient Disposition**. Of the 259, six subjects were missing either baseline or on-treatment primary efficacy data, making them unevaluable. The table in **Patient Disposition** above lists these 6 subjects and the reasons for lack of data, all well outside of the Sponsor’s control. The remaining 253 subjects make up the reviewer’s cohort for efficacy analysis (FAS1).

The Sponsor lists 31 other subjects with “important protocol deviations”. These are summarized in the Sponsor’s table below (including the 6 patients with insufficient data for efficacy evaluation) and have to do with efficacy parameters. No safety reasons were cited. There is no pattern to these by age, disease severity at baseline, treatment arm, or dosage level achieved.

**Table 14 Early PD Trial: protocol violations (source: Sponsor)**

Table 10.2: 1 Important protocol violations, Treated Set at first interim analysis, 18 weeks

Kind of protocol violation		Placebo N (%)	PPX ER N (%)	PPX IR N (%)
Number of patients with any important PV		11 (22.0)	15 (14.2)	11 (10.7)
Number of patients with important PVs related to efficacy (E)	(E)	11 (22.0)	15 (14.2)	11 (10.7)
Number of patients with important PVs related to safety (S)	(S)	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)
Compliance <80% or >120% at final visit (Visit 8)	(E)	0 ( 0.0)	5 ( 4.7)	3 ( 2.9)
Treatment stopped before Visit 7 (week 13)	(E)	1 ( 2.0)	5 ( 4.7)	6 ( 5.8)
Improper medication prior to baseline Levodopa within 2 weeks prior to baseline and/or dopamine agonists (including pramipexole) within 1 week prior to baseline	(E)	1 ( 2.0)	0 ( 0.0)	0 ( 0.0)
Prohibited medication use between screening and Visit 8	(E)	7 (14.0)	3 ( 2.8)	1 ( 1.0)
Patient does not have complete UPDRS II+III but only partial or missing for baseline or for treatment period*	(E)	0 ( 0.0)	4 ( 3.8)	2 ( 1.9)
Insufficient Baseline UPDRS II+III (equal or less than 6)	(E)	2 ( 4.0)	0 ( 0.0)	0 ( 0.0)

\* These major protocol violations also let to the exclusion from FAS 1.  
 Source Data: [Tables 15.1.2.1: 1](#) and [15.1.3.1:1](#)

### Outcome of Efficacy Assessment

*Note: This reviewer is analyzing the primary outcome variable for FAS1. This is the TS1 population who were randomized, received at least one dose of drug, and had at least one post treatment observation carried forward.*

The sponsor provided calculation of efficacy parameters for both FAS1 which was a LOCF cohort, as well as the PPS1 group which consisted of purely observed cases. It is the former intention-to-treat group that the reviewer focuses upon here. The following represent the reviewer's analyses.

### Primary Efficacy Endpoint

- The change from baseline of the sum of Parts II (Activities of Daily Living) and Part III (Motor Function) score of the UPDRS (Unified Parkinson’s Disease Rating Scale) to be assessed at Visit 8, i.e.: week 18 for PPX ER vs. PCB.

There is a statistically significant improvement in the difference of UPDRS over baseline measures in the PPX ER group compared to placebo. The IR group also reaches significance. The role of concomitant medication was unclear in the originally submitted datasets and after consultation Statistics, clarification was requested from the Sponsor. Nevertheless these were included in the reviewer’s ITT analysis.

Using the Baseline UPDRS II + III as covariate, ANCOVA was performed in SAS GLM looking at the change from baseline by treatment arm using the LOCF carried forward to Visit 8 for 253 subjects:

**Table 15 Early PD Trial: 248.524 reviewer's efficacy analysis for FAS1 at 18 weeks**

Criteria For Assessing Goodness Of Fit							
Criterion	DF	Value	Value/DF				
Deviance	249	16727.1636	67.1774				
Scaled Deviance	249	253	1.0161				
Pearson Chi-Square	249	16727.1636	67.1774				
Scaled Pearson X2	249	253	1.0161				
Log Likelihood		-889.2035					
Analysis Of Parameter Estimates							
Parameter	DF	Estimate	Standard Error	Wald 95% Confidence Limits		Chi-Square	Pr > ChiSq
Intercept	1	2.7875	1.6089	-0.366	5.9409	3	0.0832
Baseline UPDRS II + III	1	-0.295	0.0374	-0.3684	-0.2216	62.09	<.0001
PPX ER	1	-3.0128	1.4038	-5.7643	-0.2613	4.61	0.0319
PPX IR	1	-3.4412	1.4075	-6.1999	-0.6825	5.98	0.0145
Placebo	0	0	0	0	0	.	.
Scale	1	8.1311	0.3615	7.4526	8.8714		

By Sponsor’s analysis, the outcome for the efficacy of PPX ER is similarly significant, though with different mean change from baseline calculated for the UPDRS II + III than used for the reviewer’s analysis:

**Table 16 Sponsor's efficacy analysis for Early PD Trial 248.524 (source: Sponsor)**

Table 11.4.1.1.1: 1 UPDRS Part II+III total score, 18 weeks treatment, FAS 1 (LOCF)

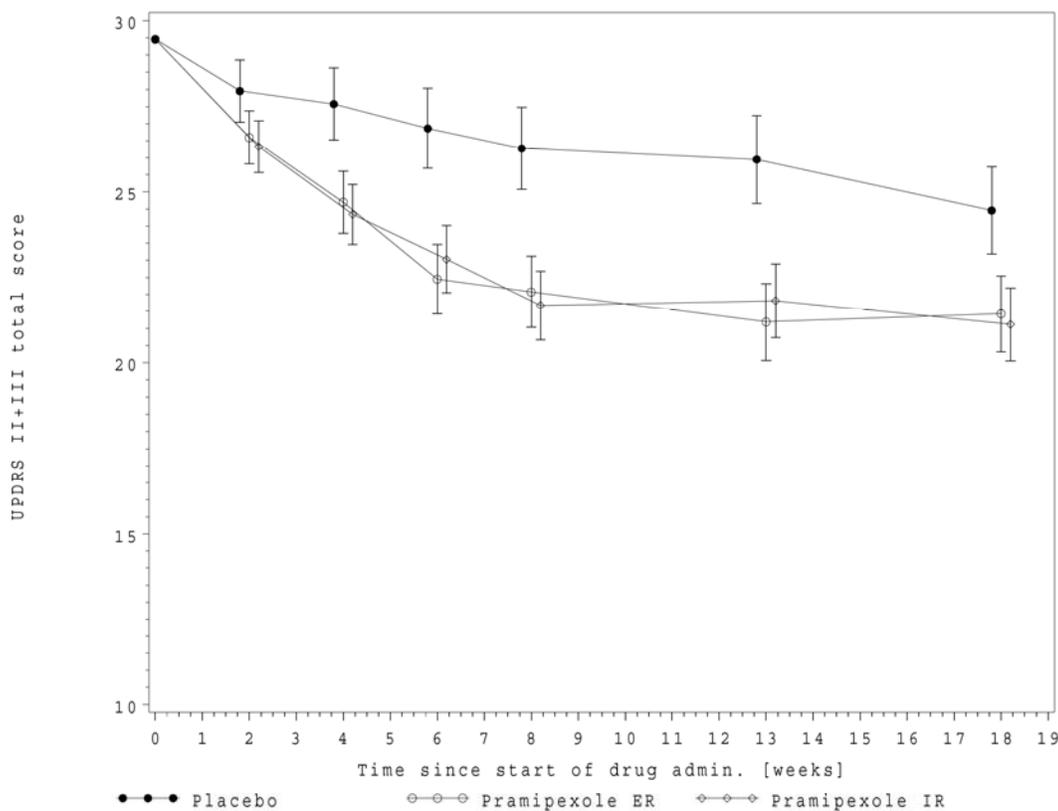
Primary Endpoint	Placebo	PPX ER	PPX IR	PPX ER vs. placebo	PPX IR vs. placebo
UPDRS Part II+III total score					
Number of Patients	50	102	101		
Baseline, Mean (SD)	30.1 (17.0)	30.5 (13.6)	28.3 (12.0)		
Week 18, Mean (SD)	24.0 (14.9)	21.3 (14.0)	19.3 (9.8)		
LS Mean Change (SE) – ANCOVA*	-5.1 (1.3)	-8.1 (1.1)	-8.4 (1.1)	0.0282	0.0153
LS Mean Change (SE) – MMRM*	-4.0 (1.2)	-8.0 (1.0)	-8.0 (1.0)	0.0016	0.0014

\*ANCOVA and MMRM with factors treatment and country and covariate baseline

Negative changes imply improvement in UPDRS Part II+III total score

Source data: [Table 15.2.1.1.1: 1](#)

**Figure 9 Early PD Trial: UPDRS Parts II + III graph (source: Sponsor)**



Source data: [Figure 15.2.1.1.1: 1](#)

**Figure 11.4.1.1.1: 1 Adjusted mean change (SE) from baseline in UPDRS Part II+III total score, FAS 1 (LOCF)**

### The effect of concomitant anti-parkinson medication

The Sponsor notes by sensitivity analysis the effect of levodopa rescue. When these cases are adjusted by carrying forward the last post treatment observation before levodopa treatment, the outcome becomes more robust.

**Table 17 Early PD Trial: effect of concomitant anti-PD medication (source: Sponsor)**

Primary Endpoint	Placebo	PPX ER	PPX IR	PPX ER vs. placebo	PPX IR vs. placebo
UPDRS Part II+III total score					
Number of Patients	50	102	101		
Baseline, Mean (SD)	30.1 ( 17.0)	30.5 ( 13.6)	28.3 ( 12.0)		
Week 18, Mean (SD)	25.7 ( 16.7)	21.2 ( 14.0)	19.3 ( 9.8)		
LS Mean Change (SE) – ANCOVA*	-2.7 (1.3)	-7.4 (1.1)	-7.5 (1.1)	0.0010	0.0006
LS Mean Change (SE) – MMRM*	-3.1 (1.2)	-7.8 (1.0)	-7.8 (1.0)	0.0003	0.0003

\*ANCOVA and MMRM with factors treatment and country and covariate baseline

Negative changes imply improvement in UPDRS Part II+III total score

Source data: [Table 15.2.1.1.3: 1](#)

However, this appears to be only a partial look at the role of concomitant anti-PD medication in this trial. As indicated above, most patients in this trial received concomitant anti-PD medication. This contributed to a “floor effect” in the UPDRS which probably reduced the robustness of the effect of the test drug. Nevertheless, the natural history of PD as measured by the UPDRS worsens at the rate of about 3 points per year. In this context, the magnitude of improvement in UPDRS is a clinically significant one for this population.

Per protocol, the procedure to be followed for adding anti-parkinson rescue medication is specified: “If a patient develops increased severity of parkinsonism (as manifested by wearing-off episodes, dose failures, “off” freezing, or early-morning off) that presents a threat to ambulation, activities of independent living, or gainful employment, open-label L-Dopa+ (i.e. standard and/or controlled release levodopa / DDC inhibitor), or a combination of L-Dopa+ and entacapone can be added to the treatment regimen. Patients have to be seen in the clinic by the investigator before receiving any open-label L-Dopa+. The efficacy assessments UPDRS II+III, PGI-I and CGI-I will be performed before introducing L-Dopa+. UPDRS II+III value will be carried forward until the last visit for the statistical analysis.”

### Secondary Efficacy Analysis

For CGI and PGI, the reviewer used a chi square analysis for the dichotomized rating of responder versus non-responder. The Sponsor analyzed these secondary endpoints by Cochran-Mantel-Haenszel (CMH) test with country stratification on FAS populations. The results are generally in agreement.

- Clinical Global Impression of Improvement (CGI-I) responder rate

The CGI is a 7 point ordinal scale which was transformed into a yes-no dichotomy. Subjects scoring 1 (very much improved) or 2 (much improved) were characterized as responders. This followed the Sponsor's practice for this analysis as well.

**Table 18 Early PD Trial: reviewer's analysis of CGI secondary outcome measure**

Categorical Clinical Global Improvement				
	Missing	Non-responder	Responder	Total
PPX ER	6	60	36	102
Placebo	0	41	9	50
<b>Total</b>	6	101	45	152
<b>Chi Square</b>	DF 2	Value 9.0432	Probability 0.0109	

Categorical Clinical Global Improvement				
	Missing	Non-responder	Responder	Total
PPX IR	2	51	48	101
Placebo	0	41	9	50
<b>Total</b>	2	92	57	151
<b>Chi Square</b>	DF 2	Value 13.0706	Probability 0.0003	

This indicates that by the investigator's impression a significantly increased number of subjects improved with PPX ER over placebo, though for a large number in each group, a robust response was not perceived. It may be that the concomitant use of anti-parkinson medication in many subjects was responsible for a lack of perceived additional improvement in motor response.

**Table 19 Sponsor's analysis of CGI secondary outcome measures (source: Sponsor)**

Table 11.4.1.2.1: 1 CGI-I responders, 18 weeks treatment, FAS 1 (LOCF)

Key secondary Endpoint	Placebo	PPX ER	PPX IR	PPX ER vs. placebo	PPX IR vs. placebo
CGI-I Responders				CMH	CMH
Number of Patients	50	100	100		
Responder [N,(%)]	9 (18.0)	37 (37.0)	48 (48.0)	0.0400	0.0012
% Responder [95% CI]	[8.6, 31.4]	[27.6, 47.2]	[37.9, 58.2]		

Source data: Table 15.2.2.1.1.1: 1

- Patient Global Impression of Improvement (PGI-I) responder rate
- The PGI is a 7 point ordinal scale which was transformed into a yes-no dichotomy. Subjects scoring themselves 1 (very much better) or 2 (much better) were characterized as responders. This followed the Sponsor's practice for this analysis as well.

**Table 20 Early PD Trial: reviewer's analysis Patient CGI**

Categorical Patient Global Improvement				
	Missing	Non-responder	Responder	Total
PPX ER	8	58	36	102
Placebo	0	44	6	50
<b>Total</b>	8	102	42	152
<b>Chi Square</b>	DF 1	Value 10.9258	Probability 0.0009	

Categorical Patient Global Improvement				
	Missing	Non-responder	Responder	Total
PPX IR	1	76	24	101
Placebo	0	44	6	50
<b>Total</b>	1	120	30	151
<b>Chi Square</b>	DF 1	Value 3.0	Probability 0.0833	

This indicates that by the subject's own impression a significantly increased number of subjects improved with PPX ER over placebo, though for a large number in each group, a robust response was not perceived.

**Table 21 Early PD Trial Sponsor's analysis of Patient CGI (source: Sponsor)**

Table 11.4.1.2.1: 2 PGI-I responders, 18 weeks treatment, FAS 1 (LOCF)

Key secondary Endpoint	Placebo	PPX ER	PPX IR	PPX ER vs. placebo	PPX IR vs. placebo
PGI-I Responders				CMH	CMH
Number of Patients	50	101	101		
Responder [N(%)]	6 (12.0)	36 (35.6)	24 (23.8)	0.0040	0.1207
% Responder [95% CI]	[4.5, 24.3]	[26.4, 45.8]	[15.9, 33.3]		

Source data: [Table 15.2.2.2.1.1: 1](#)

### Other Secondary Efficacy Analysis

The Sponsor had a variety of other secondary endpoints. Some, especially those related to the UPDRS are not independent of the primary efficacy outcome. Others relate to subgroups within the population and do not represent a question that is sufficiently powered by the number of enrolled subjects for subgroup analysis (e.g., BDI, sleep disturbance). Finally, there is the difficult-to-answer question of the effects of concomitant anti-parkinson medication, especially on quality of life scales. The Sponsor's verbatim interpretation of these secondary analyses is presented below.

- Proportion of patients with at least a 20% improvement relative to baseline in the UPDRS II+III total score

This characterization of UPDRS II + III magnifies the difference in effectiveness between placebo and treatment group but has no particular scientific rationale or statistical merit. According to the Sponsor, those reaching a "responder rate of at least 20% at week 18 was 44.0% in the placebo group compared to 67.6% in the PPX ER group and 69.3% in the PPX IR group. These differences between placebo and PPX ER as well as PPX IR were statistically significant (CMH:  $p=0.0072$  and  $p=0.0006$ , respectively). The responder rate was higher in the PPX ER and PPX IR groups than in the placebo group already from week 2, and at all further assessments."

- UPDRS I, II and III individual section scores (change from baseline)

"UPDRS Part I (4 items rating mentation behavior and mood) were not significantly changed by treatment. Part II, (Activities of Daily Living) were improved over baseline for both PPX ER and PPX IR, (ANCOVA:  $p=0.0177$  and  $p=0.0049$ , respectively). Part III (Motor Examination)."

“In FAS 1 (LOCF), the mean in UPDRS Part III total score at baseline was 22.4 points in the placebo group, 22.6 points in the PPX ER group and 20.5 points in the PPX IR group. At Week 18, the mean was 17.3 points in the placebo group compared to 15.5 points in the PPX ER group and 13.8 points in the PPX IR group. Despite a numerically larger improvement in both PPX groups, the differences in improvement from baseline between the placebo group and the PPX ER group as well as the PPX IR group were not statistically significant (ANCOVA:  $p=0.0813$  and  $p=0.0600$ , respectively).”

- Proportion of patients requiring L-Dopa supplementation during the trial

Patients whose PD represented a threat to their physical or social wellbeing were treated as medically appropriate with levodopa (with DOPA decarboxylase inhibitor) in open label fashion. This data is presented in the following table. The numbers per cell are too small to permit meaningful inference.

**Table 22 Patients requiring l-dopa rescue during the Early PD Trial (source: Sponsor)**

Secondary Endpoint	Placebo	PPX ER	PPX IR	PPX ER vs. placebo	PPX IR vs. placebo
Patients requiring L-Dopa rescue				CMH	CMH
Number of patients	50	102	101		
Patient with rescue medication [N,(%)]	7 (14.0)	3 (2.9)	1 (1.0)	0.0160	0.0017
[95% CI]	[5.8, 26.7]	[0.6, 8.4]	[0.0, 5.4]		

Source data: [Table 15.2.2.8.1: 1](#)

- Beck’s Depression Inventory (BDI) version IA (change from baseline)

The BDI is a 21 item self rated scale where higher number indicates more symptoms of depression. There was no difference among the groups. The baseline scores were low, indicating few depressive symptoms to begin with: mean (SD) Placebo: 8.8 (7.8), PPX ER: 8.8 (6.3), and PPX IR: 9.4 (8.0).

- Parkinson’s Disease Sleep Scale (PDSS) (change from baseline)

This 0 to 150 scale quantifies common aspects of nocturnal sleep problems found in PD in the form of 8 visual analog scales. A higher score reflects fewer problems. The baseline scores did not change much in the trial: mean (SD) Placebo 112.9 (23.8), PPX ER 117.8 (23.0), and PPX IR 109.9 (24.9).

- Likert Scale for pain related to Parkinson’s disease (change from baseline)

The subjects reflected little pain due to disease and treatment had no effect.

- PDQ-39 (Parkinson Disease Questionnaire-:39 item quality of life scale change from baseline)

This self evaluation addresses 8 domains of health affected by PD. The scale was completed in the month before an on-site visit. A higher score means less quality of life.

**Table 23 Early PD Trial: PDQ-39 (source: Sponsor)**

Secondary Endpoint	Placebo	PPX ER	PPX IR	PPX ER vs. placebo	PPX IR vs. placebo
PDQ-39 total score				ANCOVA	ANCOVA
Number of patients	49	91	95		
Baseline, Mean (SD)	27.5 (24.2)	28.5 (22.9)	30.1 (22.7)		
Week 18, Mean (SD)	27.7 (26.7)	22.1 (20.8)	22.2 (21.1)		
Change from baseline LS mean (SE)*	-1.9 (2.0)	-8.2 (1.8)	-9.2 (1.7)	0.0058	0.0012

Negative changes imply improvement in PDQ-39 total score

\* Adjusted (ANCOVA with treatment, centre or country) for baseline

Source data: [Table 15.2.2.10.1: 1](#)

- EQ-5D (EuroQoL quality of life scale - change from baseline)

This brief questionnaire consists of descriptive measure (with 5 dimensions: mobility, self-care, usual activity, pain/discomfort, and anxiety/depression) and a visual analog scale. Patients completed the scale based on their status on the day of the visit. A reduction in the items' score over time corresponded to an improvement in QoL, whereas an increase in the VAS score corresponded to an improvement in overall health state. According to the Sponsor, one subscale (usual activities) was significantly improved in favor of PPX ER; the rest were not.

**Table 24 Early PD Trial: EQ-5D (source: Sponsor)**

Secondary Endpoint	Placebo	PPX ER	PPX IR	PPX ER vs. placebo	PPX IR vs. placebo
EQ-5D VAS [mm]				ANCOVA	ANCOVA
Number of Patients	49	91	95		
Baseline, Mean (SD)	65.3 (22.8)	64.9 (23.9)	65.3 (22.1)		
Week 18, Mean (SD)	66.4 (17.1)	72.0 (18.3)	73.1 (16.1)		
Change from baseline LS mean (SE)*	2.9 (2.6)	7.1 (2.3)	8.4 (2.2)	0.1445	0.0509

Higher scores indicate a better health state

\* Adjusted (ANCOVA with treatment, centre or country) for baseline

Source data: [Table 15.2.2.11.1: 2](#)

## Exploration of subgroup effects

### Levodopa rescue

This reviewer’s analysis included the patient’s receiving levodopa rescue in the analysis of the primary outcome variable. For this reason, the effect of MPX ER is not as robust as the Sponsor demonstrated, though still significantly effective. Three of 102 patients in active treatment received rescue while 7 of 50 placebo patients did so.

The effect of levodopa in the 7 placebo patients was to lessen the change from baseline UPDRS II+III from a mean of -5.1 points to only -2.7 points ( i.e.: as a group the placebo patients showed less worsening than they might have otherwise. The addition of levodopa in the MPX ER group had little effect.

### Country

To observe effect of countries, their contribution to the analysis cohort (N = 253) was serially removed and the results reanalyzed. No systematic bias was found though countries contributing larger numbers of patients did have proportionally greater contribution to the results:

**Table 25 Early PD Trial: effect of country on outcome.**

<b>ANCOVA analysis: p values after country removed.</b>						
	Czechia	Germany	Taiwan	Japan	Ukraine	US
N contributed	19	45	19	63	44	24
PPX ER vs Placebo	0.0453	0.0371	0.039	<b>0.1011</b>	<b>0.0828</b>	0.0139
PPX IR vs Placebo	0.0149	<b>0.1314</b>	0.031	0.0085	0.0336	0.0049

### Second interim analysis of subjects reaching 33 weeks

This analysis was performed by the Sponsor as a demonstration of “maintenance of effect”. 84 patients completed the trial, reaching week 33 (6 months of treatment), at the time of the submission’s cut-off date. Maintenance was defined as no worsening greater than 15% in the mean change of UPDRS II + III total score from baseline to week 18. The Sponsor’s table is reproduced below:

**Table 26 Early PD Trial: maintenance of drug effect (source: Sponsor)**

Table 11.4.1.1.5: 1 Maintenance of effect in UPDRS Part II+III total score at week 18 and week 33, FAS 2 (OC)

Primary Endpoint (maintenance of effect)		Placebo	PPX ER	PPX IR
UPDRS Part II+III total score				
Number of Patients		18	35	31
Baseline	Mean (SD)	23.6 (13.5)	31.3 (13.9)	29.0 (14.5)
Week 18	Mean (SD)	19.3 (12.7)	19.5 (12.5)	17.1 (10.9)
Change from baseline	Mean (SD)	-4.2 (7.0)	-11.8 (8.1)	-11.9 (8.8)
Week 33	Mean (SD)	20.9 (12.9)	19.8 (13.4)	17.1 (10.3)
Change from baseline	Mean (SD)	-2.7 (6.7)	-11.5 (8.5)	-11.9 (9.6)

Negative changes imply improvement in UPDRS Part II+III total score  
 Source data: [Table 15.2.1.2.1: 9](#)

While the maintenance of drug effect over time is an important consideration of outcome, the reviewer feels that the analysis of this outcome is not rigorous for a variety of reasons. It is safe to say that the UPDRS would be insensitive to measure a magnitude of change this small in this size cohort. This would favor an error where change (i.e.: worsening) may be occurring but is not detectable. Selection bias also favors more “successful” patients reaching this milestone, and systematic inspection of dropouts, discontinuation and adverse events has not been performed. It is possible that only particular subgroups of subjects make it to 33 weeks for this analysis, affected by dropouts for a variety of reasons. Rescue medication (i.e.: levodopa and other symptomatic treatments of Parkinsonism) may contaminate results to a greater degree than in the 18 week analysis.

That said, 5 of 35 MPX ER patients worsened within this time frame, while 5 of 18 placebo patients did as well. The UPDRS has been estimated to progress at an average of 3 points per year in studies of untreated early PD patients. As a result, one would expect that a patient in this trial would progress 1.5 UPDRS points, on average over the six months of the trial. In this time period, mean score of the primary endpoint (UPDRS II + III) for the placebo arm went from 19.3 to 20.9, while the MPX ER arm only moved from 19.5 to 19.8.

**Outcome efficacy (exposure / response)**

The population used for the efficacy analysis reflected usual demographics and dosing seen in the early PD population. The Sponsor’s table below represents duration of treatment for the LOCF cohort. Overall, a relatively small number of subjects were treated longer than 18 weeks and at the higher dose range, i.e. had a maintenance period on a dose of at least 10 weeks duration. This means that there is a potential that both treatment and adverse effects may not have had the full exposure needed to yield an accurate assessment of the drug.

Doses to which the patient population was exposed closely resemble the range generally in clinical use for the IR product (Sponsor’s Summary of Clinical Safety (SCS) page 50):

**Table 27 Early PD Trial: dose / duration exposure (source: Sponsor)**

Table 1.2.2.7.1: 1 Number (%) of patients exposed to pramipexole ER by treatment duration and final dosage level and overall- placebo-controlled trial 248.524, 18-week analysis / TS 1

Treatment exposure	PPX ER 0.375-1.5 mg/day	PPX ER 2.25-3 mg/day	PPX ER 3.75-4.5 mg/day	Total
Number of patients (%)	26 ( 24.5)	31 ( 29.2)	49 ( 46.2)	106 (100.0)
Duration of exposure, in days				
Mean (SD)	96.0 (51.3)	112.3 (32.6)	122.2 (10.9)	112.9 (33.1)
Exposure in weeks N (%)				
N	26 (100.0)	31 (100.0)	49 (100.0)	106 (100.0)
< 1 week	4 ( 15.4)	0 ( 0.0)	0 ( 0.0)	4 ( 3.8)
1 - < 4 weeks	2 ( 7.7)	1 ( 3.2)	0 ( 0.0)	3 ( 2.8)
4 - < 8 weeks	0 ( 0.0)	3 ( 9.7)	0 ( 0.0)	3 ( 2.8)
8 - <13 weeks	1 ( 3.8)	1 ( 3.2)	1 ( 2.0)	3 ( 2.8)
13 - <18 weeks	10 ( 38.5)	16 ( 51.6)	29 ( 59.2)	55 ( 51.9)
18 - <23 weeks	9 ( 34.6)	10 ( 32.3)	19 ( 38.8)	38 ( 35.8)

Source data: [Appendix 7, Table 1.2.5.4](#)

Demographically, the population exposed to drug was appropriate for this illness with regard to age and gender and closely reflected target population demographics. The racial distribution included Caucasians and Asians but no African Americans or blacks of other ethnic origin (SCS, p 61).

**Table 28 Early PD Trial: subject demographic data (source: Sponsor)**

Table 1.3.2.1.1: 1 Demographic data, all randomised patients from placebo-controlled Trial 248.524, 18 weeks of treatment/ TS 1

248.524 (early PD)		Placebo	PPX ER	PPX IR	Total
Number of Patients		50	106	103	259
Gender					
Male	N (%)	23 (46.0)	62 (58.5)	59 (57.3)	144 (55.6)
Female	N (%)	27 (54.0)	44 (41.5)	44 (42.7)	115 (44.4)
Age [years]					
Age mean(SD)		63.2 (8.7)	61.6 (9.4)	62.0 ( 8.3)	62.1 ( 8.8)
Age classes					
Age < 65 years	N (%)	23 (46.0)	57 (53.8)	57 (55.3)	137 (52.9)
Age ≥ 65 years	N (%)	27 (54.0)	49 (46.2)	46 (44.7)	122 (47.1)
Race					
White	N (%)	32 (64.0)	67 (63.2)	62 (60.2)	161 (62.2)
Black	N (%)	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)
Asian	N (%)	18 (36.0)	39 (36.8)	41 (39.8)	98 (37.8)
Body mass index (kg/m <sup>2</sup> )					
BMI mean(SD)		26.7 (4.4)	26.0 (4.7)	26.2 ( 4.5)	26.2 ( 4.5)

Source data: Appendix 7, Table 1.3.2.1.1 and CTR 248.524 [U08-1826-01], Table 11.2.1: 1

**Safety Assessment**

Please see Section 7

**Discussion of findings and conclusion**

Because there is a single efficacy trial in this submission, this discussion is deferred to Section 6.

**5.3.2 Pivotal Trial in Advanced PD (248.525)**

*Reviewer's Note:* This trial is in progress and only safety data is submitted to this NDA. The trial is not reviewed in detail except as it illuminates conditions related to drug exposure and the patients' safety. The efficacy portion remains blinded and in progress. Safety data has been submitted for this trial with an initial cut off date for interim data on May 30, 2008, and a 120 day update with data up to September 1 2008 and SAEs to December 1, 2008.

## Phase III

### Purpose

To determine the efficacy (as measured by the change from baseline to the end of the maintenance period in the total score for UPDRS parts II and III combined), safety and tolerability of PPX ER compared with placebo in L-Dopa+ treated patients with advanced PD.

### Trial design

This is a multinational, multicenter, double-blind, double-dummy, placebo-controlled, randomized, parallel group design, planned for April 2007 – August 2008. An initial 7 week flexible titration to optimal daily dose is followed by a 26 week maintenance phase. At the end of the maintenance, subjects may enter an open label extension or taper off medication over 1 week. Trial was begun May 9, 2007 and continues running.

#### Primary endpoint:

- UPDRS (Unified Parkinson's Disease Rating Scale) parts II+III score (change from baseline to end of the maintenance period).

#### Key secondary criteria:

- Percentage of off-time during wakefulness (diary based)

#### Other secondary criteria:

- Proportion of patients with at least a 20% improvement relative to baseline in the percentage off-time during waking hours (diary based)
- Percentage on-time:
  - without dyskinesia
  - with non troublesome dyskinesia
  - without dyskinesia or with non-troublesome dyskinesia
  - with troublesome dyskinesia
  - during waking hours – diary based (change from baseline)
- Responder rate for Clinical Global Impression of Improvement (CGI-I)
- Responder rate for Patient Global Impression of Improvement (PGI-I)
- Proportion of patients with at least a 20% improvement relative to baseline in the UPDRS II+III total score
- UPDRS I, II, III and IV scores separately (change from baseline)
- BDI (Beck's Depression Inventory) version IA (change from baseline)
- PDSS (Parkinson's Disease Sleep Scale) (change from baseline)
- Likert scale for pain related to PD (change from baseline)
- PDQ-39 (Parkinson Disease Questionnaire- 39 items)
- EQ-5D (EuroQoL) (change from baseline)
- L-Dopa daily dose (change from baseline)

- Cost-effectiveness analysis will be conducted to compare treatments

**Safety endpoints:**

- Incidence of Adverse Events
- Proportion of withdrawals due to adverse events
- Vital signs (blood pressure and pulse rate)
- Weight
- Epworth Sleepiness Scale (ESS)
- Modified Minnesota Impulsive Disorders Interview (MMIDI)
- Safety laboratory parameters

**Key Inclusion**

- Idiopathic Parkinson's disease diagnosed for at least 2 years with a modified Hoehn and Yahr scale of II to IV at "on time".
- Must be treated with levodopa with or without dopa-decarboxylase inhibitor and/or entacapone, at an optimized dose, stable for at least 4 weeks prior to baseline
- Must have documented motor fluctuations with at least 2 cumulative hours of off-time every day during waking hours
- No exposure to dopamine agonists within 8 weeks prior to baseline.

**Key Exclusion**

- Atypical parkinsonian syndromes
- Dementia with MMSE < 24 at baseline
- Psychosis except drug induced hallucinations
- History of deep brain stimulation
- Significant ECG abnormality or orthostatic hypotension
- Any dopamine blocking concomitant treatments

**Concomitant Medication**

Concomitant treatment with one or more of following to be allowed if on stable doses for at least 4 weeks prior to baseline and during treatment phase: anticholinergics, MAO B inhibitors, amantadine, entacapone or other COMT-inhibitor, and beta-blockers (when used to treat Parkinson's disease).

**Trial Visits**

**Table 29 Advanced PD Trial: study checklist (source: Sponsor)**

Table 9.5: 1 Trial Flow Chart

Trial period	S <sup>1</sup>	B <sup>1</sup>	Flexible up-titration phase							Maintenance phase					Down-titration phase	
Visit number	V1	V2	TC1	V3	TC2	V4	TC3	V5	TC4	V6	V7	V8	V9	V10	V11 <sup>2</sup>	V12 <sup>2</sup>
Week	-2 to -1	0	1	2	3	4	5	6	7	8	13	18	23	28	33	34
Day	-14 to -7	0	7 ±2	14 ±2	21 ±2	28 ±2	35 ±2	42 ±2	49 ±2	56 ±3	91 ±3	126 ±3	161 ±3	196 ±3	231 ±3	238 ±3
Written informed consent	X															
Demographics	X															
Baseline conditions	X															
Inclusion/ Exclusion criteria	X	X														
Physical examination	X														X	
Ophthalmologic monitoring	X <sup>7</sup>													X <sup>7</sup>		
BP, Pulse, Weight, Height <sup>4</sup>	X	X		X		X		X		X	X	X	X	X	X	X
Check for abnormal behaviour <sup>8, 10</sup>				X		X		X			X		X	X		
Modified MIDI <sup>10</sup>		X								X		X			X	X
MMSE	X															
Modified Hoehn and Yahr	X															
Randomization		X														
Medication fax	X	X														
Instruct and supply patient diary	X	X		X		X		X		X	X	X	X	X		

Trial period	S <sup>1</sup>	B <sup>1</sup>	Flexible up-titration phase							Maintenance phase					Down-titration phase	
Visit number	V1	V2	TC1	V3	TC2	V4	TC3	V5	TC4	V6	V7	V8	V9	V10	V11 <sup>2</sup>	V12 <sup>2</sup>
Week	-2 to -1	0	1	2	3	4	5	6	7	8	13	18	23	28	33	34
Day	-14 to -7	0	7 ±2	14 ±2	21 ±2	28 ±2	35 ±2	42 ±2	49 ±2	56 ±3	91 ±3	126 ±3	161 ±3	196 ±3	231 ±3	238 ±3
Review patient diary		X		X		X		X		X	X	X	X	X	X	
UPDRS part I, II, III and IV	X	X		X		X		X		X	X	X	X	X	X	
CGI-I						X				X		X			X	
PGI-I			X	X	X	X	X	X	X	X		X			X	
PGI-I for early morning OFF-symptoms										X		X			X	
ESS		X				X				X		X			X	
BDI		X				X				X		X			X	
PDSS		X				X				X		X			X	
Pain scale		X				X				X		X			X	
PDQ-39		X										X			X	
EQ-5D		X										X			X	
Safety lab tests	X									X					X	X <sup>3</sup>
Serum pregnancy test (if applicable)	X															
12-lead ECG	X														X	X <sup>3</sup>
Dispense/ re-dispense trial medication		X		X		X		X		X	X	X	X	X	X <sup>5</sup>	

Trial period	S <sup>1</sup>	B <sup>1</sup>	Flexible up-titration phase							Maintenance phase						Down- titration phase
Visit number	V1	V2	TC1	V3	TC2	V4	TC3	V5	TC4	V6	V7	V8	V9	V10	V11 <sup>2</sup>	V12 <sup>2</sup>
Week	-2 to -1	0	1	2	3	4	5	6	7	8	13	18	23	28	33	34
Check medication compliance			X	X	X	X	X	X	X	X	X	X	X	X	X	X <sup>6</sup>
Concomitant therapy	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events <sup>9</sup>	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

- Abbreviations are for "Screening" and "Baseline".
- All assessments planned at visit 11 and at visit 12 had to be done even if a patient was prematurely withdrawn from the treatment phase.
- To be done at visit 12 only if abnormal at visit 11.
- Height was only measured at Screening (visit 1).
- At visit 11, study medication was dispensed for the down-titration phase if patients did not enter the open-label extension study
- At visit 12, medication compliance was checked during the down-titration phase
- At visit 1 and visit 10, patients were referred to an ophthalmologist for an ophthalmologic monitoring (vision control and fundoscopy). Results were supposed to be available for visit 2 and visit 11, respectively
- In case the patient experienced any abnormal behaviour, then the Modified MIDI sub-scale had to be completed. In addition to the questions about pathological gambling, compulsive sexual behaviour and compulsive buying, a separate question had to be addressed at each visit: "Since the last visit, have you experienced any other abnormal behaviours, or urges? If yes, please specify."
- In addition to reviewing adverse events the following question was supposed to be asked at TC1, V3, TC2, TC3, V5, TC4, V7, V9, V10, V12: "Since the last visit, have you experienced significant daytime sleepiness or any episodes of unexpected falling asleep?" In case of a positive answer, it was supposed to be reported as an Adverse Event.
- In case of a newly reported positive screening at any of the MMIDI sub-scales and/or at the question about any other abnormal behaviours or urges, this was supposed to be reported as an AE. These patients were supposed to be referred to a psychiatrist to evaluate the diagnosis.

## Treatments and other ancillary management

PPX ER 0.375 mg, 0.75 mg, 1.5 mg, 3.0 mg and 4.5 mg tablets, PPX IR 0.125 mg, 0.25 mg, 0.50 mg, 1.0 mg and 1.5 mg tablets and the matching placebo for both formulations will be supplied. All trial medication will be administered in a double-blind fashion to mask the type of trial drug treatment. Not all dosage formats will be identical, because the final commercial formulations will be used.

Sites with enrollment figures:

92 (76 actively enrolling) centers in 14 countries (Europe and Asia)

## Randomization and Controls

There is a 1:1:1 randomization to PPX ER, PPX IR or placebo in this trial. Block size is 3 subjects. The CRO handled the blinded assignment of subjects to intervention. To keep the trial blinded the CRO was also involved in the interim analysis, keeping the trial team from access to any results of the interim analysis.

## Subject Enrollment

This trial is in progress and enrollment is ongoing. Numbers at the time of the data cutoffs are discussed in the safety analysis in Section 7.

## Protocol Amendments

Amendment 1 (April 18, 2007): Add additional PGI scale assessments to evaluate severity of morning off period.

Amendment 2 (July 12, 2007): Questions specifically added to inquire about daytime sleepiness and unexpected falling asleep, treatment emergent compulsive behaviors and other unrecognized behavior.

Amendment 3 (November 15, 2007): Referral to psychiatrist in the event of a positive screening of mMIDI or other inquiry re: abnormal behavior.

Amendment 4 (January 17, 2008): If the interim analysis of 248.524 (PPX ER in early PD) is positive, all patients in this trial will be transferred to the open label extension prematurely. Ukraine is added and Finland deleted from trial sites. Hypersexuality and other abnormal behavior, and pruritis, rash and other hypersensitivity were added as expected side-effects.

Amendment 5 (May 8, 2008): Following FDA recommendation, a confirmatory analysis was conceived with all patients treated to 18 weeks and the planned end date of this trial was recalculated. (This revoked the premature ending of the trial in Amendment 4).

### **Trial Populations / Patient Disposition**

Subject attrition due to adverse events and withdrawal of consent is discussed in the safety analysis in Section 7.

### **Method for determining the outcome of efficacy analysis (from Sponsor's protocol)**

#### Primary analysis:

ANCOVA analysis for change from baseline at the end of the maintenance treatment period in the UPDRS II+III total score, adjusting for center (fixed effect) and baseline UPDRS II+III (covariate). The primary analysis will be based on the Full Analysis Set (using LOCF) for the comparison of PPX ER vs. placebo. Additionally, according to the closed testing principles the comparison of PPX IR vs. placebo will be performed. The Per Protocol Set (PPS) will be used for sensitivity analyses.

#### Secondary analyses:

The percentage off-time during waking hours (key secondary endpoint) will be tested using an ANCOVA model. ANCOVA or non-parametric treatment group comparisons as appropriate for secondary efficacy endpoints. The secondary analyses will be based on the Full Analysis Set (using LOCF). The trial is not powered for an inferential comparison of the active treatment groups, but PPX IR is added for sensitivity and orientation (mean maintenance doses, effect on various endpoints, to be presented by 95% confidence intervals).

#### Sample size calculation:

The sample size required to show superiority of PPX ER over placebo is 172, with an expected mean difference of 5 points between PPX ER and placebo in the change from

baseline in UPDRS II+III total score with a 90% power, assuming a within-group standard deviation of 14 points and testing at the one-sided alpha level of 0.025.

Analogously the comparison of PPX IR and placebo requires 172 patients, resulting in a total number of 516 patients (added for early drop-outs without post-baseline efficacy assessments: 3.5%).

In addition, with a treatment group size of 172 patients, it will be possible to detect an expected mean difference of 1 hour between PPX ER and placebo in the change from baseline in the percentage off-time during waking hours with 86% power, assuming a within-group standard deviation of 3 hours and testing at the one-sided alpha-level of 0.025.

Descriptive statistical methods will be used for the analysis of safety endpoints. An interim safety analysis will be performed once approximately 100 patients will have completed the trial. Only descriptive methods will be used for the safety endpoints.

## **Trial Results**

No efficacy results were submitted by the sponsor for this on-going trial. Safety is discussed in Section 7.

### **5.3.3 Overnight Switch IR to ER Trial (248.636)**

#### **Trial**

A double-blind, double-dummy, randomized, parallel groups trial to assess the efficacy, safety and tolerability of switching patients with early Parkinson's disease (PD) from PPX IR to PPX ER or PPX IR.

#### **Phase III**

#### **Purpose**

- To assess if patients with early Parkinson's disease (PD) can be successfully switched (overnight switching) from PPX IR to PPX ER
- To establish if this successful switch can be obtained with or without dose-adjustment
- To provide information about the conversion ratio (mg:mg) from PPX IR to PPX ER

#### **Trial design**

A double-blind, double-dummy, randomized, parallel group design, planned for October 2007 to July 2008. The trial began November 1, 2007 and was completed before the submission cut-off date, May 22, 2008.

Patients on stable PPX IR treatment will be randomized to continued therapy on IR or crossed over to ER for four weeks (first maintenance period). Then a period of dose adjustments may take place and observation follows for another four weeks (second maintenance phase).

Primary endpoint:

- The primary efficacy endpoint is the proportion of patients successfully switched from PPX IR to PPX ER or IR at the end of the second maintenance phase.

Secondary endpoints:

Secondary efficacy endpoints assessed at end of the first and second maintenance phases:

- Proportion of patients successfully switched from PPX IR to PPX ER or maintained on IR at the end of the first maintenance phase without a dose adjustment
- UPDRS (Unified Parkinson's Disease Rating Scale) parts II+III score (change from baseline)
- Clinical Global Impression of Improvement (CGI-I)
- Patient Global Impression of Improvement (PGI-I)
- UPDRS II and III separately (change from baseline)
- Percentage of patients requiring dose adjustment
- Proportion of patients successfully treated at end of first maintenance phase
- PPX daily dose (change from baseline)

Safety endpoints:

- Incidences of adverse events (AEs)
- Proportions of withdrawals due to AEs (either drug-related or not)
- Vital signs (blood pressure and pulse rate) and weight (change from baseline)
- Epworth Sleepiness Scale (ESS) (change from baseline)
- Modified Minnesota Impulsive Disorders Interview (mMIDI).

**Key Inclusion**

- Men or women with idiopathic PD diagnosed within 5 years, 30 years of age or older at time of diagnosis, with a modified Hoehn and Yahr scale of 1 to 3.
- Patients should be on PPX IR for at least 3 months prior to baseline. The PPX dose should be optimized (according to the investigator's judgment), greater or equal to 1.5 mg/day, stable and equally divided 3 times per day, for a least 4 weeks prior to baseline visit.
- Patients may be receiving a concomitant treatment with levodopa. However, they should not experience any motor complications (e.g. on-off phenomena, dyskinesia) under levodopa therapy.

## Key Exclusion

- Motor complications under levodopa therapy (e.g. on-off phenomena, dyskinesia) at screening visit.
- Atypical parkinsonian syndromes
- Dementia, as defined by a Mini-Mental State Exam score < 24 at screening visit
- History of psychosis, except history of drug induced hallucinations
- Clinically significant electrocardiogram (ECG) abnormalities at screening visit
- Clinically significant hypotension and/or symptomatic orthostatic hypotension
- Serum levels of AST (SGOT), ALT (SGPT), alkaline phosphatase or bilirubin > 2 ULN (on screening lab test).
- Patients with a creatinine clearance < 50 mL/min
- Any dopamine agonist (except PPX IR) within three months prior to baseline visit.
- History of discontinuation of treatment with PPX IR due to related clinically significant adverse event
- Any medication with central dopaminergic antagonist activity within 4 weeks prior to the baseline visit

## Concomitant Medication

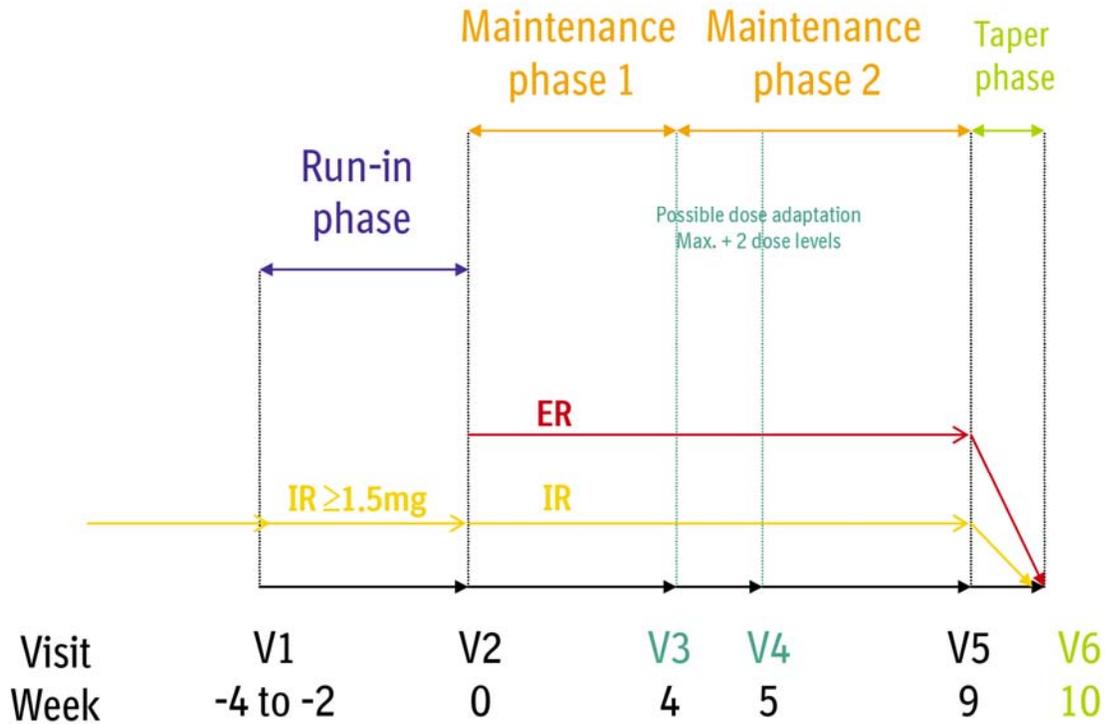
A concomitant treatment with one or more of the following drugs will be allowed (at a stable dose for at least 4 weeks prior to baseline and provided the investigator does not intent to change this treatment during the trial): L-Dopa+ (i.e. standard and/or controlled release Levodopa/DDC inhibitor), or with a fixed combination of L-Dopa+ and entacapone, anticholinergics, MAO-B inhibitors, amantadine, entacapone or other COMT inhibitors, and beta-blockers (when used to treat PD symptoms).

## Trial visits

The maximum total trial duration was 14 weeks. After an up to 4-week open-label run-in phase with PPX IR, patients were randomized to PPX ER or PPX IR in a 9-week double-blind phase, as described below:

The trial begins with a two-to-4 week open-label run-in phase with PPX IR. During this run-in phase (from Visit 1 to Visit 2), PPX IR and all other anti-parkinson treatments should be maintained at a stable dose. At the end of this run-in phase, patients were randomly switched with a 1:1 (mg:mg) conversion ratio from PPX IR, to either PPX ER or PPX IR.

**Figure 10 Overnight Switch Trial: design (source: Sponsor)**



The nine-week double-blind phase is divided into two phases:

First Maintenance Phase (from Visit 2: day 0 to Visit 3: week 4): During this maintenance phase, PPX and all other anti-parkinson treatments were to be maintained at a stable dose.

Second Maintenance Phase (from Visit 3: week 4 to Visit 4: week 5 then to Visit 5: week 9): During this maintenance phase, PPX and all other anti-parkinsonian treatments should have been maintained at a stable dose. However, a possible dose adjustment of trial medication could be performed at V3 and/or at V4 in case of worsening of the UPDRS II+III score by more than 15% compared to baseline.

**Table 30 Overnight Switch Trial: visit checklist (source: Sponsor)**

Table 9.5: 1 FLOW CHART

Period	Run-in Phase	Maintenance Phase 1	Maintenance Phase 2			Tapering Phase
			V3	V4	V 5 <sup>2</sup> End of treatment	
Visit number	V1	V2	V3	V4	V 5 <sup>2</sup> End of treatment	V6 Follow-up
Week	-4 to -2	0	4	5	9	10
Day	-28 to -14	0	28±2	35±2	63±3	70±3
Written informed consent	X					
Demographics, height	X					
Baseline conditions	X					
Inclusion/ Exclusion criteria	X	X				
Physical examination	X				X	
BP, Pulse rate and weight	X	X	X	X	X	X
modified Midi <sup>7</sup>	X				X	
Check for any other abnormal behaviour <sup>7</sup>	X		X	X	X	
Check for specific abnormal behaviour <sup>6</sup>			X	X		
MMSE	X					
Modified Hoehn and Yahr	X					
Eligibility for entering run-in phase	X					
Randomization		X				
Treatment assignment using IVRS	X	X	X	X	X	
UPDRS part II and III	X	X	X	X	X	
CGI-I			X	X	X	
PGI-I			X	X	X	
ESS		X	X	X	X	
Safety lab tests	X					
Urinary pregnancy test (if applicable)	X <sup>4</sup>					
12-lead ECG	X					

Period	Run-in Phase	Maintenance Phase 1	Maintenance Phase 2			Tapering Phase
			V3	V4	V 5 <sup>2</sup> End of treatment	
Visit number	V1	V2	V3	V4	V 5 <sup>2</sup> End of treatment	V6 Follow-up
Week	-4 to -2	0	4	5	9	10
Day	-28 to -14	0	28±2	35±2	63±3	70±3
Dispense run-in phase medication	X					
Dispense trial medication		X	X	X	X <sup>1</sup>	
Adjust trial medication, if needed			X	X		
Check medication compliance		X	X	X	X	X <sup>5</sup>
Concomitant therapy	X	X	X	X	X	X
Adverse events	X	X <sup>3</sup>	X	X	X	X

At the end of the double-blind second maintenance treatment phase, patients were eligible to enter an open-label extension trial, where they received PPX ER.

Patients not entering the open-label extension trial had two options: either to continue with PPX IR at the same dose as in the double-blind treatment (V5 dose), or to receive another treatment according the investigator's judgment. In this last case, a 1-week down-titration phase of PPX was performed.

**Treatments and other ancillary management**

Trial medication provided randomization of PPX ER to PPX IR 2:1. Final commercial formulations were used and so not all dosage formats were identical. A double dummy format administered t.i.d was used to maintain the blind.

**Table 31 Overnight Switch Trial: treatment regimen (source: Sponsor)**

Tablets → ↓Treatment group	PPX ER morning	PPX IR morning	PPX IR midday	PPX IR evening	Placebo PPX ER morning	Placebo PPX IR morning	Placebo PPX IR midday	Placebo PPX IR evening
Pramipexole ER	X					X	X	X
Pramipexole IR		X	X	X	X			

Dosage levels took into account that subjects had to be receiving at least 1.5 mg PPX daily to qualify for the trial. The dosing schedule for this trial followed the standard doses for PPX:

Dosing levels for PPX IR during the open-label run-in phase:

- 1.5 mg (0.5 mg t.i.d)
- 2.25 mg (0.5 mg t.i.d + 0.25 mg t.i.d)
- 3.0 mg (1.0 mg t.i.d)
- 3.75 mg (1.0 mg t.i.d + 0.25 mg t.i.d)
- 4.5 mg (1.5 mg t.i.d)

**Table 32 Overnight Switch Trial: dose titration levels (source: Sponsor)**

Doses during the first double-blind maintenance phase:		
PPX ER	and	Placebo matching PPX IR
1.5 mg,	+	1.5 mg (0.5 mg t.i.d),
2.25 mg (1.5 mg + 0.75 mg),	+	2.25 mg (0.5 mg t.i.d + 0.25 mg t.i.d),
3.0 mg,	+	3.0 mg (1.0 mg t.i.d),
3.75 mg (3.0 mg + 0.75 mg) or	+	3.75 mg (1.0 mg t.i.d + 0.25 mg t.i.d), or
4.5 mg in the morning	+	4.5 mg (1.5 mg t.i.d)
<u>OR</u>		
PPX IR	and	Placebo matching PPX ER

1.5 mg (0.5 mg t.i.d),	+	1.5 mg,
2.25 mg (0.5 mg t.i.d + 0.25 mg t.i.d),	+	2.25 mg (1.5 mg + 0.75 mg),
3.0 mg (1.0 mg t.i.d),	+	3.0 mg,
3.75 mg (1.0 mg t.i.d + 0.25 mg t.i.d), or	+	3.75 mg (3.0 mg + 0.75 mg) or
4.5 mg (1.5 mg t.i.d)	+	4.5 mg in the morning

Doses during the second double-blind maintenance phase with the possible dose adjustment phase consisting of the following dose levels:		
PPX ER	and	Placebo matching PPX IR
0.375 mg,	+	0.375 mg (0.125 mg t.i.d),
0.75 mg,	+	0.75 mg (0.25 mg t.i.d),
1.5 mg,	+	1.5 mg (0.5 mg t.i.d),
2.25 mg (1.5 mg + 0.75 mg),	+	2.25 mg (0.5 mg t.i.d + 0.25 mg t.i.d),
3.0 mg,	+	3.0 mg (1.0 mg t.i.d),
3.75 mg (3.0 mg + 0.75 mg) or	+	3.75 mg (1.0 mg t.i.d + 0.25 mg t.i.d), or
4.5 mg in the morning	+	4.5 mg (1.5 mg t.i.d)

OR

PPX IR	and	Placebo matching PPX ER
0.375 mg (0.125 mg t.i.d),	+	0.375 mg,
0.75 mg (0.25 mg t.i.d),	+	0.75 mg,
1.5 mg (0.5 mg t.i.d),	+	1.5 mg,
2.25 mg (0.5 mg t.i.d + 0.25 mg t.i.d),	+	2.25 mg (1.5 mg + 0.75 mg),
3.0 mg (1.0 mg t.i.d),	+	3.0 mg,
3.75 mg (1.0 mg t.i.d + 0.25 mg t.i.d), or	+	3.75 mg (3.0 mg + 0.75 mg) or
4.5 mg (1.5 mg t.i.d)	+	4.5 mg in the morning

The need to increase the dose by one dose level was assessed by the investigator at Visit 3 (week 4) and at Visit 4 (week 5), based on efficacy and tolerability. A maximum increase of 2 dose levels could be made at those visits. In case of dopaminergic side effects, the dose of trial medication could be decreased.

Clinical Review  
Kenneth Bergmann, MD, FAAN  
NDA 22-421  
Mirapex ER / pramipexole dihydrochloride extended-release tablets

## **Randomization and Controls**

Patients were randomly assigned to treatment groups with a 2:1 probability of assignment to each treatment (PPX ER: PPX IR, respectively). The randomization block size was 6, and assignment was performed through an interactive voice response system telephone contact with a third party agency.

## **Subject Enrollment**

The trial was conducted at 26 clinical trial centers in three countries. While 169 patients were enrolled, 156 patients were randomized and treated in France (57), Germany (77) and the Netherlands (22).

## **Protocol Amendments**

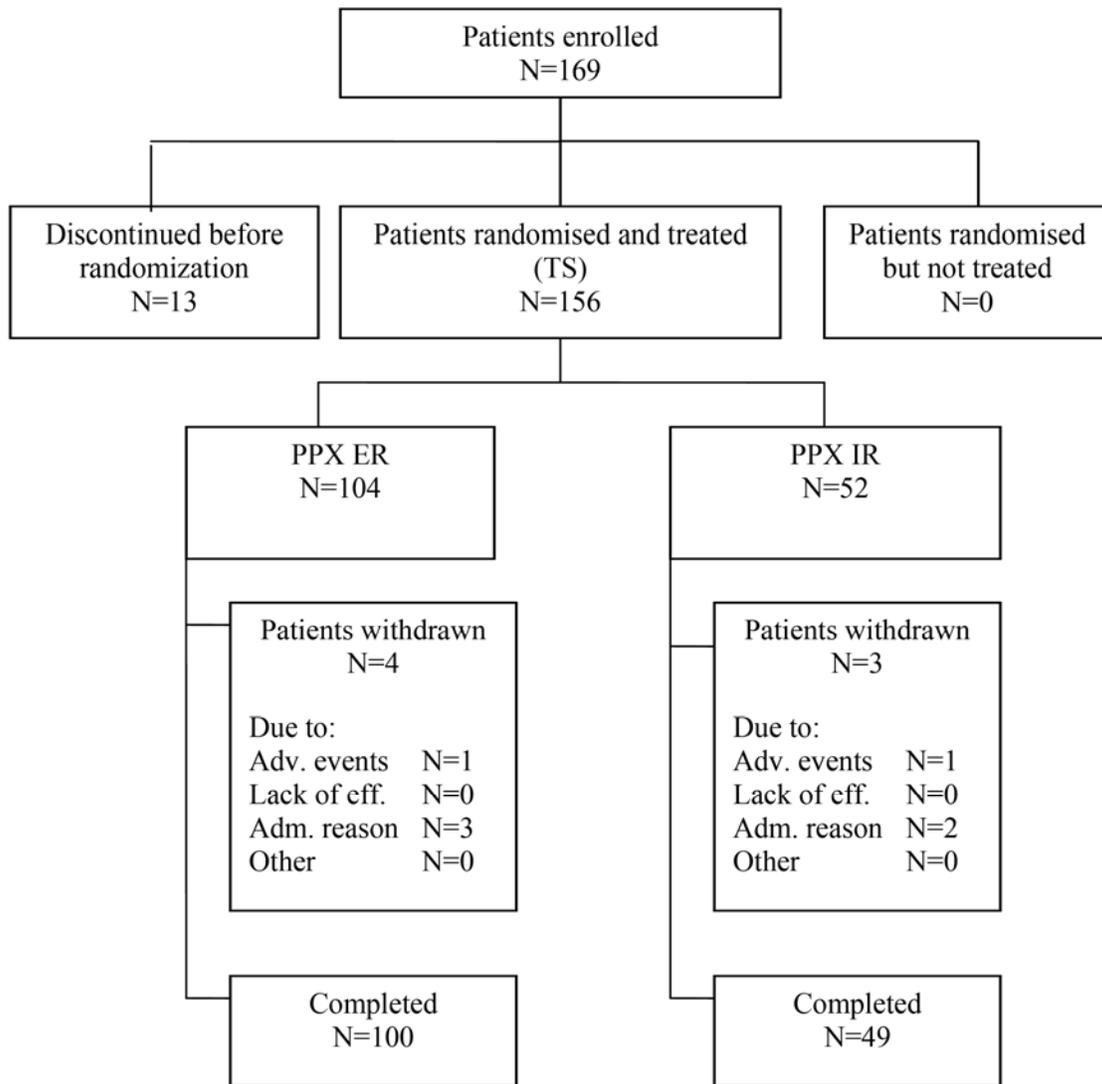
Amendment 1 (September 20, 2007) added the modified Minnesota Impulse Disorder Interview (mMIDI) and in the case of a new positive response, referral would be made to a psychiatrist for evaluation.

Amendment 2 (January 25, 2008) updated the list of expected adverse events in the protocol and investigator's brochure to include hypersexuality and other abnormal behavior, pruritis rash and other hypersensitivity.

## **Trial population and disposition**

Disposition of all the subjects is indicated in the Sponsor's flow chart below:

**Figure 11 Overnight Switch Trial: patient disposition (source: Sponsor)**



The intent-to-treat trial population consists of the 156 subjects who were randomized and received trial medication. This number is reduced by protocol violations the nature of which make 7 additional subjects unable to be evaluated. Seven patients discontinued prematurely as the Sponsor indicates in the table below:

**Table 33 Overnight Switch Trial: protocol violations (source: Sponsor)**

Table 10.2: 1 Important protocol violations for efficacy, TS

	PPX ER N (%)	PPX IR N (%)
Number of patients entered	104(100.0)	52(100.0)
Patients with any important protocol deviation	4( 3.8)	3( 5.8)
Protocol deviation		
Overall compliance lower than 80% or greater than 120% at V5	0( 0.0)	1( 1.9)
Treatment exposure less than 2 weeks - 3 days during main. phase No1	1( 1.0)	1( 1.9)
Last visit done >2 days after last intake of rand. study medication	1( 1.0)	0( 0.0)
Different treatment group assignment during db treatment	1( 1.0)	0( 0.0)
Change in a concurrent PD medication during the trial	1( 1.0)	1( 1.9)

Source data: Table 15.1.2: 1

**Table 34 Overnight Switch Trial: premature discontinuations (source: Sponsor)**

Disposition	PPX ER N (%)	PPX IR N (%)	Total N (%)
Treated (with DB randomized treatment)	104 (100.0)	52 (100.0)	156 (100.0)
Completed	100 ( 96.2)	49 ( 94.2)	149 ( 95.5)
Prematurely discontinued	4 ( 3.8)	3 ( 5.8)	7 ( 4.5)
Adverse events	1 ( 1.0)	1 ( 1.9)	2 ( 1.3)
Worsening of disease under study	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)
Worsening of other pre-existing disease	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)
Other adverse event	1 ( 1.0)	1 ( 1.9)	2 ( 1.3)
Lack of efficacy	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)
Administrative reasons	3 ( 2.9)	2 ( 3.8)	5 ( 3.2)
Non compliance with protocol	1 ( 1.0)	0 ( 0.0)	1 ( 0.6)
Lost to follow-up	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)
Refused to continue medication	2 ( 1.9)	2 ( 3.8)	4 ( 2.6)
Other	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)

Source data: [Table 15.1.1: 1](#)

### Method for determining the outcome of efficacy analysis

#### Primary analysis:

A patient was considered as successfully switched at week 9, with a possible dose adaptation, if the following condition was fulfilled:

- No worsening of the UPDRS II+III score by more than 15% from Visit 2 (week 0) to Visit 5 (week 9) and no drug-related adverse events leading to withdrawal.

Treatment group comparisons were performed using a Cochran-Mantel-Haenszel (CMH) test for the percentage of patients successfully switched in the two treatment groups with country stratification. The difference in proportions between patients successfully switched from PPX IR to IR or ER was tested with one-sided non inferiority statistical test at the 5 % level of significance and a non-inferiority margin of 15 %.

Key-secondary analysis:

A patient was considered as successfully switched at week 4, without a dose-adaptation if the following condition was fulfilled:

- No worsening of the UPDRS II+III score by more than 15% from Visit 2 (week 0) to Visit 3 (week 4) and no drug-related adverse events leading to withdrawal.

The key-secondary endpoint was tested again with a non-inferiority statistical test within a closed testing procedure.

Secondary analyses:

- An analysis of covariance (ANCOVA) was used for change from Visit 2 to Visit 3, Visit 4 and Visit 5 in the UPDRS II+III total score, adjusting for treatment and country (fixed effect) and baseline (covariate).
- For UPDRS part II and III separately an ANCOVA analogously to their combination was performed. The global improvement as measured by CGI-I and PGI-I was analyzed by a CMH test with country stratification.
- The proportion of patients switched to the same, lower or higher dose in the second maintenance phase was calculated as well.

Power calculation:

Using a one-sided test level of 0.05 and about 80% power, a sample size of 120 patients (PPS) was sufficient to test the following two hypotheses:

- in case the success rate after switch was 95% for PPX IR and 91.5% for PPX ER, a non-inferiority margin of 15% was assumed,
- in case the success rate after switch was 90% for PPX IR and 85% for PPX ER, a non-inferiority margin of 20% was assumed.

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In order to observe more patients switching to PPX ER, the sample was randomized in relation 2:1 (PPX ER: PPX IR).

## **Trial Results**

### **Demographics**

Males made up 56% of the trial cohort. Mean age was 64 years, with equivalent numbers above and below age 65. This accurately reflects general disease characteristics. The subjects were mostly white (97.4%).

Most patients had about 3 years duration of illness, and were equivalent in their PD disability and motor signs as measured by UPDRS II + III (22.2, SD 10.3). Patients were taking PPX IR for a mean of 1.5 years (SD 1.6) before entering the trial (minimum requirement 3 month stable treatment).

Co-morbidities were appropriate for this age group and population and distributed equally between the groups, with the exception of 11 cases of hypothyroidism in the PPX ER group and none in the IR group. No explanation was given. Most common disorders were hypertension, depression, constipation, hypercholesterolemia, and degenerative joint disease, as expected.

### **Concomitant medications during the trial period**

The most common concomitant anti-parkinson medication was levodopa (taken by 56.7% of PPX ER patients and 51.9% of PPX IR patients), followed by MAO B inhibitors (taken by 27.9% of PPX ER patients and 32.7% of PPX IR patients) and amantadine (taken by 23.1% of patients in each group).

**Table 35 Overnight Switch Trial: concomitant medication (source: Sponsor)**

Table 11.2: 4 Concomitant antiparkinsonian therapy by special groups of interest and INN, number and frequency, TS

Group of special interest/ Preferred Term (INN)	PPX ER N (%)	PPX IR N (%)	PPX Total N (%)
Number of patients	104 (100.0)	52 (100.0)	156 (100.0)
Patients with any PD therapy of interest	87 ( 83.7)	43 ( 82.7)	130 ( 83.3)
Levodopa +/- COMT-Inhibitors	59 ( 56.7)	27 ( 51.9)	86 ( 55.1)
Madopar	22 ( 21.2)	12 ( 23.1)	34 ( 21.8)
Sinemet	23 ( 22.1)	9 ( 17.3)	32 ( 20.5)
Levodopa + Benserazide	5 ( 4.8)	3 ( 5.8)	8 ( 5.1)
Stalevo	14 ( 13.5)	3 ( 5.8)	17 ( 10.9)
Levodopa	1 ( 1.0)	3 ( 5.8)	4 ( 2.6)
Monoaminoxidase-B-Inhibitor	29 ( 27.9)	17 ( 32.7)	46 ( 29.5)
Selegiline	18 ( 17.3)	8 ( 15.4)	26 ( 16.7)
Rasagiline	11 ( 10.6)	9 ( 17.3)	20 ( 12.8)
Amantadine	24 ( 23.1)	12 ( 23.1)	36 ( 23.1)
Amantadine	24 ( 23.1)	12 ( 23.1)	36 ( 23.1)
Dopamine Agonists	18 ( 17.3)	8 ( 15.4)	26 ( 16.7)
Pramipexole*	18 ( 17.3)	8 ( 15.4)	26 ( 16.7)
Anticholinergics	2 ( 1.9)	2 ( 3.8)	4 ( 2.6)
Trihexyphenidyl	2 ( 1.9)	2 ( 3.8)	4 ( 2.6)

\*Marketed PPX was stopped before intake of run-in medication or was taken after double-blind medication was stopped.

Source data: [Table 15.1.4: 12](#)

### Compliance with trial medication

Overall compliance at all visits was good (99.7%) and comparable in both PPX ER and PPX IR groups. Only one patient exceeded standards for compliance in the trial.

### Dosing information and exposure

Average exposure in this trial was to a mean dose of 2.7 mg/day (SD 0.9 mg), equivalent in both groups. Modal dose was 3 mg /d. Median exposure was 63 days with 98% of patients taking 4 or more weeks of treatment. If one compares the number of patients taking low, moderate, or high doses of PPX, it is stable over time in both groups. There are no differences in dose between groups by analysis of variance, acknowledging the high probability of missing a difference when there might be one due to small sample size.

**Table 36 Overnight Switch Trial: final dose exposure by trial period**

	Daily Dose	PPX ER N=104	PPX IR N=52
Baseline	< 3 mg/d	50 (48%)	20 (38%)
	3 mg/d	34 (33%)	24 (46%)
	> 3 mg/d	20 (19%)	8 (15%)
Week 4	< 3 mg/d	48 (46%)	20 (38%)
	3 mg/d	34 (34%)	22 (45%)
	> 3 mg/d	19 (18%)	7 (13%)
Week 9	< 3 mg/d	47 (45%)	18 (35%)
	3 mg/d	32 (31%)	24 (46%)
	> 3 mg/d	24 (23%)	10 (19%)

**Discontinuations, protocol deviations and violations**

Seven patients had “important protocol violations, equally distributed between the arms. These were unevaluable and excluded by the Sponsor from the analysis. Another seven discontinued prematurely but were included in the analysis.

Four subjects discontinued for adverse events, discussed further in Section 7.

**Efficacy Results**

In essence, this trial attempts to demonstrate non-inferiority , i.e.: the hypothesis is that there is no discernible difference between PPX ER and its active comparator. As such this trial is inadequately designed and powered. Inter group comparisons are statistically inappropriate. This was communicated to the Sponsor in the EOP2 meeting, 22 August 2007.

From a safety point of view, there appears to be no obvious problem when performing an overnight switch from PPX IR to an equivalent PPX ER dose.

The Sponsor notes that 84.5% of patients in the PPX ER group were successfully switched form IR to ER, compared to 94.2% of patients successfully crossing over from IR to IR (some including possible dose adaptation).

Without a possible dose adaptation, 81.6% of patients in the PPX ER group were successfully switched at the same daily dose compared to 92.3% of patients in the PPX

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IR group. By the end of two months, 80.6% of patients in the PPX ER group and 84.6% of patients in the PPX IR group had not changed their dose level compared to baseline.

Based on their findings the Sponsor feels that a switch from PPX IR to PPX ER at the same daily dose (1mg: 1mg) can be recommended. There is no apparent safety reason to disagree with this guiding statement for prescribers.

### **Safety Assessment**

This is an uncontrolled trial with regard to safety. As is presented in Section 7, IR and ER have similar safety profiles and no placebo arm was present in this trial.

### **5.3.4 Active Control Trial in PD Patients on Levodopa (248.610)**

#### **Trial**

A double-blind, double-dummy, randomized, parallel-group trial to investigate the safety, tolerability, trough plasma concentration, and efficacy of PPX ER versus PPX IR administered orally for 12 weeks in patients with Parkinson's disease (PD) on L-dopa therapy, followed by a 52-week open-label long-term treatment period to evaluate the long-term safety and efficacy of PPX ER

#### **Phase III**

#### **Purpose**

To investigate the safety, tolerability, trough plasma concentration, and efficacy of PPX ER in comparison with those of PPX IR administered orally for 12 weeks in patients with Parkinson's disease (PD) on L-dopa therapy (the double blind period). The double-blind period will be followed by the open-label 52-week administration of PPX ER to evaluate the long term safety and efficacy (the open label period). This trial is conducted entirely in Japan.

#### **Trial design**

Double-blind, double-dummy, randomized, parallel group design followed by an open-label period (dose adjustment phase and maintenance phase) Forced titration at weekly intervals to maximally tolerated dose or 4.5 mg/d.

#### **Trial Visits (Checklist)**

Double blind Phase:

**Table 37 Active Control Trial: visit checklist (source: Sponsor)**

**FLOW CHART (DOUBLE-BLIND PERIOD)**

Trial period Visit (V)	S <sup>1</sup>		B <sup>1</sup>		Double-blind period							
	V1	V2	V3	TC1	V4	TC2	V5	TC3	V6	TC4	V7	V8 <sup>2</sup>
Telephone Contact (TC)												
Week	-4 to -1	0	1	2	3	4	5	6	7	8	9	12
Day	-28 to -7	0	7±2	14±2	21±2	28±2	35±2	42±2	49±2	56±2	63±4	84±4
Written informed consent	X											
Demographics	X											
Baseline conditions	X											
Inclusion/ Exclusion criteria	X	X										
Physical examination Weight, Height <sup>3</sup>	X											X
BP, Pulse rate (Supine, standing)	X	X	X		X		X		X		X	X
MMSE	X											
Modified Hoehn and Yahr	X											
Randomisation		X										
Medication FAX	X	X										
Instruct/ supply patient diary	X	X	X		X		X		X		X	X
Review patient diary	X	X	X		X		X		X		X	X
UPDRS part I, II, III, IV		X	X		X		X		X		X	X
CGI-I			X <sup>3</sup>		X <sup>3</sup>		X <sup>3</sup>		X <sup>3</sup>		X <sup>3</sup>	X <sup>3</sup>
PGI-I			X <sup>3</sup>		X <sup>3</sup>		X <sup>3</sup>		X <sup>3</sup>		X <sup>3</sup>	X <sup>3</sup>
ESS		X	X		X		X		X		X	X
Safety lab tests	X						X					X
Pregnancy test	X											
Trough PK sampling	X		X		X		X					X
12-lead ECG	X											X
Dispense trial medication		X	X		X		X		X		X	X <sup>4</sup>
Medication compliance			X	X	X	X	X	X	X	X	X	X
Concomitant therapy	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events (including record "sudden onset of sleep")	X	X	X	X	X	X	X	X	X	X	X	X

1. Abbreviations: S=Screening, B=Baseline  
 2. All assessments planned at Visit 8 have to be done even if a patient is prematurely discontinued in the double-blind period and dispense trial medication for the down-titration.  
 3. Height will only be measured at Screening (Visit 1)  
 4. At Visit 8, dispense trial medication for open label pramipexole ER according to the switching rule.  
 5. CGI-I and PGI-I must be evaluated compared with those at Visit 2 (baseline)

**FLOW CHART (OPEN-LABEL PERIOD)**

Trial period	Dose adjustment phase					Maintenance phase							Down-titration V16 <sup>6</sup>	
	TC5	V9	TC6	V10	V11	V12	V13	V14	V15 <sup>6</sup>					
Visit number <sup>9</sup>	13	14	15	16	18	22	26	30/34	38	42/46	50	54/58 /60	64	65
Day	91±2	98±2	105±2	112±2	126±7	154±7	182±7	210±7/ 238±7	266±7	294±7/ 322±7	350±7	378±7/ 406±7/ 420±7	448±7	455±2
Physical examination							X		X				X	X
BP, Pulse and weight		X		X	X		X		X		X		X	X
Medication FAX														X <sup>11</sup>
Instruct and supply patient diary		X		X	X		X		X		X			
Review patient diary		X		X	X		X		X		X		X	
UPDRS part I, II, III, IV		X		X	X		X		X		X		X	
CGI-I		X <sup>10</sup>		X <sup>10</sup>			X <sup>10</sup>							
PGI-I		X <sup>10</sup>		X <sup>10</sup>			X <sup>10</sup>							
ESS		X		X	X		X		X		X		X	
Safety lab							X		X		X		X	X <sup>8</sup>
ECG							X		X		X		X	X <sup>8</sup>
Dispense trial medication		X		X	X		X		X		X	X	X <sup>7</sup>	
Check medication compliance	X	X	X	X	X		X		X		X	X	X	X <sup>7</sup>
Concomitant therapy	X	X	X	X	X		X		X		X	X	X	X
Adverse events (including record "sudden onset of sleep")	X	X	X	X	X		X		X		X	X	X	X

6. All assessments planned at Visit 15 and 16 have to be done even if a patient is prematurely discontinued in the open-label period. All assessments planned at Visit 8 and 16 have to be done even if a patient is prematurely discontinued in the double-blind period.
7. At Visit 15, dispense trial medication for the down-titration and at Visit 16, check medication compliance during the down-titration
8. At Visit 15 or at the timing of prematurely discontinuation in the double-blind period, if clinically significant laboratory values or ECG findings are observed, a follow-up test (laboratory test or ECG) must be done at Visit 16.
9. At Visits without visit number, medication compliance, change of concomitant therapy and occurrence of adverse events will be assessed and study medication will be dispensed
10. CGI-I and PGI-I must be evaluated compared with those at Visit 8
11. When a patient is prematurely discontinued, Medication FAX should be also sent to the sponsor.

## **Treatments and other ancillary management**

Per protocol, in the double blind period, the dose for all the patients will be escalated to maximum dose (PPX 4.5 mg per day) unless any adverse event occurs, and even if the investigator or sub-investigator finds any significant efficacy with lower doses.

In the open label period, open-label PPX ER will be administered at the same dose level as the double blinded portion. (mg:mg) switching overnight from the final visit of the double-blind period. IR arm is switched to ER; ER continues on the same.

During the first four weeks of the open-label phase, the need for up-titration or down-titration was assessed by the investigator at an on-site visit and telephone contacts based on judgment of efficacy and tolerability. After this, the maintenance dose should remain the same, though down- or up-titration was allowed based on the investigator's judgment.

## **Protocol Amendments**

Amendment 1 (January 30, 2008)

- Expected adverse reactions list is updated. Down titration for those patients leaving open label trial is clarified.

Amendment 2 (July 14, 2008)

- Dates of the trial are updated with changes to trial administrative structure.

## **Results and Safety Assessment**

This trial is blinded and ongoing. It will have little value from an efficacy point of view given the lack of a placebo control. Available exposure and safety data for deaths, discontinuations and SAEs is discussed in Section 7.

### **5.3.5 Open-label Follow-up Trial 248.633 for Early PD and Overnight Switch Trials.**

#### **Trial**

A double-blind, double-dummy, randomized, parallel-group trial to investigate the safety, tolerability, trough plasma concentration, and efficacy of PPX ER versus PPX IR administered orally for 12 weeks in patients with Parkinson's disease (PD) on L-dopa therapy, followed by a 52-week open-label long-term treatment period to evaluate the long-term safety and efficacy of PPX ER

## **Phase III**

### **Purpose**

To investigate the safety, tolerability, trough plasma concentration, and efficacy of PPX ER in comparison with those of PPX IR administered orally for 12 weeks in patients with Parkinson's disease (PD) on L-dopa therapy (the double blind period). The double-blind period will be followed by the open-label 52-week administration of PPX ER to evaluate the long term safety and efficacy (the open label period).

No primary efficacy endpoints were determined. The primary objective was to determine safety, tolerability, and trough plasma drug levels in a population of PD patients on l-dopa.

### **Trial design**

Double-blind, double-dummy, randomized, parallel group design with active control followed by open-label follow up.

This trial includes a screening phase of up to 4 weeks, then 12 weeks of double-blind period. The double-blind period will be followed by the open-label period for 52 weeks including a 4-week dose adjustment phase after switching from trial medication in the double-blind period to open-label PPX ER. At the end of the trial, patients will perform an additional maximum 1-week down-titration.

The Sponsor's objective was that all the patients should be escalated to maximum dose (PPX 4.5 mg per day) "unless any adverse event occurs, and even if the investigator or sub-investigator finds any significant efficacy with lower doses."

### **Trial Visits (Checklist)**

Double blind portion of trial:

**Table 38 Follow up Trial: double blind visit checklist (source: Sponsor)**

**FLOW CHART (DOUBLE-BLIND PERIOD)**

Trial period	S <sup>1</sup>		B <sup>1</sup>		Double-blind period							
	V1	V2	V3	TC1	V4	TC2	V5	TC3	V6	TC4	V7	V8 <sup>2</sup>
Visit (V)												
Telephone Contact (TC)												
Week												
Day												
Written informed consent	X											
Demographics	X											
Baseline conditions	X											
Inclusion/ Exclusion criteria	X	X										X
Physical examination Weight, Height <sup>3</sup>	X											X
BP, Pulse rate (Supine, standing)	X	X	X		X		X		X		X	X
MMSE	X											
Modified Hoehn and Yahr	X											
Randomisation	X	X										
Medication FAX	X	X										
Instruct/ supply patient diary	X	X	X		X		X		X		X	X
Review patient diary		X	X		X		X		X		X	X
UPDRS part I, II, III, IV		X	X		X		X		X		X	X
CGI-I			X <sup>5</sup>		X <sup>5</sup>		X <sup>5</sup>		X <sup>5</sup>		X <sup>5</sup>	X <sup>5</sup>
PGI-I			X <sup>5</sup>		X <sup>5</sup>		X <sup>5</sup>		X <sup>5</sup>		X <sup>5</sup>	X <sup>5</sup>
ESS		X	X		X		X		X		X	X
Safety lab tests	X						X					X
Pregnancy test	X											
Trough PK sampling	X						X					X
12-lead ECG	X											X
Dispense trial medication		X	X		X		X		X		X	X <sup>4</sup>
Medication compliance			X		X		X		X		X	X
Concomitant therapy	X	X	X		X		X		X		X	X
Adverse events (including record "sudden onset of sleep")	X	X	X		X		X		X		X	X

1. Abbreviations: S=Screening, B=Baseline  
 2. All assessments planned at Visit 8 have to be done even if a patient is prematurely discontinued in the double-blind period and dispense trial medication for the down-titration. All assessments planned at Visit 16 have to be done scheduled at 1-3 weeks +7 after decision of discontinuation in the double-blind period.  
 3. Height will only be measured at Screening (Visit 1)  
 4. At Visit 8, dispense trial medication for open label pramipexole ER according to the switching rule.  
 5. CGI-I and PGI-I must be evaluated compared with those at Visit 2 (baseline)

**Table 39 Open Follow up Trial: open label visit checklist (source: Sponsor)**

**FLOW CHART (OPEN-LABEL PERIOD)**

Trial period	Dose adjustment phase					Maintenance phase							Down-titration V16 <sup>6</sup>	
	TC5	V9	TC6	V10	V11	V12	V13	V14	V15 <sup>6</sup>	V16 <sup>6</sup>				
Visit number <sup>6</sup>	13	14	15	16	18	22	26	30/34	38	42/46	50	54/58 /60	64	65
Day	91±2	98±2	105±2	112±2	126±7	154±7	182±7	210±7/ 238±7	266±7	294±7/ 322±7	350±7	378±7/ 406±7/ 420±7	448±7	455±2
Physical examination							X		X				X	X
BP, Pulse and weight		X		X	X		X		X		X		X	X
Medication FAX														X <sup>11</sup>
Instruct and supply patient diary		X		X	X		X		X		X			
Review patient diary		X		X	X		X		X		X		X	
UPDRS part I, II, III, IV		X		X	X		X		X		X		X	
CGI-I		X <sup>10</sup>		X <sup>10</sup>			X <sup>10</sup>							
PGI-I		X <sup>10</sup>		X <sup>10</sup>			X <sup>10</sup>							
ESS		X		X	X		X		X		X		X	
Safety lab							X		X		X		X	X <sup>8</sup>
ECG							X		X		X		X	X <sup>8</sup>
Dispense trial medication		X		X	X		X		X		X		X	
Check medication compliance	X	X	X	X	X		X		X		X		X	X <sup>7</sup>
Concomitant therapy	X	X	X	X	X		X		X		X		X	X
Adverse events (including record "sudden onset of sleep")	X	X	X	X	X		X		X		X		X	X

6. All assessments planned at Visit 15 and 16 have to be done even if a patient is prematurely discontinued in the open-label period. All assessments planned at Visit 8 and 16 have to be done even if a patient is prematurely discontinued in the double-blind period.
7. At Visit 15, dispense trial medication for the down-titration and at Visit 16, check medication compliance during the down-titration
8. At Visit 15 or at the timing of prematurely discontinuation in the double-blind period, if clinically significant laboratory values or ECG findings are observed, a follow-up test (laboratory test or ECG) must be done at Visit 16.
9. At Visits without visit number, medication compliance, change of concomitant therapy and occurrence of adverse events will be assessed and study medication will be dispensed.
10. CGI-I and PGI-I must be evaluated compared with those at Visit 8
11. When a patient is prematurely discontinued, Medication FAX should be also sent to the sponsor.

**Subject Enrollment**

This trial is in progress and enrollment is ongoing. Numbers at the time of the data cutoffs are discussed in the safety analysis in Section 7.

## **Protocol Amendments**

None.

## **Results and Safety Assessment**

This trial is ongoing. It does not contribute efficacy data. Available exposure and safety data for deaths, discontinuations and SAEs is discussed in Section 7.

### **5.3.6 Open-label Follow-up Trial 248.634 for the Advanced PD Trial**

#### **Trial**

Long-term safety trial of open-label PPX ER in patients with advanced Parkinson's disease (PD).

#### **Phase III**

#### **Purpose**

The primary objective of this trial is to obtain long-term safety and tolerability data on PPX ER (in daily doses from 0.375 mg to 4.5 mg q.d.) in patients who have previously completed a PPX double-blind trial in advanced PD (248.525 trial).

#### **Trial design**

Double-blind transfer phase of up to six weeks followed by an open-label treatment phase of 26 weeks.

#### **Treatments and other ancillary management**

Patients treated with PPX ER or placebo in the previous 248.525 trial will stay on their treatment during the blinded transfer phase. Patients previously treated with PPX IR will be switched to PPX ER over night at the same dose level.

In the transfer phase all patients will stay on their previous dose level for the first week. They will then be down-titrated in a double blind fashion by one dose level per week, starting from their maintenance dose in the previous 248.525 trial (either placebo or active drug).

Simultaneously all patients will start an open-label up-titration with PPX ER. However, in order to maintain the blind, the patients who received PPX ER or IR during the 248.525 trial will get a placebo tablet of the lowest dose (0.375 mg) during the first week. The

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adjustment of the individual optimal dose of PPX ER (0.375 mg to 4.5 mg/day) will be done using the investigator's judgment.

The above procedures was deemed necessary by the sponsor in order to maintain the blinding for patients still being treated in 248.525, as this trial will still be on-going when the open-label extension trial 248.634 will start. The Sponsor also wishes to evaluate the efficacy and safety of switching from PPX IR to PPX ER at the same dose level (mg: mg dose).

In the open label phase of 26 weeks, all patients will be treated with PPX ER. Dose-adjustment (down- or up-titration) of PPX ER open-label is allowed.

### **Trial Visits**

**Table 40 Advanced PD Trial: open follow up visit checklist (source: Sponsor)**

**FLOW CHART**

Trial periods	B <sup>1</sup>		Transfer phase						OL phase						EOT-Taper-down phase V10 <sup>3</sup>
	V1	V2	TC1	V3	TC2	V4	TC3	V5	V6	V7	V8	V9 <sup>3</sup>			
Visit	0	1	2	3	4	5	6	8	14	20	26	32	33		
Weeks	0	7±2	14±2	21±2	28±2	35±2	42±2	56±2	98±7	140±7	182±7	224±7	231±3		
Written informed consent	X														
In-/ Exclusion criteria	X														
Record medical history	X														
Physical examination	X <sup>2</sup>										X <sup>7</sup>				
Ophthalmologic monitoring															
BP, Pulse, Weight	X <sup>2</sup>	X		X		X		X	X	X	X	X	X		
Instruct and supply patient diary	X	X		X		X		X	X	X	X	X	X		
Review patient diary	X <sup>2</sup>	X		X		X		X	X	X	X	X	X		
Hoehn and Yahr	X														
UPDRS part I, II, III, IV	X <sup>2</sup>	X		X		X		X	X	X	X	X	X		
CGI-I	X	X		X		X		X	X	X	X	X	X		
PGI-I		X		X		X		X	X	X	X	X	X		
PGI-I for early morning off-symptoms								X							
ESS	X <sup>2</sup>			X				X							
PFS-16	X														
Safety lab tests	X <sup>8</sup>														
Urinary pregnancy test <sup>4</sup> (if applicable)	X														
12 lead-ECG	X <sup>8</sup>														
Dispense/ re-dispense trial medication	X	X		X		X		X	X	X	X	X <sup>5</sup>	X		
Check medication compliance	X	X	X	X	X	X	X	X	X	X	X	X	X <sup>6</sup>		
Concomitant therapy	X	X	X	X	X	X	X	X	X	X	X	X	X		
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X		

1. Visit 1 of the 248.634 trial will be conducted on the same day as the last treatment visit (i.e. visit 11 of maintenance phase) of the previous DB trial (248.525)  
 2. Baseline assessments for trial 248.634 will be obtained from the last visit (i.e. visit 11 of maintenance phase) of the previous DB trial (248.525)  
 3. All assessments planned at visit 9 and at visit 10 have to be done even if a patient is prematurely withdrawn from trial 248.634  
 4. In case requested by EC, further urinary pregnancy tests can be done locally on a regular basis  
 5. At visit 9, dispense study medication for the down-titration phase  
 6. At visit 10, check medication compliance during the down-titration phase  
 7. At visit 8, patients will be referred to an ophthalmologist for an ophthalmologic monitoring (vision control and funduscopy). Results should be available for visit 9  
 8. Baseline laboratory assessments and 12-lead ECG for trial 248.634 will be checked from the last visit (i.e. visit 11 of maintenance phase) of the previous DB trial (248.525)  
 B = Baseline, DB = double blind, OL = open label, EOT = end of trial

### **Subject Enrollment:**

This trial is in progress and enrollment is ongoing. Numbers at the time of the data cutoffs are discussed in the safety analysis in Section 7.

### **Protocol Amendments**

Amendment 1 (January 21, 2008)

- The trial duration was extended by 48 weeks to collect long-term safety data.
- The Modified Minnesota Impulsive Disorder Interview (MMIDI) and a simple (no/yes) question about any other abnormal behaviors or urges were added.
- Patients should be referred to a psychiatrist to evaluate for and confirm the diagnosis of impulse control disorder or other psychiatric disorder, in the event of a positive screening.
- The formula used in 248.525 will be used to calculate the creatinine clearance.
- The new expected adverse reactions under the use of PPX were described as in 248.525 and 248.634.

### **Results and Safety Assessment**

This trial is ongoing. It does not contribute efficacy data. Available exposure and safety data for deaths, discontinuations and SAEs is discussed in Section 7.

#### **5.3.7 Fibromyalgia Trial (248.637)**

**Title:** A randomized, double-blind, placebo-controlled, dose titration, efficacy and safety trial of PPX ER (0.75 mg to 4.5 mg) administered orally once daily versus placebo over a 16-week maintenance phase in patients diagnosed with fibromyalgia as assessed by the American College of Rheumatology (ACR) criteria, followed by a 24-week open-label extension phase.

**Synopsis:** Included here for the sake of completeness, this is a multi-national, multi-center, randomized, DB, placebo-controlled, dose titration, efficacy and safety trial of PPX ER (0.75 mg to 4.5 mg) administered orally once daily versus placebo over a 13-week up-titration phase and a 16-week maintenance phase in patients diagnosed with fibromyalgia (FM), as defined by the American College of Rheumatology (ACR) criteria, followed by a 24-week open-label extension phase and a 1-week down-titration. In this trial, patients were up-titrated to an effective and tolerated PPX ER dose, and then continued at this dose through the maintenance phase and the 24-week open-label extension phase.

This trial was ongoing at time of the cut-off date September 1, 2008, with 11 patients randomized and treated with DB medication.

## 6 Review of Efficacy

A single efficacy trial was submitted by the Sponsor: Study 248.524 “A double-blind, double-dummy, placebo-controlled, randomized, three parallel groups study comparing the Efficacy, Safety and Tolerability of PPX ER versus placebo and versus PPX IR administered orally over a 26-week maintenance phase in patients with early Parkinson’s disease (PD)” .

This sole pivotal trial in early PD is detailed in Section 5.3.1 above. An interim analysis at 18 weeks was submitted for proof of efficacy. The findings are summarized in this section for the reader’s convenience. In brief, the Sponsor demonstrates that Mirapex ER has the ability to reverse the motor symptoms and disability in early PD as demonstrated by the UPDRS Parts II + III. This finding was corroborated by the global impression of both the investigator and the patient (CGI).

The reviewer’s comment from Section 5.3.1 is repeated here for emphasis:

***Reviewer’s Note: This analysis section was completed prior to the discovery of data integrity issues from one of the audited trial sites. Exclusion of the efficacy data derived from the five patients contributed by this site does not change the efficacy result. As a result the analysis below was not changed and includes this site. The primary statistical review covers this issue more fully.***

***In brief, the statistical reviewer indicates that with the 5 subjects from SITEID=USA-s01 excluded, the LS mean change in UPDRS is changed from -5.1, -8.1, and -8.4 (Table 11.4.1.1.1:1 in sponsor’s clinical study report, page 98) to -5.1, -8.1 and -8.6 for placebo, PPX ER and PPX IR, respectively. The p-value is changed from 0.0282 (PPX ER vs. placebo) and 0.0016 (PPX IR vs. placebo) to 0.0330 (PPX ER vs. placebo) and 0.0018 (PPX IR vs. placebo).***

***The analysis datasets submitted by the Sponsor contained a single systematic error that likely occurred due to a mistake compiling the final datasets for the NDA submission. The sponsor inadvertently submitted a key variable’s coded value in place of the actual value. The sponsor’s explanation of the data error was consistent with our findings. The analysis and conclusions concerning efficacy and safety were not affected by this error. The sponsor complied with a request to re-audit the datasets submitted in the NDA package, which did not reveal any additional errors. The reviewer is satisfied that they do not represent a risk to the integrity of the efficacy results.***

### 6.1 Indication

The Sponsors proposed labeling is for the treatment of the signs and symptoms of idiopathic Parkinson’s disease. While short term efficacy is demonstrated for early PD, no evidence of long term maintenance of effect is provided, nor is efficacy data for the

treatment of advanced PD submitted. The sponsor has submitted a second efficacy supplement for approval of Mirapex ER for the treatment of patients with advanced PD. If both efficacy supplements are approved, it may permit consolidation of the Sponsor's claim to "treatment of the signs and symptoms of Parkinson's disease", consistent with the approved indication for Pramipexole IR.

### **6.1.1 Methods**

A double blind, double dummy trial of PPX ER (once a day) versus PPX IR (t.i.d.) versus placebo in early PD was performed. After an initial titration period to usual therapeutic doses, an interim analysis was performed when approximately 250 patients reached the 18th week of this 33 week trial. At that time, the "last observation carried forward" was used for statistical analysis of the primary and secondary endpoints. Baseline values of the primary endpoint (UPDRS II + III) were used as a covariate for ANCOVA. Clinical Global Impressions were dichotomized for contingency table non-parametric analysis, separating "very much improved" and "much improved" subjects from the remainder of the population.

### **6.1.2 Demographics**

The treatment population closely modeled parameters which describe the usual PD population found in the community: mean age 61 years with median age 62 years (range 30 - 83). Gender (M : F 1.3 : 1), racial distribution and severity of illness were also consistent.

### **6.1.3 Subject Disposition**

296 subjects were screened and 259 subjects were enrolled in this efficacy cohort. Roughly 2/3 of patients were on some concomitant anti-PD therapy (equally distributed among the trial arms) which was held constant during the trial for all but 13 subjects. Six subjects were excluded due to lack of a post treatment observation for the primary outcome variable. At the end, 253 were suitable for this reviewer's analysis set.

### **6.1.4 Analysis of Primary Endpoint(s)**

The primary endpoint was the change from baseline of the sum of Parts II (Activities of Daily Living) and Part III (Motor Function) score of the UPDRS (Unified Parkinson's Disease Rating Scale, assessed at the week 18 visit. Courtesy of the primary statistical review, the mean change in UPDRS from baseline was -5.1, -8.1 and -8.6 for placebo, PPX ER and PPX IR, respectively. The p-value is 0.0330 (PPX ER vs. placebo) and 0.0018 (PPX IR vs. placebo).

### **6.1.5 Analysis of Secondary Endpoints(s)**

The key secondary criteria were the Clinical Global Impression of Improvement (CGI-I) and Patient Global Impression of Improvement (PGI-I) responder rates. Investigators felt that 36 of 102 subjects taking MPX ER were “very much improved” or “much improved”, while 9 of 50 placebo subjects were so characterized ( $\chi^2$ ,  $p = 0.0109$ ).

Patients rated themselves similarly; 36 of 102 taking MPX ER called themselves “very much improved” or “much improved”, while 6 of 50 placebo subjects considered themselves better ( $\chi^2$ ,  $p = 0.0009$ ).

This concordance is not surprising to the reviewer. From my clinical trial experience the CGIs are often evaluated right after one another during the research visit as the investigator goes through the trial procedures. Perceptions are often shared between the investigator and subject at that time (as well as throughout the period of trial) and I would consider these measures very much inter-related, duplicating a consensus between them.

The sponsor also includes figures of comparison to immediate release MPX, but the trial was neither designed nor powered for non-inferiority comparison.

### **6.1.6 Other Endpoints**

The trial was not designed for the evaluation of the many other measurement scales performed. These included scales for mood, evaluation of nocturnal sleep problems, pain, and quality of life. Analysis, which this reviewer would consider only exploratory, revealed no significant changes from baseline.

### **6.1.7 Subpopulations**

No important effect of subpopulation was found: age, race, gender, country where enrolled.

### **6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations**

Because there is a fairly close pharmacodynamic effect to the immediate release product, it may be used on a 1:1 mg for mg basis. Therefore, current dosing guidelines for the IR product in the general PD population may be extended to the ER product.

### **6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects**

Because of the short term nature of this trial, no comment may be made upon persistence of therapeutic efficacy of the PPX ER formulation. The Sponsor did a subgroup analysis of subjects reaching 33 weeks of treatment but due to

methodological considerations, it is not clear that this substantiates or refutes the possibility of tachyphylaxis to therapeutic effect.

#### **6.1.10 Additional Efficacy Issues/Analyses**

Insufficient information is currently available concerning attenuation of medication effect over time. Insufficient information is available as to efficacy in advanced PD with motor fluctuation. The brittle patient with on-off syndrome may be a more sensitive indicator of pharmacodynamic equivalence between the IR and ER formulations. This trial (Study 248.525) is in progress. Until then, evidence of efficacy in advanced disease is not available.

### **7 Review of Safety**

#### **Safety Summary**

It is this reviewer's opinion that PPX ER has substantially the same safety profile as the IR formulation with which there is over a decade's experience. This includes an increased risk for adverse events related to nausea and vomiting, sleep, behavioral aberrations, hallucinations, and orthostasis. While not a focus of this early PD experience it appears that PPX ER may increase the presence of dyskinesia in advanced PD.

No significant risk of injury to liver, kidney, or the hematopoietic system was identified.

Multiple dosage forms which look alike may pose a hazard and increase the risk of medication dispensing errors both institutionally and at home.

It is noted that the periods of active treatment that contribute to the safety analysis in the double blind placebo controlled trials are quite short. This reviewer's concern is that an inadequate period of exposure has been observed and it is difficult to fully determine the incidence of treatment emergent adverse events, especially behavioral ones. This is especially true in the Advanced PD trial (248.525) with the small amount of data contributed by patients by the time of the submission cutoff.

#### **7.1 Methods**

The original cut off of May, 2008 was extended by the 120 day safety update to September 1, 2008 and December 1, 2008 for all SAEs and deaths. At the time of the 120 day safety update, no electronic AE data files were submitted with the narrative summaries. The Sponsor indicates that the occurrence of adverse events were not different for the two time periods. All CRFs for deaths, nonfatal SAEs, AEs leading to discontinuation of treatment, and cases of impulse control disorders have been individually reviewed and verified up to the indicated cut-off dates.

Review of the CRFs for deaths and serous adverse events which were generated electronically reveals a paucity of detail. The narratives were adequate. One death which occurred during the screening period before medication administration in Study 248.610 (presumably after consent) was not reported in the safety summaries but was found in the listings of individual patients.

984 subjects have been exposed to at least a single dose of PPX ER in the Sponsor's development program. Because blinded trials are ongoing, there are a certain number of patients whose treatment assignment cannot be determined at the time of this review. They are listed as "unknown" in the tables below. This also has limited the ability of this review to understand the dose proportionality of treatment emergent side effects. The reviewer was also unable to clarify which exact patients from a given treatment arm in double blind studies went on to enter the open label follow-up trials. After request to the Sponsor, we do know the numbers of subjects who began to take open label ER after being in the blinded IR or placebo arms, and who entered open label ER from the ER blinded arm. (This revealed double counting of 240 individuals by the sponsor.) We do not know modal dose and duration of exposure to ER in the open label trials up to the safety update cut off date. Datasets from open-label follow-up trials were not submitted.

Much of this confusion likely results from the submission of data from trials that are ongoing while trying to maintain trial integrity. It has greatly added to the review time and manipulation of data by the reviewer. In addition, the quality of the dataset structure was poor. They were "ADaM-oid" in following some conventions of CDISC Analysis Data Model but lacked basic ones such as conforming unique subject identification across analysis datasets.

Additional requests were made to the Sponsor for clarification of the data electronic submission for this as well as other issues such as incomplete data related to the doses at which adverse events occurred and their time of occurrence and concurrent medication. These are included in the review to give a flavor for the disorganization of the submission and were communicated to the Sponsor as follows:

March 6, 2009 - Request for additional data re: NDA 22-421 Mirapex ER

In Study 248.524 it is evident from Tables 11.2.1:4 and 11.2.1:5 in Doc. No. U08-1826-01 that additional anti PD medication was used during the trial for a number of subjects. However, based on data set inder\_1.xpt submitted in January, 2009, it is not clear that if there was any addition or change in rescue or concomitant medication before a patient completed Visit 8 (week 18). Therefore, please ADD the following variables to data set inder\_1 and submit to the Agency:

- A variable indicating USUBJID corresponding to the PTNO for each subject;
- A variable indicating whether or not a patient completed Visit 8 (completer vs. non-completer);
- For each of the following rescue/concomitant medications, levodopa, amantadine, anticholinergics and / or MAOB-I, a variable indicating whether or not it was taken for each patient and each visit (Yes vs. No).

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- For primary endpoint (UPDRS II+III) and each of the key secondary endpoints (PGI and CGI), respectively, a variable with the last non-missing value before the start of any rescue/concomitant medicine carrying forward (LOCF); that is, values recorded after the start of any rescue/concomitant medicine were replaced by carrying forward the last non-missing value recorded before the start of any rescue/concomitant medicine.

In Study 248.524, to the adverse event data file, AE.xpt, please add the following:

- A variable for each visit number indicating whether the reported AE occurred at that visit (Yes vs. No);
- A variable indicating the dose at which this AE first occurred (numerical value, mg PPX/day).
- A variable indicating treatment arm: TPATTSLB

In addition, please update the data definition tables for these datasets accordingly.

March 6, 2009 - Request for clarification re: NDA 22-421 Mirapex ER

We understand from the protocol for Study 248.524 that patients who required anti-PD rescue medication (only I-Dopa+) were to be seen and evaluated before beginning medication and that this would be the last observation carried forward for the efficacy analysis. However, two tables in Study Doc. No. U08-1826-01 are not clear to us. Looking at Table 11.2.1:4, previous anti-parkinson therapy, it appears that 24 subjects were on medication, including 6 who were excluded from FAS1 because of I-dopa. Then in Table 11.2.1:5, 157 subjects have concomitant medications, with only 13 using levodopa. It appears that some subjects were taking more than one drug (216 occurrences in 157 patients). This has raised the following questions for us:

1. Were rescue drugs other than I-dopa+ used?
2. When (i.e. visit number) were these additional medications begun for each subject?
3. What adjustments of any anti-parkinson medications occurred during the titration and maintenance periods in the trial?
4. Were there any adjustments in dose of pre-trial anti-parkinson medication at any time during the titration and maintenance period?

For items 2, 3, and 4, we would like to know for which subjects and for which drugs and at what visit(s) this occurred. This may be presented in a data file using standard format.

A narrative explaining this would also be helpful in evaluating whether these represent possible protocol deviations. It is understood that this may require considerable effort on short notice, but it is critical to our timely evaluation of your submission.

In addition, a request from statistics was made at this time:

For data set inder\_1 submitted in January, 2009, some variables are not consistent with the same variables in other data sets in original submission. For example, subject ID number is named SUBJID in dm.xpt while named PTNO in inder\_1; SEX is set as a character variable in dm.xpt while as a numeric variable in inder\_1. Please make the variables in inder\_1 consistent with the variables in other data sets in terms of variable name and type. This request also applies to the new variables to be added to inder\_1 as requested by the Agency on March 6, 2009.

In addition, for variable COUNTRY in inder\_1, the country names are not consistent. For example, Germany is coded as 'DEU' or 'Germany' and Taiwan is coded as 'CHN' or 'Taiwan'. Please make corrections.

On April 10, 2009 we asked for absent case report forms for a case of hepatic dysfunction fulfilling criteria for Hy's Law and to clarify the possible double counting of subjects in open label trials:

Subject: Request for additional data re: NDA 22-421 Mirapex ER

1) Kindly provide case report forms and any additional medical information for Subject No. 1033 in Study 248.530 that would clarify the nature of the subject's liver dysfunction and its cause.

2) In calculating exposure data for Mirapex ER, we have been unable to clarify which patients from a given treatment arm in double blind studies went on to enter the open label follow-up trials. Specifically, we do not know who began to take open label ER after being in the blinded IR or placebo arms, and who entered open label ER from the ER blinded arm. We also do not know modal dose and duration of exposure to ER in the open label trials up to the safety update cut off date.

Our understanding is that only "subjects not discontinued," as indicated in your study reports, would be eligible for open label drug. If we are incorrect in this assumption, please correct the numbers of subjects eligible for open label treatment indicated in the chart below, and complete the rest.

**Figure 12 Requested data template to clarify double counting of PPX ER patients in follow up trials**

"Subjects not discontinued"	N	How many completers in each of these arms went on to ER open label?	Modal dose (mg/d) in open label group	Duration, to cut off date
Study 248.636 Switch		Open Label Study 248.633		
ER	100			
IR	49			

Study 248.524 Early PD		Open Label Study 248.633		
Placebo	92			
ER	175			
IR	181			

Study 248.525		Open Label Study 248.634		
Placebo	140			
ER	125			
IR	149			

### 7.1.1 Studies/Clinical Trials Used to Evaluate Safety

It is noted below in some sections where PPX studies relevant to this application were performed using the IR formulation and not repeated using the ER dosage form. IR Labeling is also referred to in some sections where it would apply equally to both the IR and ER formulations.

The trials and enrollments of exposed individuals are listed below. The full description of these trials may be found in Section 5.

- Safety and comparability of overnight switch from PPX IR to PPX ER (248.636)
- Safety data from the ongoing Phase III trial in early PD (248.524)
- Safety data from the ongoing Phase III trial in advanced PD (248.525)
- Safety data from open label extension trials (248.633 and 248.634)
- Safety data from efficacy safety and PK trial in advanced PD (248.610)
- Safety data from Phase II trial in fibromyalgia (248.637)
- QTc trial (248.545) see Section 7.4.5

Only two datasets offer blinded comparison of PPX ER and placebo. These are treatment cohorts from the trials of PPX ER in early and advanced PD. Not all trials contribute to all sections of the safety review. At the beginning of each section the datasets which were submitted for review are specified.

This table indicates the sum of all prospectively collected safety data from blinded trials for this submission. Additional data from the studies for advanced PD and the active control trial in PD patients on levodopa remains blinded and is not reflected in this table:

**Table 41 Double blind placebo controlled subjects contributing to safety data**

	Early PD 248.524	Advanced PD 248.525	Total N
PPX ER	223	147	370
PPX IR	213	164	377
Placebo	103	165	268

**Table 42 Subject exposure to PPX ER in Phase III trials (N = 842)**

	248.524	248.525	248.636	248.633 #	248.634 #	248.610	248.637
	Early PD	Adv PD	Overnight switch	Open label extension	Open label extension	Active IR comparison and open follow-up in Japan	Fibro myalgia
PPX ER	223	147	104	359	197	52 *	
PPX IR	213	164	52				
Placebo	103	165					
Unknown		34				112	11

N.B.: The sponsor double-counted 240 DB PPX ER subjects going into OL safety extensions: Early PD 85, Overnight Switch 95, Advanced PD 60, as of the cut-off date for data submission.

Notes:

\*completed subjects from the 112 who are in the ongoing double blinded portion of the trial

# Because the blinds remain unbroken in the related feeder double-blind studies, it is not possible to present the safety data stratified by former double-blind treatment assignment.

**Table 43 Subject exposure to PPX ER in Phase I-II trials (N = 142)**

Type of Trial	Trial	Objective	Design	PPX ER (N)	Duration
Bioavailability	248.529	Compare seven ER prototypes	OL	14	4 days
Bioequivalence	248.530	PPX ER vs. PPX IR; food effect at 4.5 mg /d	DB	39	7 days
Bioequivalence	248.607	PK of PPX ER vs. IR in Japanese subjects	OL	24	4 weeks
Bioavailability	248.560	In vitro / in vivo food interaction	OL	15	Single dose
Safety	248.545	Thorough QT	DB	50	7 weeks

### 7.1.2 Categorization of Adverse Events

MedDRA Version 11.0 was used for coding of adverse events by the Sponsor. AEs were considered by the Sponsor to be treatment emergent if they occurred after first

drug intake until 2 days after last drug ingestion. The two day period is a bit short for the elderly who have a  $\frac{1}{2}$  life of the drug of about 12 hours (versus 8 h in healthy volunteers). AEs outside of this timeframe were assigned to screening or post-treatment assessment periods by the Sponsor.

The Sponsor’s coding, as elaborated upon below exhibited poor translation of verbatim reports to Preferred Terms. In one case, for example, “increase in “on” period” was coded as a menstrual disorder. This suggests either computerized coding or inexpert review and prompted a careful review of all AEs. Splitting was also a common problem as demonstrated below in the case of sleep disorders and behavioral side-effects.

### 7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Because the only blinded, placebo controlled safety data comes from the early and advanced PD treatment trials, they are not pooled. These represent different populations with regard to length of disease and therefore different susceptibilities to certain adverse events, e.g.: orthostatic hypotension, falls, and behavioral disturbances.

## 7.2 Adequacy of Safety Assessments

### 7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The tables below indicate the mean and modal doses of PPX ER given to subjects and the duration of treatment in the blinded trials. The Overnight Switch Trial 248.636 does not offer a placebo controlled arm for comparison so the other two trials are used for safety comparisons.

**Table 44 Dose exposure / duration in double blind trials**

Subjects on PPX ER	N	Final Trial Dose mg (+/- SD)	Duration days (+/- SD)
DB Study 248.636 Switch	100	2.7 (0.9)	63 (9)
DB Study 248.524 Early PD	175	2.9 (1.4)	184 (70)
DB Study 248.525 Adv PD	125	2.7 (1.4)	197 (70)

**Table 45 Subjects continuing from double blind trials to open label extensions**

"Subjects not discontinued"	N	How many completers in each of these arms went on to ER open label?	Mean Daily Dose: Mg (+/- SD)	Modal dose (mg/d)	Duration (d +/- SD)
Study 248.636 Switch		Open Label Study 248.633			
ER	100	95	2.9 (1.0)	3	150 (33)
IR	49	48	2.9 (1.0)	3	148 (35)
Study 248.524 Early PD		Open Label Study 248.633			
Placebo	92	47	2.3 (1.4)	3	88 (53)
ER	175	85	3.1 (1.2)	4.5	97 (54)
IR	181	84	3.2 (1.4)	4.5	88 (52)
Study 248.525		Open Label Study 248.634			
Placebo	140	65	1.8 (1.3)	0.75	82 (52)
ER	125	60	2.5 (1.4)	1.5	97 (58)
IR	149	72	2.6 (1.4)	4.5	91 (69)

The distribution of demographics for subjects in these trials was appropriate for the disease state and reflected the population affected by PD as reported in the peer reviewed scientific literature. Appropriate numbers of subjects were studied above and below the age of 65. Children are not affected by this illness.

**Age at Onset of PD - Early PD Trial**

**Quantiles**

100.0% maximum	84.0
75.0% quartile	68.0
50.0% median	62.0
25.0% quartile	55.0
0.0% minimum	30.0

Mean	61.25
Std Dev	9.95
Std Err Mean	0.41
upper 95% CI	62.05
lower 95% CI	60.45
N	599

**Age at Onset of PD – Advanced PD Trial**

**Quantiles**

100.0% maximum	84.0
75.0% quartile	65.0
50.0% median	57.0

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25.0%	quartile	49.0
0.0%	minimum	24.0
Mean		56.29
Std Dev		11.13
Std Err Mean		0.46
upper 95% CI		57.19
lower 95% CI		55.39
N		596

### **Baseline "Off" State Hoehn and Yahr Stage - Advanced PD Trial Frequencies**

<b>Stage</b>	<b>N</b>	<b>Prob</b>
Stage 2	(87)	0.14597
Stage 2.5	(191)	0.32047
Stage 3	(204)	0.34228
Stage 4	(94)	0.15772
Stage 5	(12)	0.02013
Total	(596)	1.00000

### **7.2.2 Explorations for Dose Response**

The numbers of subjects and the dosage range to which they are exposed for the double blinded portion of this safety assessment are small, but larger than the numbers used for efficacy data in the interim analysis.

The following Sponsor's tables are taken from the Integrated Summary of Safety (ISS, Table 1.2.5.6) and reflect the exposures for the larger TS3 populations at the time of the data cutoff for the first data cutoff, which corresponds to the individual data sets submitted by the sponsor. No further data sets were submitted in the 4 Month Safety Update.

These indicate an appropriate distribution of dose and duration across the treatment groups.

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**Table 46 Early PD Trial: dose exposure by group (source: Sponsor)**

Study: 0248_0524	PPX ER 0.375-1.5 mg/day	PPX ER 2.25-3 mg/day	PPX ER 3.75-4.5 mg/day	Total
Number of patients (%)	63 ( 28.3)	68 ( 30.5)	92 ( 41.3)	223 (100.0)
Duration of exposure, in days				
Mean (SD)	102.8 (76.8)	121.0 (66.2)	139.2 (67.4)	123.4 (71.1)
Min	1	27	40	1
Q1	45.0	63.5	83.0	65.0
Median	90.0	103.0	131.0	107.0
Q3	174.0	175.0	204.0	187.0
Max	238	236	238	238
Exposure in weeks [N (%)]				
N	63 (100.0)	68 (100.0)	92 (100.0)	223 (100.0)
< 1 week	8 ( 12.7)	0 ( 0.0)	0 ( 0.0)	8 ( 3.6)
1 - < 4 weeks	5 ( 7.9)	1 ( 1.5)	0 ( 0.0)	6 ( 2.7)
4 - < 8 weeks	6 ( 9.5)	14 (20.6)	10 (10.9)	30 (13.5)
8 - <13 weeks	13 (20.6)	16 (23.5)	22 (23.9)	51 (22.9)
13 - <18 weeks	9 (14.3)	6 ( 8.8)	12 (13.0)	27 (12.1)
18 - <28 weeks	9 (14.3)	18 (26.5)	23 (25.0)	50 (22.4)
>=28 weeks	13 (20.6)	13 (19.1)	25 (27.2)	51 (22.9)

**Table 47 Advanced PD Trial: dose exposure by group (source: Sponsor)**

Study: 0248_0525	PPX ER 0.375-1.5 mg/day	PPX ER 2.25-3 mg/day	PPX ER 3.75-4.5 mg/day	Total
Number of patients (%)	62 ( 42.2)	41 ( 27.9)	44 ( 29.9)	147 (100.0)
Duration of exposure, in days				
Mean (SD)	144.6 (85.8)	149.7 (75.5)	138.3 (64.6)	144.1 (76.7)
Min	3	23	39	3
Q1	53.0	60.0	79.5	64.0
Median	169.0	171.0	134.5	162.0
Q3	227.0	214.0	202.5	224.0
Max	249	238	238	249
Exposure in weeks [N (%)]				
N	62 (100.0)	41 (100.0)	44 (100.0)	147 (100.0)
< 1 week	2 ( 3.2)	0 ( 0.0)	0 ( 0.0)	2 ( 1.4)
1 - < 4 weeks	6 ( 9.7)	1 ( 2.4)	0 ( 0.0)	7 ( 4.8)
4 - < 8 weeks	8 (12.9)	8 (19.5)	6 (13.6)	22 (15.0)
8 - <13 weeks	5 ( 8.1)	2 ( 4.9)	7 (15.9)	14 ( 9.5)
13 - <18 weeks	1 ( 1.6)	3 ( 7.3)	6 (13.6)	10 ( 6.8)
18 - <28 weeks	16 (25.8)	12 (29.3)	13 (29.5)	41 (27.9)
>=28 weeks	24 (38.7)	15 (36.6)	12 (27.3)	51 (34.7)

The demographic data for the TS 3 cohorts in these trials are found in ISS p 103, Table 1.3.2.1.9 and 10:

**Table 48 Early PD Trial: exposure by gender age and race (source: Sponsor)**

Study: 0248_0524	Male			Female		
	Placebo	Pramipexole ER	Pramipexole IR	Placebo	Pramipexole ER	Pramipexole IR
Number of patients	51	125	121	52	98	92
Race [N (%)]						
White	35 (68.6)	84 (67.2)	75 (62.0)	31 (59.6)	59 (60.2)	58 (63.0)
Asian	16 (31.4)	41 (32.8)	46 (38.0)	21 (40.4)	39 (39.8)	34 (37.0)
Age						
Mean (SD)	63.1 ( 8.6)	61.2 ( 9.7)	61.1 (10.6)	60.9 (10.4)	61.5 (10.1)	62.4 ( 8.1)
Age classes [N (%)]						
<65	27 (52.9)	77 (61.6)	67 (55.4)	28 (53.8)	54 (55.1)	52 (56.5)
>=65	24 (47.1)	48 (38.4)	54 (44.6)	24 (46.2)	44 (44.9)	40 (43.5)
PD status [N (%)]						
Early PD	51 (100.0)	125 (100.0)	121 (100.0)	52 (100.0)	98 (100.0)	92 (100.0)
Advanced PD	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)

**Table 49 Early PD Trial: exposure by age class (source: Sponsor)**

Study: 0248_0524	<65			>=65		
	Placebo	Pramipexole ER	Pramipexole IR	Placebo	Pramipexole ER	Pramipexole IR
Number of patients	23	57	57	27	49	46
Gender [N (%)]						
Male	10 (43.5)	37 (64.9)	32 (56.1)	13 (48.1)	25 (51.0)	27 (58.7)
Female	13 (56.5)	20 (35.1)	25 (43.9)	14 (51.9)	24 (49.0)	19 (41.3)
Race [N (%)]						
White	14 (60.9)	29 (50.9)	32 (56.1)	18 (66.7)	38 (77.6)	30 (65.2)
Asian	9 (39.1)	28 (49.1)	25 (43.9)	9 (33.3)	11 (22.4)	16 (34.8)
Age						
Mean (SD)	55.8 (6.8)	54.8 (7.0)	56.1 (5.8)	69.6 (3.7)	69.4 (4.4)	69.2 (4.0)
PD status [N (%)]						
Early PD	23 (100.0)	57 (100.0)	57 (100.0)	27 (100.0)	49 (100.0)	46 (100.0)
Advanced PD	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)

**Table 50 Advanced PD Trial: exposure by gender age and race (source: Sponsor)**

Study: 0248_0525	Male			Female		
	Placebo	Pramipexole ER	Pramipexole IR	Placebo	Pramipexole ER	Pramipexole IR
Number of patients	87	81	92	78	66	72
Race [N (%)]						
White	47 (54.0)	42 (51.9)	43 (46.7)	37 (47.4)	29 (43.9)	36 (50.0)
Asian	40 (46.0)	39 (48.1)	49 (53.3)	41 (52.6)	37 (56.1)	36 (50.0)
Age						
Mean (SD)	60.3 (10.4)	62.3 ( 9.5)	60.9 (10.3)	60.9 ( 9.3)	60.7 (10.5)	63.3 (10.6)
Age classes [N (%)]						
<65	49 (56.3)	42 (51.9)	60 (65.2)	49 (62.8)	41 (62.1)	34 (47.2)
>=65	38 (43.7)	39 (48.1)	32 (34.8)	29 (37.2)	25 (37.9)	38 (52.8)
PD status [N (%)]						
Early PD	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)
Advanced PD	87 (100.0)	81 (100.0)	92 (100.0)	78 (100.0)	66 (100.0)	72 (100.0)

**Table 51 Advanced PD Trial: exposure by age group (source: Sponsor)**

Study: 0248_0525	<65			≥65		
	Placebo	Pramipexole ER	Pramipexole IR	Placebo	Pramipexole ER	Pramipexole IR
Number of patients	68	62	70	48	42	47
Gender [N (%)]						
Male	33 (48.5)	30 (48.4)	46 (65.7)	26 (54.2)	28 (66.7)	25 (53.2)
Female	35 (51.5)	32 (51.6)	24 (34.3)	22 (45.8)	14 (33.3)	22 (46.8)
Race [N (%)]						
White	21 (30.9)	14 (22.6)	18 (25.7)	26 (54.2)	24 (57.1)	28 (59.6)
Asian	47 (69.1)	48 (77.4)	52 (74.3)	22 (45.8)	18 (42.9)	19 (40.4)
Age						
Mean (SD)	54.4 (6.2)	55.1 (7.2)	54.8 (7.8)	69.9 (4.0)	70.9 (4.2)	71.7 (5.1)
PD status [N (%)]						
Early PD	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)
Advanced PD	68 (100.0)	62 (100.0)	70 (100.0)	48 (100.0)	42 (100.0)	47 (100.0)

### 7.2.3 Special Animal and/or In Vitro Testing

No additional animal testing was performed for this ER formulation. The findings and concerns prompted by original preclinical studies for the PPX IR NDA apply. For example, ophthalmological examination was performed in response to a signal (degeneration and loss of photoreceptor cells) found in albino rats in a two year carcinogenicity study. This finding was not replicated in other species (albino mice, monkeys, and minipig).

### 7.2.4 Routine Clinical Testing

The collection of safety data by the sponsor was appropriate and adequate as indicated by the assessment checklists and trial events as noted in the summaries in Section 5. One exception to this was the omission of creatine (CK). Along with clinical examination including vital signs, electrocardiography, hematological and serological parameters, special emphasis was placed upon adverse events known to occur with the class of dopamine agonists. These include:

- Nausea and vomiting
- Falling asleep during activities of daily living
- Symptomatic orthostatic hypotension
- Falls
- Hallucinations
- Dyskinesia
- Behavioral abnormalities
- Retinal pathology
- Rhabdomyolysis
- Renal insufficiency

The major focus of this safety assessment is the population used in double blinded placebo controlled trials. Safety assessments from studies without placebo control were inspected for outliers in the data.

The conditions for collection and type of safety data in Study 248.524 Early PD and Study 248.525 Advanced PD were identical. The chart below indicates when they were collected:

**Table 52 Safety monitoring in early and advanced PD trials**

	Physical Exam	Ophthal Exam	Vital Signs	Queried about Abnormal Behavior	MMIDI	ESS	12 Lead ECG	Safety Lab Tests
Screening	X	X	X				X	X
Baseline			X		X	X		
Week 2			X	X				
Week 4			X	X		X		
Week 6			X	X				
Week 8			X		X	X		
Week 13			X	X				X
Week 18			X		X	X		
Week 23			X	X				
Week 28		X	X	X				
Week 33	X		X		X	X	X	X
Week 34			X		X		X	X

Vital signs: systolic and diastolic blood pressure and heart rate. This was performed supine after 5 minutes rest, then after 1 minute standing. Only symptomatic orthostasis was recorded as an event.

Skin: a skin examination was performed by the investigator to look for melanoma. (Short duration trials are inadequate to explore the effect of dopamine drug exposure upon the risk of developing melanoma. This was a safety precaution)

Ophthalmological examination (vision and fundoscopy) was performed at screening and the end of trial.

Electrocardiography was performed at screening and end of trial, as well as in a thorough QT trial.

Clinical laboratory was performed at baseline, mid trial and end of trial:

Hematology: hematocrit, hemoglobin, erythrocyte count, white blood cell count (total and differential: lymphocytes, monocytes, neutrophils, eosinophils, basophiles), platelet count.

Serum chemistry: urea, uric acid, creatinine, protein (total), albumin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma glutamyl transferase (GGT), alkaline phosphatase, total bilirubin, sodium, potassium, chloride, glucose, total cholesterol, triglycerides. Creatine was not measured.

Modified Minnesota Impulsive Disorders Interview (MMIDI) was performed at baseline, and weeks 8, 18 and 33.

Epworth Sleepiness Scale (ESS) for the assessment of increased daytime sleepiness was performed at baseline, and weeks 4, 8, 18, and 33.

Following regulatory review, the Sponsor was advised to add questions specifically inquire about daytime sleepiness and unexpected falling asleep, treatment emergent compulsive behaviors and other unrecognized behavior.

### 7.2.5 Metabolic, Clearance, and Interaction Workup

This is an extended release formulation of a previously approved product,. No new information has been developed for this section of the review.

### 7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

This class of agent (dopamine agonists) is known to have certain treatment related adverse behavioral events. This is discussed more fully below in Section 7.3.5.Submission Specific Primary Safety Concerns.

## 7.3 Major Safety Results

In summary:

**Table 53 Phase I Trials contributing to safety data (N = 142)**

Type of Study	Study	Objective	Design	PPX ER (N)	Duration
Bioavailability	248.529	Compare seven ER prototypes	OL	14	4 days
Bioequivalence	248.530	PPX ER vs. PPX IR; food effect at 4.5 mg /d	DB	39	7 days
Bioequivalence	248.607	PK of PPX ER vs. IR in Japanese subjects	OL	24	4 weeks
Bioavailability	248.560	In vitro / in vivo food interaction	OL	15	Single dose
Safety	248.545	Thorough QT	DB	50	7 weeks

- Deaths: None
- Non-fatal serious AE: 1 (norovirus infection)
- AE leading to discontinuation: 8 (all expected AEs: headache, nausea and vomiting, gastrointestinal distress, hallucination).

**Table 54 Phase III trials contributing to safety data (N = 842)**

Mirapex ER Deaths and AEs at 4 month Safety Update (ER / Total)	Deaths	Non-fatal SAE	AE leading to dropout	Impulse Disorder
248.524 Early PD	1 / 1	15 / 33	23 / 48	2 / 6
248.525 Advanced PD	0 / 2	9 / 34	8 / 25	2 / 7
248.636 Overnight switch	0	7 / 13	1 / 2	1 / 2
248.633 ER Open label extension	1	18	8	1
248.634 ER Open label extension	2	11	5	0
248.610 Japan active comparator	0 / 1	4 + blind / 10	blind / 3	0
248.637 Fibromyalgia	0	1 / 1	0	0

### 7.3.1 Deaths

Six deaths have been reported in this development program up to the cut off date of December 1, 2008. Upon review, none of these appear to be causally related to ingestion of PPX.

#### 248.524 Early PD

- Patient #4220: death on PPX ER 2.25 mg/d.

This subject was a 68 year old Asian man, was enrolled on July 31, 2007, shortly after being diagnosed with PD. He began treatment on August 15, 2007 and was titrated to level 4 (2.25 mg/d) beginning September 5, 2007. The patient stopped drug on September 11, 2007 (total of 30 days exposure). The explanation given was “Adverse event, unexpected worsening of other pre-existing disease.” In the August 28, 2007 visit AE CFR (seemingly an incorrect date) *oral cancer* is listed as a new adverse event beginning September 13, 2007 and ending (b) (6). It is not listed as a baseline condition. It is given a rating of *severe* with outcome being *fatal*. It was judged by the investigator as unrelated to the trial drug which turned out to be the PPX ER treatment arm.

#### 248.525 Advanced PD

- Patient #6144: death on PPX IR 4.5 mg/day.

This subject was an 83 year old man who was receiving PPX IR 4.5 mg/day experienced a SAE of cardiopulmonary failure and chronic renal failure, which resulted in death. Co-morbidities at the time of entry into the trial included hypertension, diabetes mellitus with neuropathy, as well as “atherosclerosis cerebri”, “atrophia cerebri”, and “atherosclerosis universalis.” Concomitant medication included Stalevo tablets 150 MG/

12.5 MG/ 200 MG p.o. daily; piracetam tablets 2400 MG p.o. daily; pentoxyphillin tablets 800 MG p.o. daily; Vinpocetine tablets 10 MG p.o. daily; Glicazide tablets 160 MG p.o. daily; enalapril tablets 10 MG p.o. daily; bisoprol tablets 5 MG p.o. daily; metformin tablets 1 G p.o. daily; pregabalin 150 MG p.o. daily; domperidone, calcium, dobesilate, rilmendin, aspirin, hydrochlorothiazide and Quamatel. The patient was enrolled October 31, 2007. He developed hyperglycemia and dehydration, with delusions, on June 17, 2008. He was admitted to the hospital on (b) (6), and transferred to Psychiatry due to his delusions (b) (6). Pneumonia was also noted on chest x-ray (b) (6) (b) (6). He was transferred to Internal Medicine (b) (6) when he died due to cardio-respiratory insufficiency. Autopsy was not performed.

- Patient # 8029: death on placebo.

This subject was a 47 year old Asian man who began blinded medication December 18, 2007. He had a history of hypertension treated with metoprolol. On (b) (6), (b) (6) he was hospitalized for coma secondary to stroke. He died the next day. He was on placebo at that time. Review of the datasets reveals he had been in the PPX IR treatment arm and was titrated off.

#### 248.633 Open label extension (from early PD)

- Patient # 2082: death on PPX ER 3.75 mg/day.

This subject was a 63 year old white male with 1 year history of PD. He entered this extension trial on September 8, 2008, titrated to 3.75 mg/d by October 14, 2008. Co-morbidities included peripheral neuropathy (lower limbs), hypercholesterolemia, and Lyme disease. He drowned in a fishing mishap on (b) (6).

#### 248.634 Open label extension (from advanced PD)

- Patient #6342: death on PPX ER (unknown dose)

This subject was a 65 year old white man with a 13 year history of PD. He had entered 248.525 on November 21, 2007 and entered this extension trial on July 9, 2008. Co-morbidities include ten year history of coronary artery disease with history of myocardial infarction in (b) (6), and hypercholesterolemia. He was taking Acard 75 mg, Zocor 20 mg, Madopar 250 mg, Madopar HBS 250 mg, and Amantix 100mg. A "severe" stroke was reported (b) (6). This resulted in death. Further details are not available.

- Patient #7902: death on PPX ER 1.5 mg/day.

The subject was a 71 year old Asian man who had begun the double blind trial, completing it on June 16, 2008 and transferred into the open label extension. Co-morbidities included coronary artery disease, s/p two vessel angioplasty, renal disease and hypertension. He had had an episode of pneumonia in (b) (6). He was also taking levodopa and entacapone. On September 1 and 2, 2008, he developed progressive difficulty breathing with cough. On (b) (6) he was hospitalized for unresponsiveness, hypotension, with lung findings suggesting pneumonia. He was admitted to ICU for multiple organ failure secondary to septic shock. Sputum grew Serratia and Klebsiella. He progressively declined despite aggressive medical

treatment (hypotension, unresponsiveness, no urine output) and died on (b) (6) (b) (6), due to multiple organ failure secondary to septic shock. PPX ER had been discontinued on September 6.

#### 248.610 Active IR comparison and open follow-up in Japan

No deaths were reported. However, patient #1127, a 65 year old man, (b) (6) (b) (6) during the screening period. He enrolled July 28, 2008 but died (b) (6) before receiving drug.

### **7.3.2 Non-fatal Serious Adverse Events**

In Phase I trials, one non-fatal serious event occurred in 248.545, the thorough QT trial. A 47 year old healthy man was on the 14<sup>th</sup> treatment day in the placebo to PPX arm when he developed the onset of severe gastrointestinal symptoms of abdominal cramps, nausea, sweating, myalgia and diarrhea. He had an episode of syncope and low systolic blood pressures were documented. He was hospitalized and recovered fully after 6 days with rehydration. Stool tests were positive for norovirus. He was on placebo at the time.

No other serious non-fatal events occurred in the other Phase I trials (248.529, 248.530, 248.607, and 248.560) except the case of Hy's Law described below.

In Phase III, the nonfatal SAEs are tallied in Table 57, below. The narratives of these AEs were reviewed. Many were incidental significant medical illness and a few were adverse events of known to occur with PPX but which rapidly resolved, not requiring the subject to leave the trial. In this regard they are similar to the ones listed below which did lead to discontinuation. No unexpected SAEs suggesting a safety signal were found.

### **7.3.3 Dropouts and/or Discontinuations**

The following adverse events and other happenings led to discontinuation of treatment in Phase I trials:

#### 248.529 Comparing ER Prototypes

Two events led to treatment discontinuation. This trial was a multiple dose, seven-way, cross-over formulation-finding trial comparing the oral bioavailability of seven prototype slow release formulations with 0.75 mg PPX (four days each) to immediate release tablets at steady state in healthy male volunteers. In the lower dosage arms one 29 year old man subject suffered orthostatic hypotension 3.4 h after 0.125 mg PPX IR. It lasted 50 minutes and was reported as an AE. Another subject had a tachycardia (HR of 106 bpm) observed without symptoms one hour after first dose of PPX IR 0.25 mg on the fourth day of exposure. It was not reported as an AE. In both cases the investigator removed the patients from the trial.

#### 248.530 PPX ER vs. IR; food effect

According to the Sponsor, four subjects prematurely discontinued medication in this seven day trial due to adverse events. However Table 10.1:3 in the trial final report indicates 10 other subjects withdrawing for *consent withdrawn for "private reasons"*(7), *non compliance* (1) which was really a protocol deviation as the subject was discovered to have hypertension during the trial, *bad vein condition* (1) and *other* " also *"private reason"* (1).

For the subjects with adverse events judged to be drug related, they were

- (PPX ER 3.75 mg) auditory and visual hallucinations for 5 days in 32 year old man,
- (PPX ER 0.375 mg) tremor 5 hours after taking medication and this 45 year old man withdrew himself from the trial,
- (PPX ER 3.0) headache and nausea in a 21 year old woman, 47 h and 79 h after her first dose of medication at this level.

#### 248.545 Thorough QT Trial

Of subjects (n=50) exposed to PPX, only one discontinued the trial. This 32 year old woman had experienced nausea and headache on moxifloxacin, and on PPX titration to 2.25 mg/d she developed progressive heartburn, and single episode of vomiting, at which time she withdrew her consent to participate. This episode resolved on drug cessation. Total exposure time was 11 days.

#### 248.607 PK studies in healthy Japanese subjects, and: 248.560 *in vitro* – *in vivo* food interaction

No events.

In Phase III trials, premature discontinuation and withdrawal of consent is illustrated in the table below for the double blind placebo controlled multicenter trials in early and advanced PD. Overall, by chi square analysis, there is no difference in discontinuations related to adverse events between IR and ER, and a mere trend toward significance between ER and placebo. (Pearson probability,  $p = 0.052$ ). However, discontinuations as a whole were significantly higher over all in the PPX ER group relative to both IR ( $p = 0.0038$ ) and placebo ( $p = 0.0169$ ). In the early PD trial, there is only a trend that more total discontinuations occurred in the ER than IR group ( $p = 0.08$ ). But while ER had more discontinuations overall than placebo ( $p=0.018$ ), IR did not. There was only a trend when discontinuations related to AEs were considered ( $p=.065$ ). In the advanced PD trial, there were no significant differences in discontinuations among treatment arms.

**Table 55 Discontinuations in Phase III trials**

	Placebo	PPX ER	PPX IR	Blinded	Total
<b>248.524 Early PD: N enrolled and randomized</b>	103	223	213	0	539
Premature Discontinuation (N due to adverse events):	11 (4)	48 (23)	32 (18)		91 (45)
Refused to continue (withdrew consent "without AE"):	0	15	9		24
<b>248.525 Advanced PD: N enrolled and randomized</b>					
<b>248.525 Advanced PD: N enrolled and randomized</b>	165	147	164	34	510
Premature Discontinuation (N due to adverse events):	25 (8)	22 (8)	15 (8)	1	63 (25)
Refused to continue (withdrew consent "without AE"):	7	3	2		12
<b>Total enrolled and randomized:</b>					
<b>Total enrolled and randomized:</b>	268	370	377	34	1049
Total premature discontinuation (N due to adverse events):	43 (12)	88 (31)	58 (26)	0	190 (69)
Percent all discontinuation by treatment arm:	16%	24%	15%		18%
Percent of all discontinuation attributed to AEs	4%	8%	7%		7%

However, the reviewer has concerns about the under-reporting of common expected adverse events such as GI intolerance (nausea and vomiting), or psychiatric side effects (delusion, hallucinations). Narratives of patients who discontinued by withdrawal of consent or personal reasons were not provided. The reviewer's suspicion is that withdrawal of consent may at times occur in the presence of an intolerable but not serious AE. One narrative that was provided in order to explain the change of an AE to withdrawal of consent illustrates such a happenstance. This gives the reviewer pause to wonder and strongly suggests to me that withdrawals secondary to AEs were undercounted and underreported:

This example from the ISE is not clearly written, but the inference is that while the patient withdrew due to hallucinations (an accepted side effect of the drug) it was changed for unknown reason to “withdrawal of consent.” It is unclear what was meant by “missed to change the coding for the adverse event”, but that is aside from the point being emphasized by the reviewer. .

**Figure 13 Example of withdrawal from trial due to AE coded as "withdrawal of consent" (source: Sponsor)**

**7.5.3 Adverse event narratives not included in study reports**

**Clinical Trial Narrative for Reporting of Adverse Events  
leading to premature treatment discontinuation in Trial 248.524**

**Site Number: 7001**

**Patient Number: 4402**

**EudraCT number: 2007-000073-39**

At the time of cut-off for this interim analysis, the investigator changed the reason for discontinuation in this 76 years old male patient treated with pramipexole IR 2.25 mg from ‘discontinuation due to AE’ to 'withdrawal of consent, but missed to change the coding for the adverse event of moderate auditory hallucinations. As the confirmed reason for discontinuation in this patient was not an AE, no case narrative is provided.

Final mean daily dose of PPX in 248.524 and 248.525 by treatment group indicates that exposure among PPX groups was comparable.

**Table 56 Drug exposure in Early and Advanced PD Trials (source: Sponsor)**

Exposure to treatment per study		Placebo	PPX ER	PPX IR	Blinded data*	Total
248.524	N	103	223	213	0	539
	Mean (SD)	3.27 (1.31)	2.91 (1.39)	2.96 (1.39)		3.00 (1.38)
	Median	3.75	3.00	3.00		3.00
248.525	N	165	147	164	34	510
	Mean (SD)	2.95 (1.42)	2.65 (1.43)	2.76 (1.43)	3.22 (1.31)	2.82 (1.43)
	Median	3.00	2.25	3.00		3.00
Total for the 2 trials	N	268	370	377	34	1049
	Mean (SD)	3.08 (1.39)	2.81 (1.41)	2.87 (1.41)	3.22 (1.31)	2.91 (1.40)
	Median	3.00	3.00	3.00		3.00

Source data: [Appendix 7, Table 1.2.1.9](#)

\* blinded data= PPX ER or IR for trial 248.610 and PPX ER or IR or placebo for Trial 248.525

The narratives of all AEs leading to discontinuation were reviewed. A few were related to the occurrence of incidental medical illness. The majority consisted of the occurrence of an adverse event that is known to occur as a result of PPX treatment and present in the existing labeling for PPX IR. In this group of narratives, no unexpected SAEs were found to suggest a safety signal.

One case of liver dysfunction fulfilling **Hy's Law** occurred in a Phase I pharmacokinetic trial and this is reviewed below in **Section 7.4.2 Laboratory Functions**.

Phase III Trials:

In addition to review of the AEs that led to discontinuation or drop out, there were other SAEs that did not result in these outcomes. All narratives were provided and reviewed. No events were found to suggest a safety signal in this group of narratives, as well. These represented either unrelated medical events, or expected side effects that were not severe enough to cause discontinuation in the trial. These do not include cases of impulse dyscontrol, which are discussed separately below.

**Table 57 Number of SAE in Phase III trials not leading to discontinuation**

<b>SAE not leading to death or discontinuation</b>			
	<b>PPX ER</b>	<b>PPX IR</b>	<b>Placebo</b>
<b>248.524 Early PD</b>	10	9	5

<b>248.525 Advanced PD</b>	7	10	12
<b>248.610 PPX Japan OL Trial</b>	4	N/A	
<b>248.633 OL Long Term Trial</b>	7		
<b>248.634 OL Long Term Trial</b>	21		
<b>248.637 OL Fibromyalgia Trial</b>	1		

### 7.3.5 Submission Specific Primary Safety Concerns

- Nausea and vomiting

Clinical experience with the IR product reveals that nausea and vomiting are among the most common of adverse events. This is a property of all dopamine drugs, is generally dose dependent, and often attenuates with time. It is likely a direct effect upon the pars postrema (chemotactic trigger zone) in the brainstem. This is borne out in the MAED Service review of AE.XPT using DM.XPT as the denominator.

It figures as a prominent effect in the more drug-naïve early PD patient. In the advanced PD patient it is present but analysis is complicated by the amount of anti PD drug all the subjects are taking and the limited sample available to this interim analysis. Chronic exposure may attenuate this specific complaint. However, as demonstrated by the SOC for gastrointestinal complaints e.g. (heartburn, dysphagia, epigastric pain, constipation, diarrhea, among others), this system is greatly affected by dopaminergic drugs in general and PPX specifically.

**Table 58 Early and Advanced PD Trials: nausea and vomiting**

	<b>PLACEBO</b>	<b>PPX ER</b>	<b>PPX IR</b>
<b>248.524 Early PD</b>	<b>(N=103)</b>	<b>(N=223)</b>	<b>(N=213)</b>
Nausea	7 ( 6.8%)	41 ( 18.4%)	47 ( 22.1%)
Vomiting	0 ( 0.0%)	9 ( 4.0%)	6 ( 2.8%)
Gastrointestinal disorders (SOC)	15 ( 14.6%)	95 ( 42.6%)	93 ( 43.7%)
	<b>PLACEBO</b>	<b>PPX ER</b>	<b>PPX IR</b>
<b>248.525 Advanced PD</b>	<b>(N=165)</b>	<b>(N=147)</b>	<b>(N=164)</b>
Nausea	20 ( 12.1%)	16 ( 10.9%)	18 ( 11.0%)
Vomiting	6 ( 3.6%)	2 ( 1.4%)	9 ( 5.5%)
Gastrointestinal disorders (SOC)	39 ( 23.6%)	33 ( 22.4%)	37 ( 22.6%)

It is reasonable to assume that there is a dose related response by the brainstem's chemotactic trigger zone (CTZ) to DAs along a gradient from nausea to vomiting. This has been demonstrated for apomorphine (Yahr, Clough, and Bergmann, Lancet (1982): 2(8300) 709-710). The greater sensitivity of the CTZ in early as opposed to advanced PD patients is suggested by the following. 6 patients discontinued from the early PD trial for nausea and / or vomiting: PPX ER = 5, PPX IR=1, Placebo = 0. Five of the patients did so at the lowest dose: 0.375 mg/day. Only two patients discontinued in the advanced PD trial: one on placebo and one on ER. Of the 15 early PD subjects who reported vomiting, only 8 also had nausea reported as an AE. In the reviewer's opinion, this is likely an artifact of the data collection process; if an investigator hears vomiting reported as an adverse event, they are unlikely to stop and ask whether the subject was also nauseated.

- Sleep dysfunction

A variety of sleep dysfunction have been reported to occur during treatment of PD with DAs in the peer reviewed literature. These include the paroxysmal onset of sleep ("sleep attacks", sudden onset of sleep (SOOS)) and excessive daytime sleepiness. Dopamine agonist related insomnia also occurs and its relationship to daytime sleepiness is variable.

Two measures of sleep are used in the early and advanced PD trials.

The Epworth Sleepiness Scale (ESS) measures the likelihood of falling asleep during eight activities of daily living, on a 0 – 3 ordinal scale. (Johns, Sleep 1991:14:540-545; mean control score was 5.9+/- SD 2.2. The cutoff for pathological sleepiness is > 10.)

The Parkinson's Disease Sleep Scale (PDSS) is a visual analog scale covering a wide range of phenomena describing the quality of sleep. Items of the PDSS address the following (from Chaudhuri, et al, J Neurol Neurosurg Psychiatry 2002:73:629-635):

- \*overall quality of night's sleep (item 1);
- \*sleep onset insomnia(item 2);
- maintenance insomnia (item 3);
- nocturnal restlessness (items 4 and 5);
- nocturnal psychosis (*distressing* dreams and hallucinations) (items 6 and 7)
- nocturia (items 8 and 9);
- nocturnal motor symptoms (items 10–13);
- \*sleep refreshment (item 14);
- #daytime dozing (item 15).

\* These items poorly differentiate from controls in validation study

# This item correlates well with total ESS (High score on this item significantly correlates (-0.59) with low total ESS score.)

Study 248.524 Early PD

In AE.XPT, 180 subjects had an AE reported for increased sleepiness of some sort during treatment: PPX ER = 86; PPX IR = 79; Placebo = 15. The sudden onset of sleep or sleep attacks were coded in both the nervous system and psychiatric SOC. Only 11 such events were noted: PPX ER = 4; PPX IR = 6; Placebo = 1.

AE Preferred Terms reflected a wide variety of increased sleepiness coded under different SOCs with prominent splitting as a result. These were consolidated for the incidence above. (Excluded from this analysis were terms related to insomnia or sleep disturbance such as vivid dreams, REM disorder and nightmare.)

**Table 59 Early PD Trial: grouping verbatim sleep related responses**

248.524 Early PD Trial Sleep-Related Adverse Events		
SOC	PT	A few verbatim examples:
General disorders and administration site conditions	Fatigue	Excessive exhaustion
		Day tiredness
		Increased tiredness
		Worsening of fatigue (lethargy)
		Fatigue
Nervous system disorders	Lethargy	Lethargy
	Sedation	Sedation
	Hypersomnia	Hypersomnia
		Significant sleeping
	Somnolence	Daily somnolency
		Daytime sleepiness
		Drowsiness
		Significant sleepiness
Psychiatric disorders	Sleep attacks	Sleep disorder
		Sleepiness attacks
		Episode of unexpected falling asleep

In addition, a single yes / no sleepiness screening question was asked at visits and telephone calls where the ESS was not performed during the trials (Visits 3,5,7,9,10,11,and 12 and four telephone calls). “Since the last visit, have you experienced significant daytime sleepiness, or any episodes of unexpected falling asleep?” If the answer was yes, per protocol it was to be reported as an Adverse Event.

Over the course of all the relevant encounters, there were 2930 yes / no queries in 487 subjects concerning sleepiness of which 332 were positive responses. Multiple responses by a given subject were merged into a single value by the reviewer with a positive response being retained in order to look at number of individuals reporting excessive sleepiness in each group. By contingency analysis, there were significantly fewer such complaints among those receiving placebo (Pearson  $\chi^2$  p < 0.0015).

**Table 60 Early PD Trial: excessive daytime sleepiness**

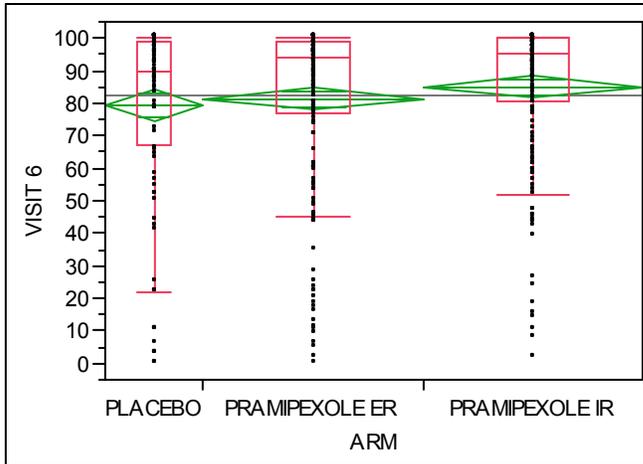
Count (row %) Expected	No	Yes	
<b>PLACEBO</b>	79 (86%) 65	13 (14%) 27	92
<b>PRAMIPEXOLE ER</b>	134 (67%) 141	66 (33%) 59	200
<b>PRAMIPEXOLE IR</b>	130 (67%) 137	65 (33%) 58	195
	343	144	487

PDSS15 “Have you unexpectedly fallen asleep during the day?” is rated by using a visual analog scale. The distance from the left margin of the line to the subject’s response is measured using a transparent overlay scale in millimeters. 0 mm along the line indicates “frequently” and 100mm would indicate “never”. Analysis reveals the following:

Visit 6 (week 8) was the end of the drug titration and beginning of the maintenance period. The baseline response to PDSS q15 (Visit 2 at randomization) was used as a covariate to control for the individual response to the disease state or other anti PD medications the patient might be taking: No difference was noted among the groups.

Level	N	Mean	Std Error	Lower 95%	Upper 95%
PLACEBO	92	79.3855	2.5999	74.277	84.494
PRAMIPEXOLE ER	204	81.2948	1.7303	77.895	84.695
PRAMIPEXOLE IR	193	84.9379	1.7429	81.513	88.362

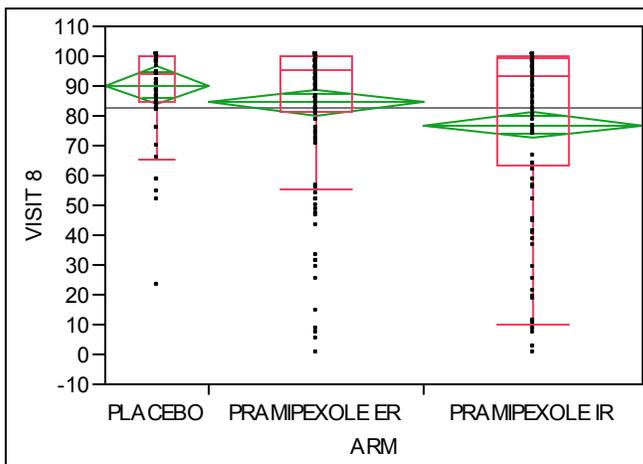
**Figure 14 Early PD Trial: PDSS Question 15 at randomization**



However, analysis at Visit 8 (week 18, or 10 weeks into dose stabilization) reveals that the active treatment groups are developing more sleepiness with treatment: This is especially notable in the distribution of outliers: ANOVA  $p > 0.0014$

Level	N	Mean	Std Error	Lower 95%	Upper 95%
PLACEBO	62	90.1368	3.1731	83.893	96.380
PRAMIPEXOLE ER	129	84.5677	2.2128	80.214	88.922
PRAMIPEXOLE IR	127	76.8304	2.1905	72.520	81.141

**Figure 15 Early PD Trial: PDSS Question 15 at 18 weeks**



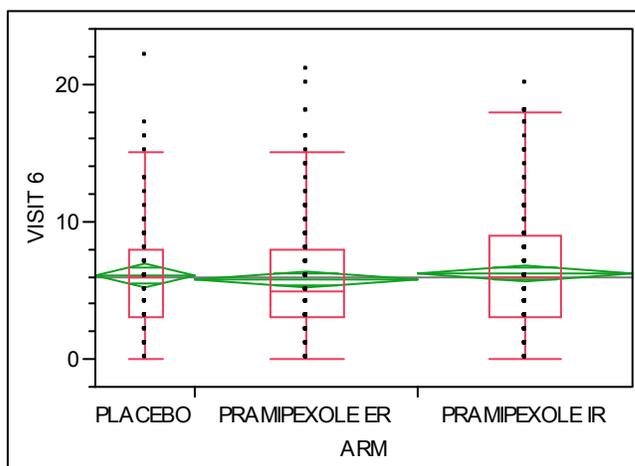
Similar analysis was performed with the eight item Epworth Sleep Scale. A higher total score reflected an increased tendency for daytime sleepiness (range 0 to 24). Like the

PDSS, Visit 6 (end of titration period) and Visit 8 (maintenance period at week 18) were analyzed using Visit 2 as the baseline covariate. (A score greater than 10 is considered to be clinically significant.)

No difference was noted among the groups at the end of the titration period at Visit 6.

Level	N	Mean	Std Error	Lower 95%	Upper 95%
PLACEBO	91	6.08144	0.44223	5.2124	6.9505
PRAMIPEXOLE ER	204	5.77692	0.29708	5.1931	6.3607
PRAMIPEXOLE IR	194	6.22487	0.30176	5.6319	6.8179

**Figure 16 Early PD Trial: Epworth Sleep Scale at end of titration period**



A trend toward increased sleepiness in the PPX IR group is apparent at 18 weeks (ANCOVA  $p < 0.0667$ ):

Level	N	Mean	Std Error	Lower 95%	Upper 95%
PLACEBO	62	5.65826	0.56569	4.5451	6.7714
PRAMIPEXOLE ER	131	6.07432	0.39292	5.3011	6.8475
PRAMIPEXOLE IR	128	7.08625	0.39239	6.3141	7.8584

Insomnia and disturbed sleep was reported by 29 subjects: PPX ER = 13, PPX IR = 13, Placebo = 3. After taking into account the 2:2:1 randomization, patients taking PPX had more than twice the incidence of disturbed sleep as the placebo group.

### 248.525 Advanced PD

In the advanced PD trial data is reported on 476 subjects: PPX ER = 147; PPX IR = 164; Placebo = 165.

**AE.XPT**

In AE.XPT, 76 subjects had an AE reported for increased sleepiness of some sort during treatment: PPX ER = 22; PPX IR = 28; Placebo = 26. The sudden onset of sleep or sleep attacks were coded in both the nervous system and psychiatric SOC. Only 11 such events were noted: PPX ER = 1; PPX IR = 9; Placebo = 1.

AE Preferred Terms were consolidated for the incidence above. (Excluded from this analysis were terms related to insomnia or sleep disturbance such as vivid dreams, REM disorder and nightmare.)

**Sleepiness Screening Question**

There were 1963 yes / no queries during treatment in 237 subjects concerning sleepiness of which 73 were positive responses. Multiple responses by a given subject were merged into a single value with a positive response being retained in order to look at number of individuals reporting excessive sleepiness in each group. There was no difference in number of positive responses among the groups.

**Table 61 Advanced PD Trial: excessive daytime sleepiness**

<b>Count (row %) Expected</b>	<b>No</b>	<b>Yes</b>	
<b>PLACEBO</b>	57 (71 %) 55	23 (29 %) 25	80
<b>PRAMIPEXOLE ER</b>	53 (73 %) 51	20 (27 %) 22	73
<b>PRAMIPEXOLE IR</b>	54 (64 %) 58	30 (36 %) 26	84
	164	73	237

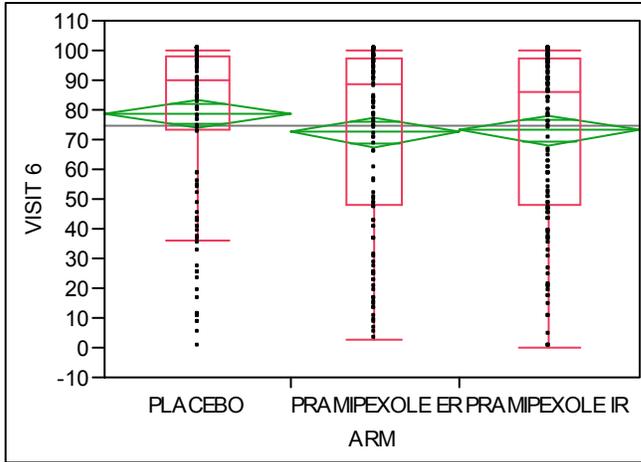
**PDSS q 15**

At Visit 6 (end of the titration period) using baseline response as covariate revealed no differences among the groups:

**Quantiles**

<b>Level</b>	<b>10%</b>	<b>25%</b>	<b>Median</b>	<b>75%</b>	<b>90%</b>
PLACEBO	29	73	90	98	100
PRAMIPEXOLE ER	19.5	47.75	88.5	97	100
PRAMIPEXOLE IR	24.4	48	86	97	100

**Figure 17 Advanced PD Trial: PDSS Question 15 at end of drug titration**

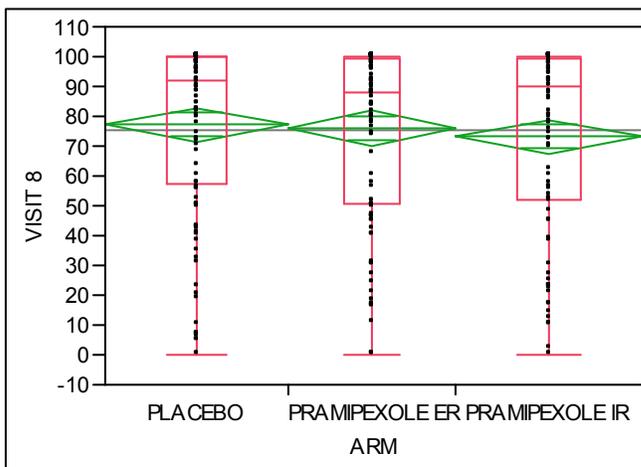


At Visit 8 (10 weeks after Visit 6, on a stabilized dose) using the subject's baseline response as covariate also revealed no differences among the groups:

**Quantiles**

Level	10%	25%	Median	75%	90%
PLACEBO	30.2	57	92	100	100
PRAMIPEXOLE ER	27.9	50.75	88	99	100
PRAMIPEXOLE IR	21	52	90	99.5	100

**Figure 18 Advanced PD Trial: PDSS Question 15 at 18 weeks**



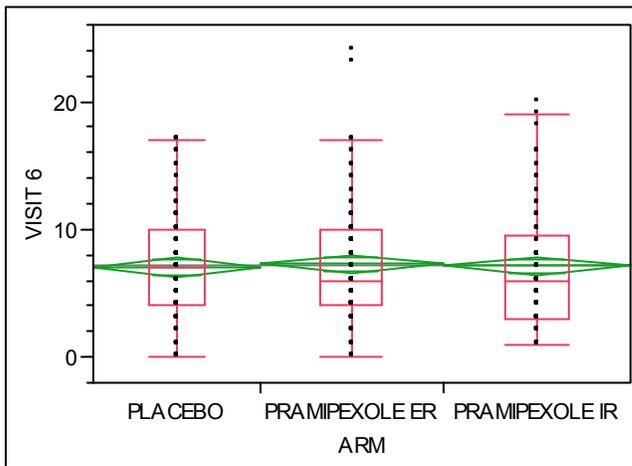
Epworth Sleep Scale

Analysis was performed with the eight item Epworth Sleep Scale for Visit 6 (end of titration period) and Visit 8 (maintenance period at week 18) using Visit 2 as the baseline covariate. (An ESS score greater than 10 is considered to be clinically significant.)

**Quantiles**

Level	10%	25%	Median	75%	90%	Maximum
PLACEBO	2	4	7	10	13	17
PRAMIPEXOLE ER	2	4	6	10	14	24
PRAMIPEXOLE IR	2	3	6	9.5	14	20

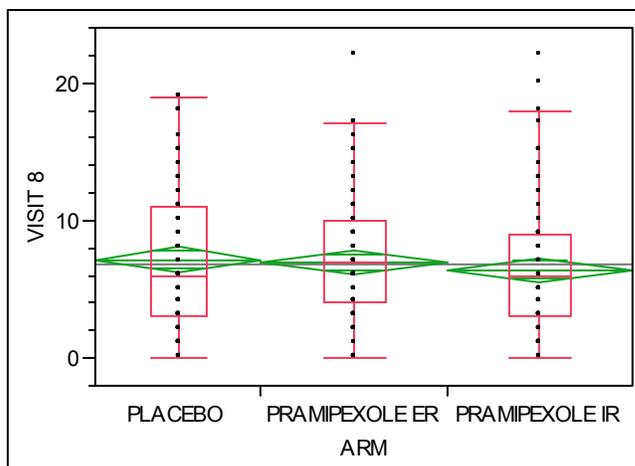
**Figure 19 Advanced PD Trial: Epworth Sleep Scale at end of titration**



**Quantiles**

Level	10%	25%	Median	75%	90%	Maximum
PLACEBO	2	3	6	11	15	19
PRAMIPEXOLE ER	2	4	7	10	14	22
PRAMIPEXOLE IR	1	3	6	9	14.1	22

**Figure 20 Advanced PD Trial: Epworth Sleep Scale at week 18**



No difference was noted among the groups for either period.

Insomnia and disturbed sleep was reported by 28 subjects: PPX ER = 9, PPX IR = 9, Placebo = 10. No differences occurred among the treatment arms.

- Symptomatic orthostatic hypotension

The Sponsor excluded from the early and advanced PD blinded trials patients with “clinically significant hypotension (i.e. supine systolic blood pressure < 90 mmHg) and/or symptomatic orthostatic hypotension (i.e. clinical symptoms of orthostatic hypotension associated with a decline = 20 mmHg in systolic blood pressure and a decline = 10 mmHg in diastolic blood pressure, at one minute after standing compared with the previous supine systolic and diastolic blood pressure obtained after 5 minutes of quiet rest) either at screening visit or at baseline visit.”

Also specified by the Sponsor: was that “only symptomatic orthostatic hypotension was to be recorded as an adverse event.” (Emphasis added by reviewer.)

Symptomatic orthostatic hypotension and associated symptoms such as syncope need to be evaluated in context. These events represent the severe end of the spectrum of dopamine agonist-associated disordered blood pressure control (see also the general effect on blood pressure in **Section 7.4.3 Vital Signs** below).

Several factors complicate the assessment of the occurrence of orthostatic hypotension in these trials. It is an accepted side effect of DAs and as such may not be reported as an AE. Some patients with episodes of syncope may have fairly normal blood pressure between events. It may only occur at specific time, e.g. post prandially when blood flow is diverted to the splanchnic bed. Many patients will only have documented orthostasis

after standing on their feet for longer than the one minute period allotted for this measurement in these studies (the well-accepted trial standard). Finally, some patients do not experience being faint-headed and are not aware of their generally low BP, which may result in falls as opposed to overt syncope.

Because of this, what is reported here is almost certainly just the “tip of the iceberg”.

In addition, given the lack of a diagnostic biomarker, a certain amount of misdiagnosis (as much as 10 or 15%) with inclusion of atypical parkinsonian disorders is inevitable in trials of early PD. It is likely that this trial includes patients with early multiple system atrophy (atypical Parkinsonism with autonomic insufficiency) but these should be equally distributed among the treatment groups.

#### Trial 248.524 Early PD

For example, the Sponsor reports the following events from the interim analysis of 248.524 (p 177, U08-1826-01), totaling 13 instances among 259 patients (5%):

**Table 62 Early PD Trial: orthostatic reactions (source: Sponsor)**

Table 12.5: 5 Frequency [N (%)] of patients with treatment emergent orthostatic hypotension, Treated Set at first interim analysis, 18 weeks

	Placebo N (%)	PPX ER N (%)	PPX IR N (%)
Number of patients treated	50 (100.0)	106 (100.0)	103 (100.0)
Number of patients with asymptomatic orthostatic reactions	1 ( 2.0)	4 ( 3.8)	5 ( 4.9)
Number of patients with symptomatic orthostatic reactions	0 ( 0.0)	1 ( 0.9)	0 ( 0.0)
Number of patients orthostatic hypotension reported as AE	1 ( 2.0)	1 ( 0.9)	0 ( 0.0)

Source data: [Tables 15.3.2.1: 4](#) and [15.3.4.1: 3](#) and [Section 16.2, Listing 7.1.2.1, Listing 7.1.3.3 and Listing 3.1.1.](#)

Orthostatic hypotension was defined as a decline  $\geq 20$  mmHg in systolic blood pressure (BP) and a decline  $\geq 10$  mmHg in diastolic BP. Symptomatic orthostatic hypotension was defined as an orthostatic hypotension accompanied by clinical symptoms.

As a result, the sponsor indicates in the Summary of Clinical Safety (p 207, U08-3710-01) that *“in patients treated up to 18 weeks in the early PD trial 248.524 asymptomatic orthostatic hypotension was reported in 4 (3.8%) pramipexole ER patients, 5 (4.9%) pramipexole IR patients and 1 (2.0%) placebo patient; symptomatic orthostatic hypotension was reported in 1 (0.9%) pramipexole ER patient.”*

As performed by the reviewer, a simple tabulation of subjects with a drop in systolic BP of  $> 20$  mmHg on standing from the vital signs (VS.xpt) dataset reveals that 69 of 539 subjects, (12.8%) had a drop in SBP at some visit during the trial.

Using the adverse event dataset (AE.xtp) as numerator and the demographic dataset (DM.xpt) as the denominator, review of reported adverse events using MAED Service to look for any term remotely related to hypotension revealed the following (MedDRA v11.0). SOC and SMQ were unrevealing, but it is clear that there is a disconnect between asymptomatic orthostasis and the counting of clinically significant events. Higher level terms tend to be of less use as these events may be captured as either vascular or CNS events.

**Table 63 Early PD Trial: reviewer's tally of BP related events**

248.524 Early PD			
Preferred Term	Placebo (N=103)	PPX ER (N=223)	PPX IR (N= 213)
Hypotension	1 (1.0%)	1 (0.4%)	5 (2.3%)
Orthostatic Hypotension	1 (1.0%)	5 (2.2%)	1 (0.5%)
Dizziness Postural	0 (0%)	1 (0.4%)	2 (0.9%)
Syncope	0 (0%)	2 (0.9%)	2 (0.9%)
High Level Group Term			
Blood pressure disorders	2 (1.9%)	6 (2.7%)	6 (2.8%)

It is also clear that the coding of the verbatim terms may have contributed to underreporting. For example, the PT “dizziness” occurs in 42 additional subjects (PPX ER = 19, PPX IR = 19, Placebo = 4). This much more closely approximates the numbers and proportion of subjects with SBP drop > 20 mmHg who were reportedly “asymptomatic”. The term “giddiness” would add 21 more subjects (PPX ER = 5, PPX IR = 12, Placebo = 4).

Another concern is that the subjects who discontinued from the trial by withdrawal of consent may have done so due to a perceived but unreported common adverse event (see section on hallucinations for an example of this). Other complaints associated with clinically significant hypotension include imbalance, gait disorder, cold sweats, headache, asthenia, and falls, but there is insufficient information to attribute these events to hypotension.

Trial 248.525 Advanced PD

Similar results apply to the analysis of the trial in advanced PD.

**Table 64 Advanced PD Trial: reviewer's tally of blood pressure related events**

248.525 Advanced PD			
Preferred Term	Placebo (N=165)	PPX ER (N=147)	PPX IR (N= 164)
Hypotension	1 (1.6%)	1 (0.7%)	0 (0%)
Orthostatic Hypotension	2 (1.2%)	3 (2.0%)	1 (0.6%)
Dizziness Postural	1 (0.6%)	1 (0.7%)	5 (3.0%)
Syncope	0 (0%)	1 (0.7%)	2 (1.2%)

The PT “dizziness” occurs in 41 additional subjects (PPX ER = 9, PPX IR = 22, Placebo = 10), again suggesting that this symptom may be related to a disturbance of blood pressure.

This, together with the data presented in 7.4.3 Vital Signs, suggests that the Sponsor’s claim that the frequency of asymptomatic orthostatic hypotension was no different from placebo is incorrect.

- Falls

Falls and related events (fractures, lacerations, and injuries) were assessed. In the early PD trial, these were experienced by 21 patients, a few multiple times. There were 29 patients with falls or injuries related to falls in the advanced PD trial. These were all proportionally distributed among the treatment arms:

249.524 Early PD: PPX ER = 9, PPX IR = 8 and Placebo = 4.

249.525 Advanced PD: PPX ER = 12, PPX IR = 8 and Placebo = 9.

- PD-related motor phenomena

PPX was not associated with untoward illness related motor effects with the exception of abnormal involuntary movements seen in treated advanced PD. It should be noted that documented motor fluctuations were a requirement for entrance into the advanced PD trial. It is therefore expected that treatment would induce increased dyskinesia in some percentage of subjects. This likely represents those subjects most severely affected in that regard, but the full evaluation of the significance of this finding will require the final efficacy and adverse event report for this trial in the Sponsor’s NDA for treatment of advanced PD.

**Table 65 Early and Advanced PD Trials: reviewer's tally of motor related adverse events**

<b>PD - related Preferred Terms</b>	<b>PLACEBO</b>	<b>PPX ER</b>	<b>PPX IR</b>
<b>248.524 Early PD</b>	<b>(N=103)</b>	<b>(N=223)</b>	<b>(N=213)</b>
Balance disorder	1 ( 1.0%)	5 ( 2.2%)	0 ( 0.0%)
Tremor	1 ( 1.0%)	4 ( 1.8%)	4 ( 1.9%)
	<b>PLACEBO</b>	<b>PPX ER</b>	<b>PPX IR</b>
<b>248.525 Advanced PD</b>	<b>(N=165)</b>	<b>(N=147)</b>	<b>(N=164)</b>
Dyskinesia	13 ( 7.9%)	23 ( 15.6%)	24 ( 14.6%)
Muscle spasms	1 ( 0.6%)	0 ( 0.0%)	4 ( 2.4%)
Dystonia	2 ( 1.2%)	1 ( 0.7%)	0 ( 0.0%)
Parkinson's disease	1 ( 0.6%)	0 ( 0.0%)	1 ( 0.6%)
Balance disorder	2 ( 1.2%)	1 ( 0.7%)	1 ( 0.6%)
Musculoskeletal stiffness	2 ( 1.2%)	1 ( 0.7%)	1 ( 0.6%)
Tremor	3 ( 1.8%)	3 ( 2.0%)	2 ( 1.2%)

- Behavioral abnormalities

A wide variety of behavioral aberration has been associated with increased dopaminergic tone in the brain. The extent of phenomena is likely due to the fact that, beyond motor systems, several dopamine tracts innervate various regions of the frontal lobes. These may be grouped in broad categories loosely associated with brain regions: compulsive behavior, memory retrieval, multitasking and abstract thinking, among others.

The current practice for the collection of behavioral adverse events in clinical trials lags behind this knowledge and does not systematically inquire about all the possible phenomena that can result from DA treatment. Increasing the granularity of complaints reduces their significance, fragmenting findings into small, seemingly unrelated categories.

For this reason, the reviewer has grouped all Preferred Terms from AE.XPT that reflect behavior change. While this may superficially appear arbitrary, the consistency of result supports this method. Behavioral abnormalities for the purpose of this review are construed to be any possible surrogate of cognitive, conative, or behavioral process. The results suggest a significant and pervasive change in behavior associated with PPX treatment. This is almost certainly a class effect, and these are seen to a lesser extent with levodopa treatment as well. The advanced PD population is smaller and treated for a shorter time period. The reviewer believes the smaller number of events for the PPX

ER group is due to the inadequate sample and bias of this unplanned interim safety analysis in 248.525.

**Table 66 Early PD Trial: preferred terms suggesting cognitive or behavioral adverse events**

<b>PD - related Preferred Terms 248.524 Early PD</b>	<b>PLACEBO (N=103)</b>	<b>PPX ER (N=223)</b>	<b>PPX IR (N=213)</b>
Hallucination	0 ( 0.0%)	6 ( 2.7%)	9 ( 4.2%)
Hallucination, auditory	0 ( 0.0%)	0 ( 0.0%)	2 ( 0.9%)
Libido increased	0 ( 0.0%)	0 ( 0.0%)	2 ( 0.9%)
Panic attack	0 ( 0.0%)	2 ( 0.9%)	0 ( 0.0%)
Anxiety	1 ( 1.0%)	2 ( 0.9%)	6 ( 2.8%)
Nightmare	0 ( 0.0%)	1 ( 0.4%)	3 ( 1.4%)
Depression	0 ( 0.0%)	4 ( 1.8%)	2 ( 0.9%)
Confusional state	0 ( 0.0%)	3 ( 1.3%)	1 ( 0.5%)
Libido decreased	1 ( 1.0%)	2 ( 0.9%)	0 ( 0.0%)
Aggression	1 ( 1.0%)	1 ( 0.4%)	0 ( 0.0%)
Excessive sexual fantasies	1 ( 1.0%)	1 ( 0.4%)	0 ( 0.0%)
Compulsive shopping	0 ( 0.0%)	1 ( 0.4%)	2 ( 0.9%)
Memory impairment	1 ( 1.0%)	1 ( 0.4%)	3 ( 1.4%)
Hallucination, visual	1 ( 1.0%)	6 ( 2.7%)	4 ( 1.9%)
Amnesia	0 ( 0.0%)	2 ( 0.9%)	1 ( 0.5%)
Disturbance in attention	0 ( 0.0%)	2 ( 0.9%)	1 ( 0.5%)
Aphasia	0 ( 0.0%)	1 ( 0.4%)	1 ( 0.5%)
Global amnesia	0 ( 0.0%)	1 ( 0.4%)	1 ( 0.5%)
Sleep talking	0 ( 0.0%)	1 ( 0.4%)	1 ( 0.5%)
Abnormal dreams	2 ( 1.9%)	4 ( 1.8%)	3 ( 1.4%)
<b>TOTAL</b>	<b>8 ( 7.8%)</b>	<b>41 (18.4%)</b>	<b>42 (19.7%)</b>

**Table 67 Advanced PD Trial: preferred terms suggesting cognitive or behavioral adverse events**

<b>PD - related Preferred Terms 248.525 Advanced PD</b>	<b>PLACEBO (N=165)</b>	<b>PPX ER (N=147)</b>	<b>PPX IR (N=164)</b>
Hallucination, visual	0 ( 0.0%)	3 ( 2.0%)	7 ( 4.3%)
Hallucination	2 ( 1.2%)	6 ( 4.1%)	9 ( 5.5%)
Pathological gambling	0 ( 0.0%)	0 ( 0.0%)	2 ( 1.2%)
Psychotic disorder	0 ( 0.0%)	0 ( 0.0%)	2 ( 1.2%)
Dementia	1 ( 0.6%)	0 ( 0.0%)	3 ( 1.8%)
Abnormal dreams	3 ( 1.8%)	0 ( 0.0%)	1 ( 0.6%)
Delusion	0 ( 0.0%)	1 ( 0.7%)	2 ( 1.2%)
Disorientation	0 ( 0.0%)	1 ( 0.7%)	1 ( 0.6%)
Illusion	0 ( 0.0%)	1 ( 0.7%)	1 ( 0.6%)
Depressed mood	1 ( 0.6%)	1 ( 0.7%)	0 ( 0.0%)
Hallucination, auditory	1 ( 0.6%)	1 ( 0.7%)	0 ( 0.0%)
Abnormal behaviour	1 ( 0.6%)	2 ( 1.4%)	3 ( 1.8%)
Mood altered	1 ( 0.6%)	0 ( 0.0%)	1 ( 0.6%)
Visual disturbance	1 ( 0.6%)	0 ( 0.0%)	1 ( 0.6%)
Compulsive shopping	1 ( 0.6%)	1 ( 0.7%)	2 ( 1.2%)
<b>Total</b>	<b>12 (7.2%)</b>	<b>17 (11.6%)</b>	<b>35 (21.3%)</b>

As indicated in the introduction to this section the reviewer has concern that cognitive and psychiatric AEs may be under-reported. In the table below are all patients in the placebo controlled trials that appear to have discontinued for behavioral reasons, regardless as to whether it was reported as an AE or attributed to treatment. The dose at which the event occurred is also noted. There is no suggestion of a dose response pattern with this number of events.

**Table 68 Discontinuation related to behavioral events in the Early and Advanced PD Trials**

Discontinuations related to behavior (phenomena and dose range)	PLACEBO	PPX ER	PPX IR
<b>248.524 Early PD</b>	<b>(N=103)</b>	<b>(N=223)</b>	<b>(N=213)</b>
Hallucinations	0	3 (2.25, 4.5, and 4.5 mg/d)	2 (0.375, 3.5 mg/d)
Anxiety	0	1 (3.0 mg/d)	1 (0.375 mg/d)
Diminished cognition	0	1 (0.75 mg/d)	0
Impulse control disorder	1	4 (1.5 -2.5 mg/d)	3 (1.5 - 3.75 mg/d)
Total	1	9	6

Discontinuations related to behavior (phenomena and dose range)	PLACEBO	PPX ER	PPX IR
<b>248.525 Advanced PD</b>	<b>(N=165)</b>	<b>(N=147)</b>	<b>(N=164)</b>
Hallucinations	0	2 (0.75, 1.5 mg/d)	5 (0.375 -2.25 mg/d)
Delusion, psychosis	1	1 (4.5 mg/d)	1 (3.75 mg/d)
Impulse control disorder	1	1 (2.25 mg/d)	2 (4.5, 4.5 mg/d)
Diminished cognition	1	0	0
Total	3	4	8

No instances of impulse control disorder were noted in Phase I studies. In the Early PD trial, six subjects were reported to have impulse control disorder, but only two were underwent psychiatric consultation as required by protocol.

Analysis of UPDRS Part I individual items 1-4 for intellectual impairment, thought disorder, depression, and motivation reveals no disproportionate positive responses for the drug treatment groups compared to placebo using  $\chi^2$  analysis for this ordinal variable.

Questioning for dopamine dyscontrol syndrome was performed using the modified Minnesota Impulsive Disorders Interview (mMIDI). This has three modules to document compulsive sexual behavior, buying, and gambling. A positive response engenders further questioning. A negative response to the initial question in each module ends the interview for that section. A major fault of the scale is that it is directed to the trial subject. In the reviewer's experience, patients who experience these compulsions due to dopaminergic medication have very little sense that it is aberrant. It is common for these events to come to light via the spouse/partner or, in the case of sexual compulsion, via law enforcement.

The responses for the initial screening question were analyzed in QS.XPT: Note that a majority of early PD patients were on other anti-PD medication at baseline. For both the early and advanced PD studies, there were limited short-term exposures to treatment and small number of treatment emergent cases of compulsive behavior. Each group in each trial had more subjects responding positively at baseline than was seen as treatment emergent events. The presence of concomitant antiparkinson drug treatment makes specific conclusions difficult. In the advanced PD trial, the rate of positive treatment emergent responses in the DA treated group was twice that of the placebo. Given the limited sample, the significance of this is not clear.

**Table 69 Screening of impulse control disorder in Early and Advanced PD Trials**

<b>Instances of positive response to any mMIDI screening questions.</b>	<b>PLACEBO</b>	<b>PPX ER</b>	<b>PPX IR</b>
<b>248.524 Early PD</b>	<b>(N=103)</b>	<b>(N=223)</b>	<b>(N=213)</b>
N, randomization	103	223	212
N, week 18	92	204	193
N, week 33	63	131	127
<b>Yes response at randomization</b>	<b>14 (14%)</b>	<b>22 (10%)</b>	<b>28 (13%)</b>
<b>Treatment emergent event</b>	<b>6 (6%)</b>	<b>12 (5%)</b>	<b>14 (7%)</b>

<b>Instances of positive response to any mMIDI screening questions.</b>	<b>PLACEBO</b>	<b>PPX ER</b>	<b>PPX IR</b>
<b>248.525 Advanced PD</b>	<b>(N=165)</b>	<b>(N=147)</b>	<b>(N=164)</b>
N, randomization	165	147	164
N, week 18	145	129	145
N, week 33	110	98	110
<b>Yes response at randomization</b>	<b>13 (8%)</b>	<b>12 (8%)</b>	<b>20 (12%)</b>
<b>Treatment emergent event</b>	<b>5 (3%)</b>	<b>10 (7%)</b>	<b>8 (5%)</b>

## 7.4 Supportive Safety Results

### 7.4.1 Common Adverse Events

All five Phase I studies were completed before the September, 2008 cut off date.

The unblinded safety data was reported by the sponsor in narrative form and individual study reports were reviewed. As the Sponsor reports, tolerability was “good” in 84% of subjects who took 2.25 mg daily and in 77% of subjects taking 4.5 mg/d.

There were many expected side effects noted in the healthy volunteers. This is common to all DAs. It may be that the PD population with a dopamine deficiency is not as sensitive to DA related side effects. An accelerated titration to 4.5 mg in three days was used in Phase I, as opposed to a week or more in the trial population. This certainly would contribute to the incidence of autonomic and gastrointestinal side effects.

No unexpected effects were reported. Those noted most commonly in these unblinded studies included: nausea (with occasional vomiting), headache, orthostatic hypotension, sinus tachycardia, heartburn, diarrhea, ‘nasal pharyngitis” (nasal congestion is associated with DAs) fatigue, dizziness, insomnia, somnolence and psychiatric disturbances.

Phase III Trials:

Using MAEDService data-mining software with AE.xpt as the numerator and DM.xpt as denominator, these tables indicate the numbers of patients reporting any adverse event:

**Table 70 Subjects reporting at least one adverse event in Early and Advanced PD Trials**

<b>248.524 Early PD</b>	<b>PLACEBO</b>	<b>PPX ER</b>	<b>PPX IR</b>
<b>AT LEAST ONE EVENT REPORTED:</b>	<b>(N=103)</b>	<b>(N=223)</b>	<b>(N=213)</b>
PT	70 (68.0%)	183 (82.1%)	161 (75.6%)

<b>248.525 Advanced PD</b>	<b>PLACEBO</b>	<b>PPX ER</b>	<b>PPX IR</b>
<b>AT LEAST ONE EVENT REPORTED:</b>	<b>(N=165)</b>	<b>(N=147)</b>	<b>(N=164)</b>
PT	96 (58.2%)	82 (55.8%)	104 (63.4%)

There are intrinsic physiological differences in patients who have early versus advanced Parkinson's disease which may result in different susceptibility to adverse events. Patients with advanced disease may show increasing risk of toxic encephalopathy or autonomic side effects. Early patients with greater dopamine tone may have more nausea and vomiting. For this reason, these populations were not pooled by the reviewer for this analysis. This is evident in general tally of adverse effects.

Treatment emergent adverse events incident to the controlled trial in early PD (248.524), where events occurred in more than 1% of subjects treated with PPX ER and were numerically twice as frequent as the placebo group are noted. Nothing suggested a low frequency idiosyncratic adverse event.

**Table 71 Early PD Trial: Treatment Emergent Adverse Events**

248.524 Early PD			
Preferred Term (MedDRA v11-0)	PLACEBO (N=103)	PPX ER (N=223)	PPX IR (N=213)
Somnolence	12 ( 11.7%)	74 ( 33.2%)	68 ( 31.9%)
Nausea	7 ( 6.8%)	41 ( 18.4%)	47 ( 22.1%)
Constipation	2 ( 1.9%)	28 ( 12.6%)	24 ( 11.3%)
Dizziness	7 ( 6.8%)	23 ( 10.3%)	24 ( 11.3%)
Fatigue	4 ( 3.9%)	13 ( 5.8%)	11 ( 5.2%)
Dry mouth	1 ( 1.0%)	12 ( 5.4%)	8 ( 3.8%)
Edema peripheral	5 ( 4.9%)	10 ( 4.5%)	13 ( 6.1%)
Vomiting	0 ( 0.0%)	9 ( 4.0%)	6 ( 2.8%)
Muscle spasms	2 ( 1.9%)	9 ( 4.0%)	3 ( 1.4%)
Fall	1 ( 1.0%)	8 ( 3.6%)	7 ( 3.3%)
Insomnia	2 ( 1.9%)	8 ( 3.6%)	7 ( 3.3%)
Headache	7 ( 6.8%)	7 ( 3.1%)	14 ( 6.6%)
Cough	0 ( 0.0%)	7 ( 3.1%)	5 ( 2.3%)
Vertigo	1 ( 1.0%)	7 ( 3.1%)	3 ( 1.4%)
Hallucination	0 ( 0.0%)	6 ( 2.7%)	9 ( 4.2%)
Abdominal pain upper	1 ( 1.0%)	6 ( 2.7%)	8 ( 3.8%)
Asthenia	1 ( 1.0%)	6 ( 2.7%)	3 ( 1.4%)
Hallucination, visual	1 ( 1.0%)	6 ( 2.7%)	4 ( 1.9%)

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Balance disorder	1 ( 1.0%)	5 ( 2.2%)	0 ( 0.0%)
Abdominal discomfort	0 ( 0.0%)	5 ( 2.2%)	1 ( 0.5%)
Orthostatic hypotension	1 ( 1.0%)	5 ( 2.2%)	1 ( 0.5%)
Arthralgia	2 ( 1.9%)	5 ( 2.2%)	1 ( 0.5%)
Sleep disorder	1 ( 1.0%)	5 ( 2.2%)	6 ( 2.8%)
Dyspepsia	1 ( 1.0%)	5 ( 2.2%)	5 ( 2.3%)
Increased appetite	1 ( 1.0%)	5 ( 2.2%)	4 ( 1.9%)
Musculoskeletal stiffness	0 ( 0.0%)	4 ( 1.8%)	0 ( 0.0%)
Visual disturbance	0 ( 0.0%)	4 ( 1.8%)	0 ( 0.0%)
Basal cell carcinoma	1 ( 1.0%)	4 ( 1.8%)	0 ( 0.0%)
Depression	0 ( 0.0%)	4 ( 1.8%)	2 ( 0.9%)
Anorexia	2 ( 1.9%)	4 ( 1.8%)	8 ( 3.8%)
Pyrexia	0 ( 0.0%)	4 ( 1.8%)	3 ( 1.4%)
Vision blurred	1 ( 1.0%)	4 ( 1.8%)	2 ( 0.9%)
Diarrhea	2 ( 1.9%)	4 ( 1.8%)	6 ( 2.8%)
Tremor	1 ( 1.0%)	4 ( 1.8%)	4 ( 1.9%)
Abnormal dreams	2 ( 1.9%)	4 ( 1.8%)	3 ( 1.4%)
Asthma	0 ( 0.0%)	3 ( 1.3%)	0 ( 0.0%)
Pharyngolaryngeal pain	0 ( 0.0%)	3 ( 1.3%)	0 ( 0.0%)
Sedation	0 ( 0.0%)	3 ( 1.3%)	0 ( 0.0%)
Cataract	0 ( 0.0%)	3 ( 1.3%)	1 ( 0.5%)
Confusional state	0 ( 0.0%)	3 ( 1.3%)	1 ( 0.5%)
Stomach discomfort	1 ( 1.0%)	3 ( 1.3%)	1 ( 0.5%)

<b>System Organ Class (MedDRA v11-0)</b>	<b>PLACEBO (N=103)</b>	<b>PPX ER (N=223)</b>	<b>PPX IR (N=213)</b>
Gastrointestinal disorders	15 ( 14.6%)	95 ( 42.6%)	93 ( 43.7%)
Nervous system disorders	26 ( 25.2%)	101 ( 45.3%)	95 ( 44.6%)
Psychiatric disorders	9 ( 8.7%)	40 ( 17.9%)	50 ( 23.5%)
General disorders and administration site conditions	12 ( 11.7%)	38 ( 17.0%)	34 ( 16.0%)
Respiratory, thoracic and mediastinal disorders	2 ( 1.9%)	18 ( 8.1%)	10 ( 4.7%)
Metabolism and nutrition disorders	4 ( 3.9%)	13 ( 5.8%)	22 ( 10.3%)
Investigations	0 ( 0.0%)	9 ( 4.0%)	6 ( 2.8%)

Neoplasms benign, malignant and unspecified	1 ( 1.0%)	6 ( 2.7%)	2 ( 0.9%)
Ear and labyrinth disorders	2 ( 1.9%)	8 ( 3.6%)	4 ( 1.9%)
Eye disorders	6 ( 5.8%)	17 ( 7.6%)	11 ( 5.2%)
Musculoskeletal and connective tissue disorders	17 ( 16.5%)	31 ( 13.9%)	26 ( 12.2%)
Injury, poisoning and procedural complications	6 ( 5.8%)	14 ( 6.3%)	9 ( 4.2%)
Reproductive system and breast disorders	1 ( 1.0%)	3 ( 1.3%)	2 ( 0.9%)
Vascular disorders	7 ( 6.8%)	16 ( 7.2%)	17 ( 8.0%)
Renal and urinary disorders	3 ( 2.9%)	6 ( 2.7%)	6 ( 2.8%)

Treatment emergent adverse events incident to the controlled trial in advanced PD (248.525), where events occurred in more than 1% of subjects treated with PPX ER and were numerically more frequent than the placebo group are noted: Once again, nothing suggested a low frequency idiosyncratic adverse event.

**Table 72 Advanced PD Trial: Treatment Emergent Adverse Events**

<b>248.525 Advanced PD</b>			
<b>Preferred Term (MedDRA v11-0)</b>	<b>PLACEBO (N=165)</b>	<b>PPX ER (N=147)</b>	<b>PPX IR (N=164)</b>
Dyskinesia	13 ( 7.9%)	23 ( 15.6%)	24 ( 14.6%)
Somnolence	24 ( 14.5%)	22 ( 15.0%)	24 ( 14.6%)
Nausea	20 ( 12.1%)	16 ( 10.9%)	18 ( 11.0%)
Headache	6 ( 3.6%)	12 ( 8.2%)	6 ( 3.7%)
Constipation	9 ( 5.5%)	11 ( 7.5%)	9 ( 5.5%)
Dizziness	9 ( 5.5%)	8 ( 5.4%)	18 ( 11.0%)
Fall	5 ( 3.0%)	8 ( 5.4%)	6 ( 3.7%)
Insomnia	4 ( 2.4%)	7 ( 4.8%)	8 ( 4.9%)
Anorexia	3 ( 1.8%)	6 ( 4.1%)	1 ( 0.6%)
Hallucination	2 ( 1.2%)	6 ( 4.1%)	9 ( 5.5%)
Salivary hypersecretion	0 ( 0.0%)	4 ( 2.7%)	1 ( 0.6%)
Diarrhea	2 ( 1.2%)	4 ( 2.7%)	2 ( 1.2%)
Hallucination, visual	0 ( 0.0%)	3 ( 2.0%)	7 ( 4.3%)
Arthralgia	3 ( 1.8%)	3 ( 2.0%)	7 ( 4.3%)
Orthostatic hypotension	2 ( 1.2%)	3 ( 2.0%)	1 ( 0.6%)
Pain	2 ( 1.2%)	3 ( 2.0%)	1 ( 0.6%)

Anxiety	2 ( 1.2%)	3 ( 2.0%)	2 ( 1.2%)
Cough	2 ( 1.2%)	3 ( 2.0%)	3 ( 1.8%)
Tremor	3 ( 1.8%)	3 ( 2.0%)	2 ( 1.2%)
Malaise	0 ( 0.0%)	2 ( 1.4%)	0 ( 0.0%)
Vomiting	6 ( 3.6%)	2 ( 1.4%)	9 ( 5.5%)
Chest pain	0 ( 0.0%)	2 ( 1.4%)	1 ( 0.6%)
Dyspepsia	1 ( 0.6%)	2 ( 1.4%)	4 ( 2.4%)
Abdominal pain upper	1 ( 0.6%)	2 ( 1.4%)	3 ( 1.8%)
Abnormal behavior	1 ( 0.6%)	2 ( 1.4%)	3 ( 1.8%)
Hyperhydrosis	1 ( 0.6%)	2 ( 1.4%)	1 ( 0.6%)
Musculoskeletal pain	1 ( 0.6%)	2 ( 1.4%)	1 ( 0.6%)
Edema peripheral	4 ( 2.4%)	2 ( 1.4%)	4 ( 2.4%)
Sleep disorder	2 ( 1.2%)	2 ( 1.4%)	1 ( 0.6%)

<b>System Organ Class (MedDRA v11-0)</b>	<b>PLACEBO (N=165)</b>	<b>PPX ER (N=147)</b>	<b>PPX IR (N=164)</b>
Nervous system disorders	54 ( 32.7%)	55 ( 37.4%)	66 ( 40.2%)
Psychiatric disorders	15 ( 9.1%)	23 ( 15.6%)	30 ( 18.3%)
Musculoskeletal and connective tissue disorders	15 ( 9.1%)	17 ( 11.6%)	19 ( 11.6%)
Injury, poisoning and procedural complications	9 ( 5.5%)	12 ( 8.2%)	8 ( 4.9%)
Eye disorders	8 ( 4.8%)	9 ( 6.1%)	4 ( 2.4%)
Metabolism and nutrition disorders	4 ( 2.4%)	8 ( 5.4%)	5 ( 3.0%)
Investigations	6 ( 3.6%)	8 ( 5.4%)	11 ( 6.7%)
Skin and subcutaneous tissue disorders	5 ( 3.0%)	6 ( 4.1%)	4 ( 2.4%)

### 7.4.2 Laboratory Findings

Laboratory reference ranges and criteria for clinically significant abnormalities were reviewed (ISS, Tables 3.1.1 and 3.1.2).

Measures of central tendencies revealed no significant differences in the placebo controlled trials for:

- Hematology (hematocrit, hemoglobin, total red and white cell counts, neutrophils, eosinophils, and platelets),

- Electrolytes (sodium, potassium, and chloride)
- Metabolic indices: (glucose, cholesterol, triglyceride, uric acid, total protein and albumin).

Shift tables were also reviewed for hematological parameters and review of the subjects with changes did not appear to fall into a pattern or represent an idiosyncratic event.

Below is the Sponsor's table of patients with possibly clinically significant hematological changes for the combined early and advanced PD trials (ISS, Table 3.4.4):

**Table 73 Hematology results for combined Early and Advanced PD Trials (source: Sponsor)**

Parameter/ Treatment	N	Decrease	Increase	Parameter/ Treatment	N	Decrease	Increase
Haematocrit				Neut., poly. (segs), absol.			
Placebo	209	1 ( 0.5)	0	Placebo	209	0	0
PPX ER	288	2 ( 0.7)	0	PPX ER	288	1 ( 0.3)	0
PPX IR	297	5 ( 1.7)	0	PPX IR	297	1 ( 0.3)	0
Haemoglobin				Rosinophils, absol.			
Placebo	209	4 ( 1.9)	0	Placebo	209	0	0
PPX ER	288	7 ( 2.4)	0	PPX ER	288	0	0
PPX IR	297	5 ( 1.7)	0	PPX IR	297	0	0
Red blood cell ct.				Baso, absol.			
Placebo	209	1 ( 0.5)	0	Placebo	209	0	0
PPX ER	288	0	0	PPX ER	288	0	0
PPX IR	297	0	0	PPX IR	297	0	0
White blood cell ct.				Lymphocyte, absol.			
Placebo	209	0	0	Placebo	209	0	0
PPX ER	288	1 ( 0.3)	0	PPX ER	288	0	0
PPX IR	297	0	0	PPX IR	297	0	0
Platelets				Monocyte, absol.			
Placebo	206	0	0	Placebo	209	0	0
PPX ER	287	0	0	PPX ER	288	0	0
PPX IR	295	0	0	PPX IR	297	0	0

Parameter/ Treatment	N	Decrease	Increase
Neut., poly (segs)			
Placebo	209	0	0
PPX ER	289	1 ( 0.3)	0
PPX IR	297	0	0
Eosinophils			
Placebo	209	0	1 ( 0.5)
PPX ER	289	0	5 ( 1.7)
PPX IR	297	0	4 ( 1.3)
Basophils			
Placebo	209	0	0
PPX ER	289	0	0
PPX IR	297	0	0
Lymphocytes			
Placebo	209	0	0
PPX ER	289	0	0
PPX IR	297	0	0
Monocytes			
Placebo	209	0	0
PPX ER	289	0	0
PPX IR	297	0	0

Hepatic and renal functions are discussed further below.

Hepatic Function:

One 43 year old man (248.530 PPX ER vs. IR; food effect with seven day exposure to drug, subject no. 1033) developed stomach pain 78 h and jaundice 96 h after beginning on PPX ER 3.0 mg in June 2006: **AST 3.8 x ULN, ALT 8.5 x ULN, and T Bilirubin 4 x ULN.** The patient had his medication stopped at Visit 6 (see Table 74); this represented a total exposure to drug of 19 days. Liver enzymes returned to normal in 15 days (see table that follows). Review of data print-outs indicates that the patient is a “non-drinker”. No vital sign or ECG abnormality was detected.

**Table 74 A single case of "Hy's Law"**

Visit	Date	AST [U/L] 0-37.99	ALT [U/L] 0-40.99	Alkaline phos- phatase [U/L] 40-129	GGT [U/L] 40-129	LDH [U/L] 40-129	Amylase [U/L] 40-129	Bili total [mg/dL] 0-0.999	Bili direct [mg/dL] 0-0.299
Screening	23 May 2006	22	18	58	25	127	66	0.80	0.20
V2	02 June 2006	25	25	58	22	119	61	0.70	0.20
V6	21 June 2006	151	348	95	184	163	117	4.10	2.20
V6 (2)	22 June 2006	123	302	-	167	-	62	2.60	1.50
V11	25 June 2006	69	201	-	133	-	-	1.90	0.70
Post- treatment 1	29 June 2006	38	99	73	103	114	68	1.20	0.50
Post- treatment 2	06 July 2006	-	35	-	70	-	-	-	-

CRFs and a narrative were requested for review. A medical consultation was sought and after sonography which found gall bladder sludge, it was felt that the patient had cholestasis.

The patient participated in three additional unrelated trials at this CRO. One year later, in 2007, he was excluded from a trial for elevated GGTP. Another time bilirubin was elevated, and on another occasion one year later hepatic function tests were again elevated. Hepatitis serology for B and C were negative.

The patient was contacted for follow-up by the Sponsor in April 2009, and he describes three or four painful event thought to be related to his gall bladder. These have been triggered by fatty foods. The Sponsor concluded that this event is not related to drug.

While the reviewer agrees that there is insufficient data to attribute this to drug, there remains some question. It is possible that this subject has some tendency to susceptibility to drug induced hepatic dysfunction. There is no post-marketing data to suggest drug related liver dysfunction (see below and Section 8, Postmarket Experience)

Phase III placebo controlled data (Studies 248.524 and 525) for hepatic function was reviewed. No parametric differences were revealed in measures of central tendency. A survey for outliers revealed the following:

Total Bilirubin: None at 3x ULN. Cases at 2 x ULN:

**Table 75 Bilirubin in Early and Advanced PD Trials**

Total Bilirubin > 2 x ULN	PTNO	ARM	Baseline	Week 8	Week 33
248.524 Early PD	2576	IR	1.1	2.2	0.8
	3203	ER	1.9	2.3	1.3
	3522	ER	1.9	2.1	2
248.525 Advanced PD	7226	IR	2.1	1.6	1.3
	7463	IR	1.7	2	1.9
	7823	PCB	1.6	2	
	8177	IR	2.2	2.4	
	8442	IR	2.1	1.9	

Two subjects had elevations of both SGOT and SGPT > 2 x ULN. One subject in the IR arm of 248.524 had elevations at screening that returned to normal during drug treatment. The other subject with increasing enzyme elevations during the trial was in the placebo arm.

No cases fulfilling Hy's Law (ALT and AST > 3 x ULN; ALT or AST > 3 x ULN with total bilirubin > 2 x ULN and alkaline phosphatase < 2 x ULN) were uncovered and no signal for serious hepatic dysfunction was found.

Post marketing analysis by OSE for Preferred Terms including *hepatic* or *liver* revealed a variety of liver phenomena including inflammation, abscess, tumor, cyst, injury and test abnormality. No clear significance may be attached to these and, taken as a whole, no safety signal is indicated. No EBO5 was greater than 0.27.

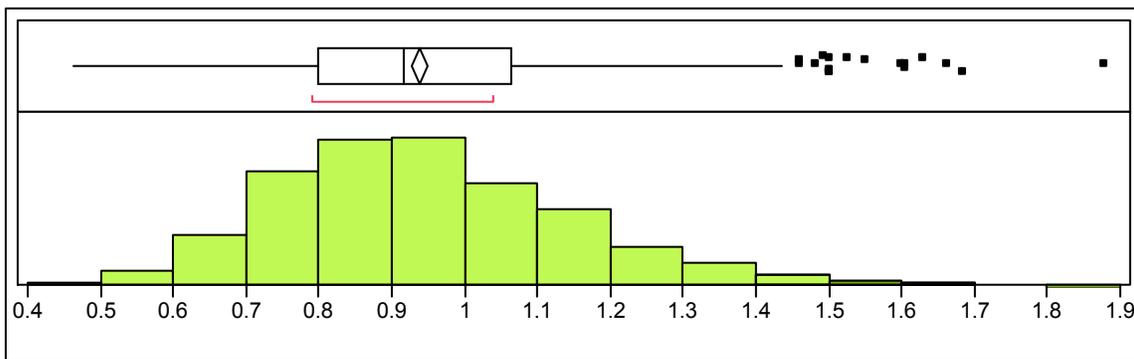
Renal Function:

Study 248.524 Early PD:

Creatinine (normal: 0.6 to 1.2 mg/dL) and urea (normal: 1.7-3.9 mmol/L) were included in the safety laboratory tests. No differences were noted by the Sponsor among the treatment groups using parametric analyses.

Analysis for outliers revealed the following distribution for all creatinine samples in the Early PD trial:

**Figure 21 Early PD Trial: creatinine**



There were 109 abnormal results (greater than 1.2 mg/dL) in 42 patients, none higher than 1.88 mg/dL equally represented among the treatment arms. All 42 subjects had elevated creatinine at baseline. Analysis for paired data revealed no change from baseline to 18 weeks within or between the treatment arms. In individuals stood out as having large shifts in creatinine during the trial.

Mean urea was 5.1 mmol/L (95% CI 4.98 – 5.18). There was a statistically significant difference from base line to week 18 between both the ER and IR groups and placebo, lowering urea during treatment by 0.3 to 0.4 mmol/L. This may reflect the physiological effects of dopamine agonists increasing renal blood flow. However this does not represent a clinically meaningful finding.

VISIT 6	4.91191	t-Ratio	-2.94627
VISIT 1	5.21467	DF	473
Mean Difference	-0.3028	Prob >  t	0.0034
Std Error	0.10276	Prob > t	0.9983
Upper95%	-0.1008	Prob < t	0.0017
Lower95%	-0.5047		
N	474		
Correlation	0.16309		

<b>ARM</b>	<b>Count</b>	<b>Mean Difference</b>	<b>Mean Mean</b>
PLACEBO	86	-0.031	5.2421
PRAMIPEXOLE ER	201	-0.435	5.0096
PRAMIPEXOLE IR	187	-0.285	5.0388

3 individuals had clinically significant elevations in urea from baseline to 11, 13 and 18.3 mmol/L. All 3 had creatinine in the normal range at baseline, which did not change. They were all in the placebo arm.

Study 248.525 Advanced PD:

Baseline creatinine ranged from 0.5 to 1.7 mg/dl. Changes by week 18 ranged from -1.1 to +0.84 mg/dl.

Baseline urea ranged from 2.1 to 12.3 mmol/L (mean 5.6, 95% CI 5.4 to 5.7 mmol/L). Changes by week 18 ranged from -8.6 to 7.7 mmol/L. Looking at outliers with changes above the 75% of change, 4 were in placebo and one each in ER and IR arms. All of these subjects had creatinine in the normal range with no significant change over the over the treatment period.

No safety signal for renal dysfunction was found.

### 7.4.3 Vital Signs

Heart Rate:

In Early PD Study 248.524, no clinically meaningful heart rate changes were found among the treatment groups when baseline rate was compared to rate on drug. Mean supine HR was 73 BPM. There was a small increase in HR from supine to standing in a paired analysis. While statistically significant among treatment arms (MPX ER 5.4, MPX IR 5.8, and PCB 4.8 BPM), this is not of clinical importance. There was no intra individual difference of significance from HR change at baseline before randomization to week 18 on stable treatment. In Advanced PD Study 248.525, results are identical. The mean resting HR was 74.8 BPM which rose to 78.8 on standing. There were no meaningful differences related to group or treatment.

Outlier analysis of all instances of tachycardia (HR > 100 BPM) revealed no consistent pattern and there were no differences in distribution of occurrences across all treatment arms in both studies.

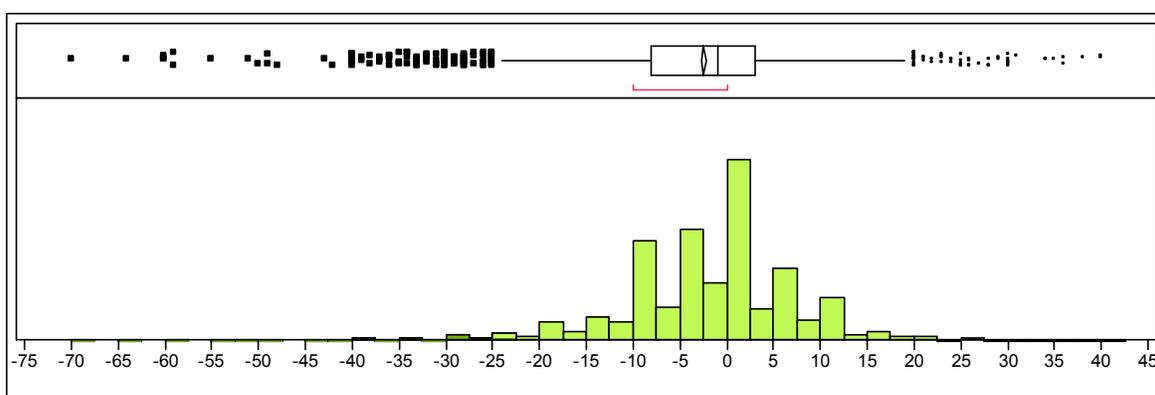
Blood pressure:

While measures of central tendency revealed little, analysis of outliers showed that more cases of orthostatic blood pressures (defined as > 20 mmHg drop from supine to standing) occurred in active treatment arms.

Study 248.524 Early PD: 16 subjects had orthostasis noted at the screening and or randomization visit and were excluded from this analysis. 53 additional subjects had a visit after randomization where a drop in systolic blood pressure (SBP) was first encountered (note that randomization was 2:2:1). The mean SBP drop was 30.9 mmHg SD 6.9 (95% CI – 28.6 to – 33.2). The degree of SBP drop in an individual did not change over the course of the trial. The number of occurrences is not different among the treatment arms.

Drop in systolic blood pressure (mmHg) on standing for one minute:

**Figure 22 Early PD Trial: SBP drop on standing (mm Hg)**



**Table 76 Early PD Trial: treatment emergent orthostasis**

	SBP drop > 20 mmHg	ER	IR	Placebo	Total
<b>248.524 Early PD</b>	Yes	26 (12 %)	20 (9 %)	7 (7 %)	53
	No	179 (84 %)	196 (88%)	95 (92 %)	470
	Excluded at BL	8 (4 %)	7 (3 %)	1 (1 %)	16
	Total	213	223	103	539

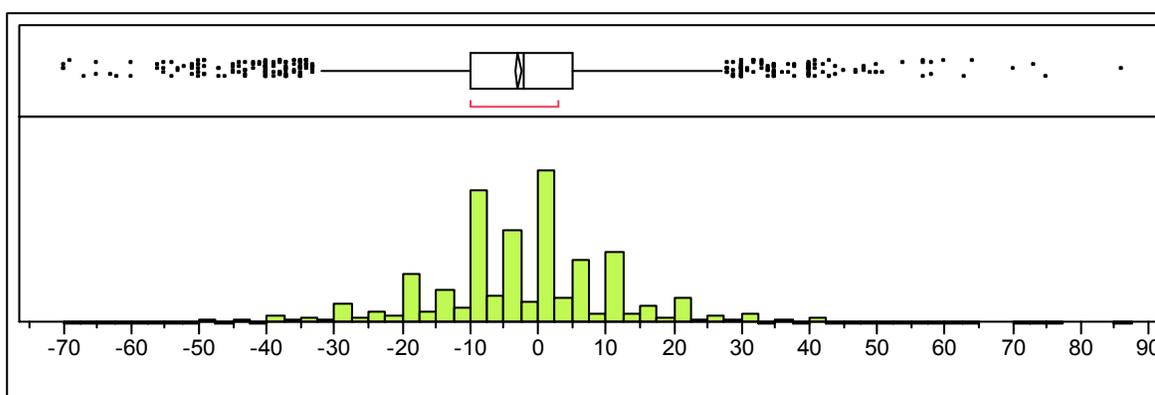
This was very consistent across treatment arms and showed no group effect for gender or age. Mean age for this group was 64 years SD 6.8 (95% CI 62.2-65.9) indicating it was not a phenomenon of advanced age. There are insufficient data for dose response analysis.

Study 248.525 Advanced PD: 84 subjects had orthostasis noted at the screening and /or randomization visit and were excluded from this analysis. This illustrates that autonomic dystrophy is a PD-related phenomenon occurring with greater frequency as

the illness progresses. 95 additional subjects had a visit after randomization where a drop in systolic blood pressure (SBP) was first encountered (note that randomization was 1:1:1). The mean SBP drop was 31.0 mmHg SD 7.1 (95% CI – 29.5 to -32.4). The degree of SBP drop in an individual did not change over the course of the trial. The magnitude of SBP change is not different among the treatment arms. Mean age for this group was 62.1 years SD 9.6 (95% CI 60.2 to 64.1) indicating it was not a phenomenon of advanced age and more likely due to duration of disease.

Drop in systolic blood pressure (mmHg) on standing for one minute:

**Figure 23 Advanced PD Trial; SBP drop on standing (mm Hg)**



**Table 77 Advanced PD Trial: treatment emergent orthostasis**

	SBP drop > 20 mmHg	ER	IR	Placebo	Total
<b>248.525 Advanced PD</b>	Yes	26 (18 %)	38 (23 %)	31 (19 %)	95
	No	91 (62 %)	95 (58 %)	111 (67 %)	297
	Excluded at BL	30 (20 %)	31 (19 %)	23 (14 %)	84
	Total	147	164	165	476

The IR label states: *“In clinical trials of pramipexole, however, and despite clear orthostatic effects in normal volunteers, the reported incidence of clinically significant orthostatic hypotension was not greater among those assigned to Mirapex® (pramipexole dihydrochloride) tablets than among those assigned to placebo.”* This current analysis of asymptomatic orthostasis provides additional support for this and does not indicate a need for more forceful language.

#### 7.4.4 Electrocardiograms (ECGs)

The effect of PPX on heart rate is discussed above in Section 7.4.3. Discontinuations for reasons of arrhythmia were few in this application; no ventricular arrhythmias were reported. No subjects discontinued treatment due to arrhythmia. There were no clinically relevant ECG changes noted by the Interdisciplinary Review Team for QT Studies (QT-IRT).

The thorough QT Trial 248.545 protocol was submitted to the QT-IRT and comments were sent to the Sponsor on 27 June 2007. The Sponsor had already initiated the trial. Concern was expressed about the proposed two stage design because of the possibility that assay sensitivity may not be established. It was recommended that three treatment arms be performed concurrently. The maximum dose of 4.5 mg/d was acceptable due to tolerability. It was felt that the likelihood of side effects above that dose in clinical practice would not remain undetected in the patient population. The trial report and ECG data was submitted to the IRT-QT for review and this is summarized below.

Unfortunately because, as predicted, the assay sensitivity was not established in Stage 2 of the trial, the results are inconclusive. The review states:

“Without a concurrent positive control, the study design cannot exclude small effects (<10 ms) on the QTc interval. The data do provide some reassurance that pramipexole is not a big QTc prolonger. A plot of the change from baseline for placebo and pramipexole arms shows overlapping confidence intervals at each time point (Figure 5). There was no evident pramipexole concentration-..QTc relationship. Furthermore, pramipexole immediate release (IR) tablets have been approved since 1997 without reports of QTc prolongation in the AERs database.

We do not accept the two-stage design with moxifloxacin administered to subjects only during the first stage, as indicated in our previous comments to the sponsor’s submitted protocol (b) (4) for this study dated on May 22 2007. This design is problematic for the following reasons: 1) Moxifloxacin was not randomized with the study drug treatments; 2) the time between moxifloxacin and placebo was five days while the time between the study drug and placebo was at least 21 days; and 3) the statistical analysis showed that .QTcF values of placebo in two different stages were significantly different at almost all time points, which indicates that the period effect (between first and second stage) may be confounded by the treatment effect. Therefore, using the first stage assay sensitivity result to claim assay sensitivity in the second stage is not valid. We do not believe further analysis of existing data will be meaningful.”

That said, the IRT suggested the following change to the Sponsor’s proposed label: “No dose- or exposure-related effect on mean QT intervals was observed; however, the study did not have a valid assessment of assay sensitivity.” Complete label suggestions are given in their consultation.

A modest rise in supine SBP (10 mmHg), DBP (7mmHg) and HR (10 bpm) were noted in these normal subjects compared to placebo; this effect is felt to be due to the forced titration schedule, one not used in the patient population. The increase in HR was noted to a more modest degree in the trial. The BP elevation was seen in some subjects but many had a drop with change in posture.

In correspondence dated January 26, 2009, the Sponsor has requested a Labeling Supplement – Change Being Effected for NDA 20667PPX IR. They propose the following language for the Clinical Pharmacology section (Pharmacodynamics);

(b) (4)



In the reviewer’s opinion, these changes reflect no significant physiological change, are not clinically important, and occur in a situation not likely to be encountered in clinical practice. The verbiage could safely be omitted from the both the IR and ER label.

#### 7.4.5 Special Safety Studies/Clinical Trials

- Retinal pathology

Eye examinations for vision and funduscopy were performed by an ophthalmologist at screening and week 28 in both the early and advanced PD trials. Abnormalities were not a reason for exclusion from the trials. “Clinically significant changes” from baseline were reported as AEs.

In looking at the results of funduscopy or vision examination from screening visit to week 28 in 248.524 Early PD, there are no statistically significant differences among the groups:

**Table 78 Early PD Trial: funduscopy from Screening to Week 28 for 179 subjects reaching this milestone**

Count (Randomized 1:2:2)	Normal at both visits	Δ Normal to Abnormal	Δ Abnormal to Normal	Abnormal at both visits	
<b>PLACEBO</b>	15	6	9	3	33

<b>PRAMIPEXOLE ER</b>	35	9	23	5	72
<b>PRAMIPEXOLE IR</b>	22	10	34	8	74
	72	25	66	16	179

**Table 79 Early PD Trial: visual exam from Screening to Week 28**

Count (Randomized 1:2:2)	Normal at both visits	Δ Normal to Abnormal	Δ Abnormal to Normal	Abnormal at both visits	
<b>PLACEBO</b>	11	6	12	4	33
<b>PRAMIPEXOLE ER</b>	24	8	27	13	72
<b>PRAMIPEXOLE IR</b>	21	14	27	12	74
	56	28	66	29	179

Analysis of adverse events by MAED Service software yielded no particular pattern of ophthalmological dysfunction.

Likewise, the use of concomitant ophthalmological medications did not suggest differing degrees of eye complaints among the groups:

248.524 Early PD:

N (%); Placebo = 23 (22.3); ER = 50 (22.4); IR = 46 (21.6).

248.525 Advanced PD:

N (%); Placebo = 25 (15.2); ER = 15 (10.2); IR = 17 (10.4).

The sponsor is performing an open label, randomized, parallel group, flexible dose, blinded ophthalmological assessment safety study under IND 34,850 (Study 248.538) as proposed in a FDA teleconference on March 20, 2002 with Pharmacia, the previous sponsor. Enrollment closed on September 18, 2008 with 246 patients randomized. Their goal is to have 200 patients complete 12 months and 134 patients complete 24 months of treatment. As of May 8, 2009, 164 have reached one year and 124 have reached the 2 year milestone. A final report is anticipated in March 2011.

- Rhabdomyolysis:

CK was not included in the serum chemistry surveillance. In the IR labeling 1 case of rhabdomyolysis is reported, but post marketing data mining by OSE for Preferred Terms indicates 14 reported cases for *rhabdomyolysis*, plus 2 additional cases of *myoglobin*

*blood* and 1 of *myoglobinuria*. However, such events are not rare and have diverse etiologies. No clear significance may be attached to this and, given the paucity of data, no safety signal is apparent.

#### **7.4.6 Immunogenicity**

No investigations of immunogenicity were submitted.

### **7.5 Other Safety Explorations**

#### **7.5.1 Dose Dependency for Adverse Events**

Beyond those phenomena noted above, there is no simple relationship between adverse events and the dose of pramipexole at which they begin. This has been observed of dopamine agonists in general. The same is true of the beneficial clinical effects. It has not been possible to predict the dose of optimal clinical effect for any particular patient.

#### **7.5.2 Time Dependency for Adverse Events**

While the studies are structured with a titration phase and maintenance phase, the former is short enough that treatment emergent effects of any particular dose may be obscured by a rapid rate of titration. Nevertheless, the Sponsor notes that Early PD trial patients had more adverse event in general in the titration phase regardless of the dosage form of pramipexole: Titration Phase TEAE (ER 72%, IR 70%); Maintenance Phase TEAE (ER 33%, IR 36%) The events (more than 2 % over those seen in the placebo arm) include: somnolence, nausea, constipation, fatigue, dry mouth, vertigo, upper abdominal pain, depression, muscle spasms, hallucinations, visual hallucinations, visual disturbance, and vomiting [ These are noted in the labeling for the IR product. This experience is mirrored in the Advanced PD trial but the limited sampling from this trial makes robust conclusions difficult.

#### **7.5.3 Drug-Demographic Interactions**

Patients with significant hepatic or renal dysfunction were excluded from the trials of PPX ER. The Clinical Pharmacology review deals in depth with the question of the use of PPX ER in renal failure. This is an important consideration for this drug which is largely excreted unchanged by the kidneys. Based upon their review, this reviewer recommends not approving the use of the extended release formulation of pramipexole in patients with moderate renal impairment.

The Sponsor investigated differences in response to drug in subjects younger and older than 65. There were small differences with TEAE found more frequently in younger

patients (79 vs 74%). These were not qualitatively different except for visual hallucinations found more frequently in the older group (2% vs 13%). This is consistent with the IR label as well. Race and gender had no apparent impact on safety.

### 7.5.4 Drug-Disease Interactions

The relationship of disease characteristics (age at onset of PD, length of disease) and the development of major disease related impairments (dementia, gait failure, motor fluctuations) is a complex one, even before introducing the factor of drug treatment. The Sponsor makes few inferences about this and the reviewer considers this appropriate and beyond the reach of the available data. The one exception to this is the appearance of dyskinesia as a TEAE in the Advanced PD trial. In the patient with motor fluctuation, the addition of any dopaminergic agent without dose reduction in concomitant treatment will result in an increase of this phenomenon. A definitive statement concerning the relationship of PPX ER to dyskinesia will have to wait for fuller analysis of this data when this trial is submitted in full in the forthcoming NDA 22514 for PPX ER in Advanced PD

### 7.5.5 Drug-Drug Interactions

No new drug-drug interaction trials were performed with PPX ER. However population pharmacokinetic data from Trial 248.524 in Early PD led to the following suggestion for labeling in the Clinical Pharmacology review:

*“Drugs affecting gastrointestinal motility or gastric pH: Population pharmacokinetic analysis suggests that co-administration of antacids (b) (4) decreases the oral clearance of pramipexole by about (b) (4), while anticholinergics (b) (4), propulsive (b) (4), and proton pump inhibitors (b) (4) are likely to have little effect on the oral clearance of pramipexole.”*

## 7.6 Additional Safety Evaluations

### 7.6.1 Human Carcinogenicity

Class labeling for PPX IR and all dopaminergic medications states that *“Epidemiological studies have shown that patients with Parkinson’s disease have a higher risk (2- to approximately 6-fold higher) of developing melanoma than the general population. Whether the increased risk observed was due to Parkinson’s disease or other factors, such as drugs used to treat Parkinson’s disease, is unclear.”* The development program for PPX ER did not illuminate this relationship further due to limited numbers of subjects and relatively short term exposure.

## **7.6.2 Human Reproduction and Pregnancy Data**

No pregnancies occurred during the course of the clinical development program. There is one case report of a successful pregnancy resulting in a normal baby while being treated with PPX for PD (Mucchuit, et al. *Mov Dis* 19 (9):1114-5, 2004).

## **7.6.3 Pediatrics and Assessment of Effects on Growth**

The clinical development program for PPX ER was performed in adults above the age of 18. Parkinson's disease generally occurs in middle age. Growth effects were not studied.

## **7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound**

No overdose was reported during the clinical development program, nor is any reported in the literature for the IR product. PPX has not been systematically studied for abuse potential. In a rat model of cocaine self-administration, PPX had no significant effect. Where there are clinical reports of addiction to dopaminergic agents in the PD literature, the reviewer does not feel these are credible. There is no evidence of true withdrawal with autonomic discharge, evidence of habituation to dose, or the generation of other addiction related behaviors.

## **7.6.5 Potential for Medication Error Due to Appearance**

This section is added to the clinical review to supplement the reviews from other disciplines which touch upon safety related to the packaging and appearance of PPX ER. The potential for medication error through pharmacy dispensing or at-home use by the patient is addressed.

In physical package, the ER pills are dispensed in bottles of 30, with the underlying assumption that a patient will on average take one tablet a day. IR tablets are dispensed in bottles of 90, assuming a TID dosing schedule of a single strength tablet. The bottles are different in appearance (ER bottle is taller and round). Bottle labels indicate the difference by adding a pink bar to the Sponsor's logo, with Mirapex ER followed by "Extended-release Tablets" in bold type.

The reviewer finds that the pills themselves have a lack of uniformity in appearance which provides a potential basis for confusion. There are 6 IR and 5 ER mg strength tablets. All are white. No consistent shape differentiates IR from ER. The ovoid tablets of the three largest ER doses are very close in size. The tablets are embossed with codes that are unrelated to the strength of the tablets. These are indicated in Table 82 below. All these features would increase the risk for the patient and healthcare provider to confuse what the patient is taking, unless the pills were closely inspected at each visit and the patient specifically warned about the look-alike nature of the tablets.

**Table 80 Mirapex IR and ER tablet embossing (from proposed label)**

Tablet Embossing (* scored)					
IR Strength	Top	Bottom	ER Strength	Top	Bottom
0.125	BI	83	0.375	(b) (4)	
0.25*	BI BI	84 84	0.75	(b) (4)	
0.5*	BI BI	85 85	1.5	(b) (4)	
0.75	BI	101	3	(b) (4)	
1.0*	BI BI	90 90	4.5	(b) (4)	
1.5*	BI BI	91 19			

It is assumed that many patients will have both dosage forms at home at certain times. Most often this will occur if their prescription is changed to the ER formulation. However, it may also happen that the patient is given sample bottles by their healthcare provider not just to start the patient on therapy but also to offset the cost of medication. A photograph of the tablets follows in Figure 24. Potentially common dose conversions from PPX IR taken TID to PPX ER taken once daily dosing are indicated by the yellow arrows in the picture.

It is worth noting that many PD medications differentiate immediate release from extended formulation by color, and often by shape in addition.

Errors may result in both under- and over-dosage. Under-dosage may lead to increased incidence of falls, while over-dosage could provoke hallucinations and behavioral aberrations related to impulse control disorder. In either case, there could be serious adverse consequences to pill confusion.

There are at least two possible solutions available to resolve this issue. Both would necessitate a Complete Response to the Sponsor. One proposal would be to keep the tablet white but change embossing to indicate “ER” and make the shape of the ER tablets consistent, with greater gradations of size, and more readily identifiable with regards to mg dose. The fabricating facility would have to retool, and a new version of the pills would require dissolution studies. Other CMC requirements may also have to be fulfilled. However this requirement would be simpler than suggesting color coding of tablets. This would necessitate a fuller investigation of the new formulation including studies of dissolution and long term stability. The reviewer would find the first solution an acceptable compromise between the risk of medication error and hardship to patients resulting from the delay of getting this medication to market.

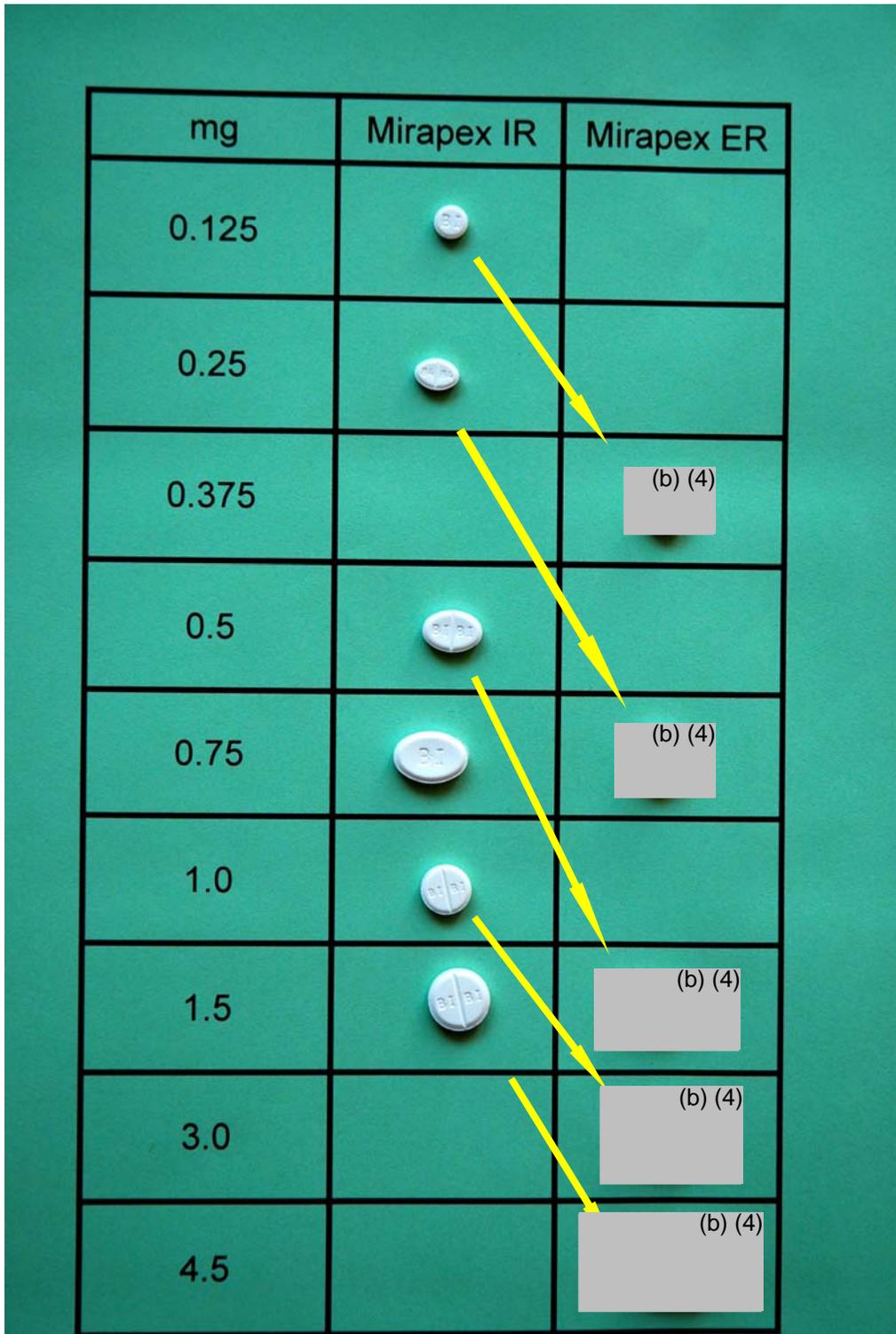


Figure 24 Photograph of Mirapex IR and ER tablets (see text)

## 7.7 Additional Submissions

None.

## 8 Postmarket Experience

No post-marketing experience exists with PPX ER.

Data mining performed within AERS by OSE for events reported for PPX IR revealed the following events with an EB05 greater than 2. No events were unexpected. The disproportionately high EB05 scores for the behavioral abnormalities associated with PPX IR likely reflect the social influences which affect the pattern of data submission to this voluntary reporting system, and not the rate of occurrence of these phenomena. As such it should be interpreted with great caution, and the reviewer sees this only as confirmatory of the sorts of abnormalities that one may see associated with the use of this agent, not a qualitative estimate of prevalence.

**Table 81 Results of Datamining of PPX IR in AERS database (source: OSE)**

PT	SOC	N	EBGM	EB05	EB95
Pathological gambling	Psych	685	153.897	144.5	163.811
Gambling	SocCi	118	162.629	139.4	188.804
Sleep attacks	Psych	63	154.7	125.1	189.585
Compulsive shopping	Psych	90	146.608	122.8	173.875
Hypersexuality	Psych	96	110.042	92.73	129.813
Obsessive-compulsive disorder	Psych	430	97.227	89.75	105.185
Sudden onset of sleep	Nerv	64	90.104	72.99	110.249
Hyperphagia	Metab	107	78.869	67.08	92.241
Compulsions	Psych	28	85.941	62.2	116.345
Libido increased	Psych	74	65.184	53.61	78.654
Bankruptcy	SocCi	8	97.841	51.91	171.37
Impulse-control disorder	Psych	26	61.323	43.82	83.954
Mood disorder due to a general medical condition	Psych	9	78.219	43.2	132.736
Jealous delusion	Psych	7	83.221	42.03	151.478
Compulsive sexual behaviour	Psych	10	68.05	38.86	112.433
On and off phenomenon	Nerv	8	65.02	34.49	113.909
Obsessive-compulsive personality disorder	Psych	8	60.252	31.96	105.574
Emotional distress	Psych	315	27.161	24.73	29.773

Economic problem	SocCi	59	30.5	24.49	37.628
Binge eating	Psych	16	36.348	23.54	54.151
Narcolepsy	Nerv	13	27.847	17.06	43.397
Restless legs syndrome	Nerv	64	18.339	14.85	22.442
Posture abnormal	Musc	16	17.68	10.49	26.983
Parkinson's disease	Nerv	42	13.417	9.997	17.417
Hallucination	Psych	221	10.967	9.761	12.277
Limb discomfort	Musc	24	14.381	9.275	20.489
Dyskinesia	Nerv	87	10.034	8.199	12.156
Fear	Psych	79	9.83	7.937	12.054
Stress	Psych	88	9.463	7.757	11.471
Akinesia	Nerv	14	14.824	7.032	24.592
Hallucination, visual	Psych	49	8.859	6.706	11.674
Road traffic accident	Inj&P	76	6.835	5.618	8.279
Delusion	Psych	36	7.125	5.274	9.677
Sleep disorder	Psych	74	6.416	5.268	7.77
Muscle rigidity	Musc	31	6.879	4.977	9.571
Abnormal behaviour	Psych	89	5.739	4.804	6.817
Sedation	Nerv	85	5.565	4.64	6.634
Hypomania	Psych	13	8.815	4.459	17.63
Somnolence	Nerv	175	4.778	4.213	5.401
Movement disorder	Nerv	38	5.484	4.166	7.132
Impulsive behaviour	Psych	11	8.693	4.064	19.083
Paraphilia	Psych	4	39.991	4.048	111.325
Depression	Psych	284	4.434	4.018	4.883
Neuroleptic malignant syndrome	Nerv	26	5.325	3.811	7.321
Personality change	Psych	22	5.386	3.735	7.644
Drug intolerance	Genrl	29	4.982	3.639	6.708
Marital problem	SocCi	7	11.342	3.416	31.198
Hallucination, auditory	Psych	22	4.557	3.177	6.389
Psychotic disorder	Psych	41	3.992	3.072	5.119
Dystonia	Nerv	19	4.483	3.04	6.444
Injury	Inj&P	77	3.635	3.005	4.365
Suicidal ideation	Psych	93	3.422	2.879	4.044
Chorea	Nerv	7	6.495	2.732	20.091
Anxiety	Psych	194	3.055	2.712	3.433
Condition aggravated	Genrl	166	3.057	2.687	3.466
Mania	Psych	24	3.778	2.68	5.209
Restlessness	Psych	35	3.441	2.591	4.499
Periodic limb movement disorder	Nerv	4	20.911	2.567	78.109
Weight increased	Inv	153	2.932	2.563	3.341

Adverse drug reaction	Genrl	26	3.557	2.558	4.845
Paranoia	Psych	26	3.492	2.511	4.755
Delirium	Psych	30	3.27	2.407	4.363
Motor dysfunction	Nerv	12	3.859	2.369	6.034
Psychomotor hyperactivity	Nerv	18	3.516	2.364	5.078
Theft	SocCi	5	8.324	2.303	35.277
Suicide attempt	Psych	52	2.898	2.298	3.617
Divorced	SocCi	4	15.167	2.255	66.257
Feeling guilty	Psych	5	7.361	2.219	32.068
Hallucination, olfactory	Psych	4	13.834	2.184	63.119
Alcohol use	SocCi	11	3.591	2.158	5.705
Insomnia	Psych	140	2.474	2.149	2.836
Legal problem	SocCi	6	4.603	2.135	12.418
Activities of daily living impaired	SocCi	25	2.925	2.09	4.005
Confusional state	Psych	114	2.432	2.081	2.829
Abnormal dreams	Psych	30	2.781	2.047	3.711
Orthostatic hypotension	Vasc	20	2.961	2.033	4.198
Drug effect decreased	Genrl	58	2.493	2.002	3.076

## 9 Appendices

### 9.1 Literature Review/References

Citations are noted in the text.

### 9.2 Labeling Recommendations

#### Background:

The Mirapex IR label exists in non PLR format. The Sponsor provided a PLR draft for this IR label as well as proposing the ER label. Only the ER label is addressed at this time. Three CBEs are pending, and these are discussed below.

The Sponsor provides an annotated draft label in eCTD 1.2 citing support from sections in the application for support. The last revised version is received June 19, 2009. In general, it will need considerable editing as it appears to have been largely copied from the IR label. (b) (4)

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

Clinical Review  
Kenneth Bergmann, MD, FAAN  
NDA 22-421  
Mirapex ER / pramipexole dihydrochloride extended-release tablets

[REDACTED] (b) (4)

[REDACTED]

### **9.3 Advisory Committee Meeting**

No advisory committee consideration was sought for this application.

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

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/s/

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KENNETH J BERGMANN

08/13/2009

Final primary clinical review; discussed with TL and DD.

GERALD D PODSKALNY

08/20/2009



## CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Pivotal Study #1 248.524 Indication: Treatment of early Parkinson's disease.  Pivotal Study #2 248.525 Indication: Treatment of advanced Parkinson's disease. Interim safety analysis submitted. Efficacy portion still in progress and data not submitted. 3 arm: ER, IR, PCB.				IR, and PCB.
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			Review will determine whether indication for advanced PD is supported by the PK and early PD trials.
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?		X		Given the illness's similar prevalence and phenotype worldwide, this is not seen as an issue.
<b>SAFETY</b>					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (e.g., QT interval studies, if needed)?	X			QT study 248.545 will require review. Usual therapeutic doses not exceeded in study.
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure <sup>1</sup> ) been exposed at the dose (or dose range) believed to be efficacious?	X			
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
23.	Has the applicant submitted the coding dictionary <sup>2</sup> used for mapping investigator verbatim terms to preferred terms?	X			
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			

<sup>1</sup> For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

<sup>2</sup> The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

## CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			
<b>OTHER STUDIES</b>					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			But adequacy of study remains to be reviewed
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included ( <i>e.g.</i> , label comprehension, self selection and/or actual use)?			X	
<b>PEDIATRIC USE</b>					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			PD doesn't occur in children
<b>ABUSE LIABILITY</b>					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?	X			Animal study suggests no abuse potential.
<b>FOREIGN STUDIES</b>					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?		X		But regional endpoint assessments are discussed. Clinical trial sites in Europe and North America.
<b>DATASETS</b>					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			But will defer to Statistics opinion based upon closer inspection of the structure of the database.
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			Data dictionary and computational dictionary provided
<b>CASE REPORT FORMS</b>					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			CRFs transcribed to forms from electronic data entry.
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	X			
<b>FINANCIAL DISCLOSURE</b>					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
<b>GOOD CLINICAL PRACTICE</b>					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

# CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

**IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? \_\_\_ Yes \_\_\_**

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

None at this time.

Kenneth Bergmann	12/12/2008
Reviewing Medical Officer	Date
Norman Hershkowitz	12/12/2008
Clinical Team Leader	Date

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/s/

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Kenneth Bergmann  
12/17/2008 01:43:58 PM  
MEDICAL OFFICER  
You already reviewed and OKed this.

Norman Hershkowitz  
12/19/2008 09:00:24 AM  
MEDICAL OFFICER

**Interdisciplinary Review Team for QT Studies Consultation:  
Thorough QT Study Review**

<b>NDA</b>	NDA 22-421
<b>Brand Name</b>	MIRAPEX® ER™/Sifrol®
<b>Generic Name</b>	Pramipexole Dihydrochloride
<b>Sponsor</b>	Boehringer Ingelheim Pharmaceuticals, Inc
<b>Indication</b>	Idiopathic Parkinson's Disease (PD)
<b>Dosage Form</b>	Tablets (ER and IR)
<b>Drug Class</b>	Nonergot dopamine agonist
<b>Therapeutic Dosing Regimen</b>	0.375 to 4.5 mg/day (ER and IR)
<b>Duration of Therapeutic Use</b>	Chronic
<b>Maximum Tolerated Dose</b>	4.5 mg ER q.d. and 1.5 mg IR t.i.d.
<b>Submission Number and Date</b>	N 000 October 23 <sup>rd</sup> , 2008
<b>Review Division</b>	DNP / HFD 120

**1 SUMMARY**

This study is inconclusive because assay sensitivity cannot be established in stage 2. Without a concurrent positive control, the study design cannot exclude small effects (<10 ms) on the QTc interval. The data do provide some reassurance that pramipexole is not a big QTc prolonger. A plot of the change from baseline for placebo and pramipexole arms shows overlapping confidence intervals at each timepoint (Figure 5). There was no evident pramipexole concentration- $\Delta\Delta$ QTc relationship. Furthermore, pramipexole immediate release (IR) tablets have been approved since 1997 without reports of QTc prolongation in the AERs database.

We do not accept the two-stage design with moxifloxacin administered to subjects only during the first stage, as indicated in our previous comments to the sponsor's submitted protocol (b) (4) for this study dated on May 22 2007. This design is problematic for the following reasons: 1) Moxifloxacin was not randomized with the study drug treatments; 2) the time between moxifloxacin and placebo was five days while the time between the study drug and placebo was at least 21 days; and 3) the statistical analysis showed that  $\Delta$ QTcF values of placebo in two different stages were significantly different at almost all time points, which indicates that the period effect (between first and second stage) may be confounded by the treatment effect. Therefore, using the first stage assay sensitivity result to claim assay sensitivity in the second stage is not valid. We do not believe further analysis of existing data will be meaningful.

## 2 PROPOSED LABEL

The sponsor has proposed the following description of the study in the label. Our suggestions are shown using red strike out font for deletions and blue font for insertions. We defer all final labeling decisions to the review division.

### 12.2 Pharmacodynamics

The effect of pramipexole on the QT interval of the ECG was investigated in a clinical study in 60 healthy male and female volunteers. All subjects initiated treatment with 0.375 mg MIRAPEX ER tablets administered once daily, and were up-titrated every 3 days to 2.25 mg and 4.5 mg daily. No (b) (4) dose- or exposure-related effect on mean QT intervals was observed; however, the study did not have a valid assessment of assay sensitivity. (b) (4)



The effect of pramipexole on QTc intervals at higher exposures achieved either due to drug interactions, renal impairment, or at higher doses has not been systematically evaluated.

## 3 BACKGROUND

### 3.1 PRODUCT INFORMATION

Pramipexole is a nonergot dopamine agonist with full intrinsic activity. It shows high selectivity for interacting with receptors of the D2 subfamily which consists of D2, D3 and D4 receptors. Pramipexole exhibits higher affinity for the D3 receptor subtypes than for D2 or D4 subtypes. Boehringer-Ingelheim has developed an extended-release (ER) formulation of pramipexole for the treatment of signs and symptoms of idiopathic Parkinson's Disease (PD). This formulation, which has a slower release of the active ingredient than that of the IR formulation will allow patients to treat their symptoms with a single daily dose, instead of three doses per day.

### 3.2 MARKET APPROVAL STATUS

Pramipexole immediate release (IR) tablets were first authorized in the USA in 1997 and are marketed as Mirapex®. These tablets are also commercially available in the European Union (EU), Norway, Switzerland, Canada, South Africa, and South America as well as in countries in Eastern Europe, Near East and Asia, including Japan. In these locations the drug product is marketed as Sifrol®, Mirapexin® or Pexola®. Pramipexole IR tablets are indicated for the treatment of signs and symptoms of either early Parkinson's disease (PD) or advanced PD in combination with levodopa as well as for Restless Legs Syndrome.

### 3.3 PRECLINICAL INFORMATION

From the study report

“The possible effects of PPX on the myocardial repolarising current  $I_{K_r}$  was investigated in an in vitro model in which HEK293 cells were stably transfected with the human cDNA for HERG protein. Such cells express transmembrane channels conducting a current closely resembling  $I_{K_r}$ . PPX was tested in this model in concentrations from 0.3 to 30  $\mu\text{M}$ . Even with the very high concentration of 30  $\mu\text{M}$ , less than 50% inhibition of the current was seen and an  $\text{IC}_{50}$  was estimated to be 34.7  $\mu\text{M}$  [U04-1157]. Given that PPX in patients reaches concentration of only up to 10 nM (with maximum recommended dose, even in case of renal disease or concomitant medication of cimetidine), this suggests that there is a very wide safety margin (of around 3000) for this mechanism of repolarisation-induced arrhythmia. Therefore, there is no preclinical basis for the assumption that PPX has the potential to affect the QT interval.

“Anesthetized pigs were instrumented for the measurement of systemic arterial blood pressure, left ventricular pressure and LV dP/dt, and the ECG. Following a 30 min control, pretreatment period, treatments were begun first using the solvent for 30 min followed by pramipexole in doses of 1, 3 and finally 10 mg/kg. At each level, the heart was paced to 100 or 120 bpm for 5 min to allow comparison of ECG parameters at matched heart rates since a heart rate increase with pramipexole was anticipated. Indeed, the doses of 1 and 10 mg/kg pramipexole were associated with dose-dependent increases in both heart rate and arterial blood pressure. The LV-dP/dtmax was not altered.

“There was a dose-dependent reduction in the QT interval at matched heart rates. The shortened QT interval may be a result of the sympathetic activation seen in higher doses. At the end of the pramipexole treatment, dofetilide was administered i.v. and each animal responded with a prolongation of the QT interval, thereby, demonstrating the responsiveness of the model (report in preparation).

“Action potentials were measured in isolated guinea pig papillary muscles and the effect of pramipexole was tested in cumulative concentrations of 0.1, 0.3, 1.0, 3.0, and 10.0  $\mu\text{M}$  (n=5). Another group (n=5) received equivalent concentrations of the vehicle (DMSO). Measurements were taken at a stimulation frequency of 0.33 Hz (20 cycles/min) and included action potential duration to 10%, 30% and 90% repolarisation, resting membrane potential, maximal velocity of phase 0 upstroke, action potential overshoot, amplitude, and the force of contraction. None of the parameters was affected by pramipexole in the concentrations tested, except for a tendency towards an increase in force of contraction in concentrations of 3 and 10  $\mu\text{M}$ .”

### 3.4 PREVIOUS CLINICAL EXPERIENCE

From NDA 22,421, clinical overview, summary of clinical safety.

“Based on the results of this clinical development program, the safety profile of pramipexole ER can be summarized as follows:

- “Pramipexole ER in PD patients is generally well tolerated. In the placebo-controlled study in early PD without concomitant levodopa treatment, the most common adverse events (frequency  $\geq 5\%$  and greater than placebo) were somnolence, nausea, constipation, fatigue, and dry mouth. Approximately 10% of the pramipexole ER treatment group, compared to 4% in the placebo group, discontinued due to adverse events in this early PD study. In the placebo-controlled study in advanced PD with concomitant levodopa treatment, the most common adverse events (frequency  $\geq 5\%$  and greater than placebo) were dyskinesia, nausea, constipation, insomnia, dizziness, headache. Approximately 4% of the pramipexole ER treatment group, compared to 4% in the placebo group, discontinued due to adverse events in this advanced PD study. Overall (i.e., both placebo-controlled trials pooled), the adverse events most commonly causing discontinuation of study drug in more than one patient on pramipexole ER compared with placebo were nausea and vomiting.
- “The safety and tolerability profile of pramipexole ER does not appear to differ from that of pramipexole IR either when used to treat patients with early PD not on levodopa or when used to treat patients with advanced PD on concomitant levodopa. In addition, pramipexole ER does not appear to differ from pramipexole IR in regards to the frequency of overall adverse events, serious adverse events, adverse events leading to drug discontinuation; frequency of common adverse events; or frequency of adverse events of special interest.
- “PD patients on pramipexole IR can be switched overnight to pramipexole ER at the same daily dose. In an active-control clinical trial, only one of 104 (1.0%) patients discontinued drug treatment due to an adverse event when blindly switched overnight from pramipexole IR to pramipexole ER at the same daily dose.
- “No new or unexpected safety or tolerability issue emerged during the clinical development program of pramipexole ER.”

*Reviewer’s comments: No seizures, sudden death or ventricular arrhythmias were reported in pramipexole’s ER clinical program. Two syncopal episodes were reported, one in the placebo and one in the pramipexole’s arm. There were no clinically relevant ECG changes reported.*

### **3.5 CLINICAL PHARMACOLOGY**

Appendix 6.1 summarizes the key features of pramipexole’s clinical pharmacology.

## **4 SPONSOR’S SUBMISSION**

### **4.1 OVERVIEW**

The QT-IRT reviewed the protocol concurrently while this study was being conducted in June, 2007.

The sponsor submitted the thorough QT study report 248.545 for pramipexole, including electronic datasets and waveforms to the ECG warehouse.

*Reviewer's Comments: The sponsor should be advised not to initiate TQT study without IRT review of protocol. In this case, the sponsor proceeded with the study while the IRT was reviewing the protocol.*

## **4.2 TQT STUDY**

### **4.2.1 Title**

A double-blind, randomized, placebo-controlled study with two sequential two-way cross-over parts to demonstrate that the influence of pramipexole up to 4.5 mg daily on the QT interval of the ECG in healthy male and female volunteers is comparable with placebo, with a positive control (two-way cross-over moxifloxacin versus placebo)

### **4.2.2 Protocol Number**

248.545

### **4.2.3 Study Dates**

May 11, 2007 — October 9, 2007

### **4.2.4 Objectives**

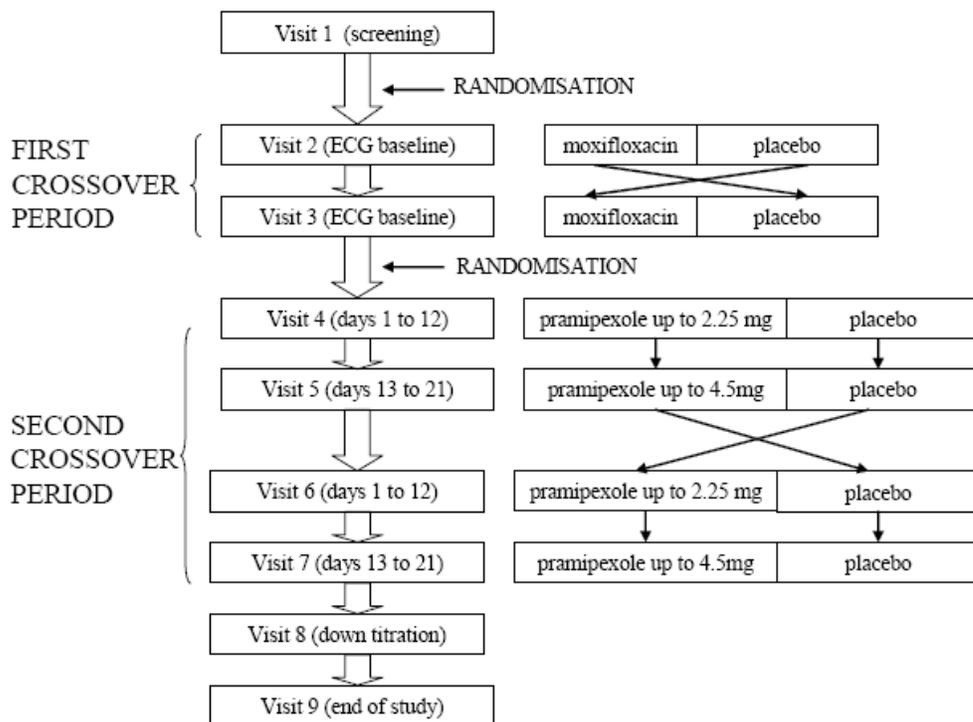
The objective of this study was to demonstrate that pramipexole does not prolong the QT interval more than placebo.

### **4.2.5 Study Description**

#### **4.2.5.1 Design**

The study was a single-centre, double-blind, randomized, placebo-controlled study with 2 sequential two-way crossover parts to demonstrate that the influence of pramipexole on the QT/QTc interval of the ECG of healthy male and female volunteers is similar with placebo. Schematic representation of the design is in Figure 1:

**Figure 1: Two Stage Randomization Treatment Sequence**



*Reviewer's Comments: We disagree with the sponsor's two-stage design where there was no randomization between moxifloxacin and drug treatments. Also, the potential period effect might be confounded with the treatment effect. As indicated in our analysis in Section 5.2, the placebo effect for moxifloxacin comparison is different from that for pramipexole comparison.*

#### **4.2.5.2 Controls**

The sponsor used both placebo and positive (400 mg moxifloxacin) controls in two separate stages.

#### **4.2.5.3 Blinding**

Subjects and the investigator were blinded to treatment during the second two-way crossover (pramipexole and placebo) part. For visit 6, on days 1 to 4 down-titration, a double-dummy design was used.

For the first two-way crossover (moxifloxacin and placebo), treatment was not blinded. However, the site responsible for ECG assessment was blinded during both the moxifloxacin crossover and the pramipexole crossover.

#### **4.2.6 Treatment Regimen**

##### **4.2.6.1 Treatment Arms**

As indicated in Figure 1, treatments are divided into two independent stages: moxifloxacin crossover and pramipexole crossover.

In moxifloxacin crossover, in the first period (visit 2), one arm received 400 mg of moxifloxacin, and one arm received placebo, in the second period (visit 3), the moxifloxacin arm switched to placebo while the placebo arm switched to moxifloxacin.

In pramipexole crossover, in period one (Visit 4), one arm received pramipexole ER up-titration to 2.25 mg/day (Day 12), one arm received placebo for 12 days. After PK sampling and ECGs recording, pramipexole arm continued up-titration to 4.5 mg/day on day 21, placebo continued to day 21 as well, PK samples were collected and ECGs were recorded again. In period two, the pramipexole arm switched to placebo while the placebo arms received pramipexole up-titration to 2.25 mg/day (day 12) and 4.5 mg/day (day 21). On days for PK sampling (day 12 and 21), the pramipexole arm was given pramipexole IR t.i.d.

#### **4.2.6.2 Sponsor's Justification for Doses**

“The 4.5 mg pramipexole was found to be the highest tolerated daily dose in healthy volunteers. In trial 248.116, a three-week up-titration of IR tablets to reach a 1.5 mg t.i.d dose was found causing gastrointestinal adverse events (nausea and vomiting) in half of the subjects. In another trial using pramipexole ER with up to 4.5 mg pramipexole, 18% of the healthy volunteers reported nausea and 10% reported vomiting. These data suggest that the tolerability of up to 4.5 mg pramipexole administered as ER tablets in healthy volunteers is acceptable for the purpose of a TQT. At the same time, a TQT with the ER formulation of pramipexole can provide a systemic exposure equivalent to 1.5 mg pramipexole IR t.i.d. Pramipexole IR tablets provide a better predictable maximum plasma concentration during the first 4 hours after administration.

Due to the pharmacokinetic and metabolic properties of pramipexole, only a limited potential for an increase in plasma level due to drug interactions exists. Significant over-dosage is not expected to remain undetected due to the profile of side effects. The dose of 4.5 mg once daily was considered to cover the exposure levels expected clinically. Patients with limited clearance capacity (renal insufficiency) will never receive the highest daily dose of 4.5 mg”.

*Reviewer's Comments: The chosen dose is acceptable. Since 4.5 mg/day is the highest tolerable dose in healthy volunteers, it is suitable to consider it as the supra-therapeutic dose for TQT study.*

#### **4.2.6.3 Instructions with Regard to Meals**

All treatments (moxifloxacin, pramipexole or placebo) were administered in the morning, 30 to 60 minutes after intake of breakfast. Alcoholic beverage, grapefruit juice, caffeine-containing foods or beverage (e.g., coffee, energy drinks) were not allowed within 48 hours before any ECG recording. Additionally, alcoholic beverages were not allowed during visits 4 to 8, from 48 hours before first dosing until 48 hours after last dosing, to avoid sedating effects in combination with pramipexole.

*Reviewer's Comment: The meal arrangement is acceptable. While meal type affects the systemic exposure (AUC) of pramipexole for both IR and ER tablets, the meal type does not affect the  $C_{max}$  following IR tablets.*

#### 4.2.6.4 ECG and PK Assessments

Blood samples for pharmacokinetic measurements of pramipexole were taken at 1.0, 1.5, 2.0, 3.0, 4.0 and 7.0 h relative to drug application time on days 12 and 21 (i.e. on all days with an ECG profile during the pramipexole or placebo dosing period). ECGs were recorded at the same time points.

*Reviewer's Comment: The selected timing points of ECGs and PK are acceptable. The  $T_{max}$  of pramipexole is about 1.5 hours, which is covered by the selected time window. The sponsor did not report PK of moxifloxacin.*

#### 4.2.6.5 Baseline

Baseline value is defined as the ECG measurements before dose on the same day.

#### 4.2.7 ECG Collection

The study was performed at [REDACTED] (b) (4)

ECGs were recorded digitally. Interval measurements were performed using digital ECGs.

All ECGs except those obtained at screening or end-of-study examination were sent to a central ECG laboratory for interval measurement [REDACTED] (b) (4)

For the first two-way crossover (moxifloxacin and placebo), treatment was not blinded. However, the site responsible for ECG assessment was blinded during both the moxifloxacin crossover and the pramipexole crossover. Within the ECG laboratory, the staff involved with interval measurements and assessments was blinded with regard to the date and recording time of the ECGs. Each interval measurement was performed as a batch by a single reviewer for a given subject in a random and blinded sequence.

Each interval measurement was performed as a batch by a single reviewer for a given subject in a random and blinded sequence. No more than 2 different readers were to evaluate the ECGs of this study. For quality assurance and control of the measurements, all ECGs of a subject were compared with respect to the overall variance of the measured intervals, in order to detect accidental switching of leads or false subject assignments of the ECGs.

Interval measurements were performed on one lead, usually lead II. If lead II showed a flat T wave or was immeasurable for any reason, lead V2 was to be used, or, if that lead was immeasurable, then lead I was to be used. Information on the lead used was recorded. All interval measurements in one subject were to be performed on the same lead. Intervals were assessed on 4 wave forms from the lead chosen. Heart rate in bpm was calculated as 60 s/RR (in seconds). The measurements of the single wave forms were stored in the data base as raw data. All ECGs with measurable leads in at least 2 waveforms entered the analysis. Only the mean values were used for display and analysis. For each QT interval, the RR interval preceding the QT was measured and used for frequency correction.

A board-certified cardiologist over-read the ECGs obtained. Only 1 of the 3 ECGs at one time point was selected randomly and interpreted. All additional (unscheduled) ECGs recorded due to safety reasons at the study site were also interpreted. ECG interpretation included general (normal, abnormal, not interpretable), arrhythmia, conduction delays or other abnormalities (no or yes, specified if yes), T wave morphology (normal, flat, inverted or biphasic) and U wave morphology (normal or abnormal) findings.

QT and QTcB values generated by the monitors or their manual corrections by the investigators were used for the exclusion criteria (Sponsor's report, Page 37)) and for safety assessment during the study. The ECG recordings taken at screening and end-of-study examination were not assessed centrally.

#### **4.2.8 Sponsor's Results**

##### **4.2.8.1 Study Subjects**

A total of 60 subjects (female and males) 21 to 50 years of age with a BMI of 18.5 to 29.9 kg/m<sup>2</sup> were enrolled and randomized.

Of the 60 treated subjects, 59 completed treatment with moxifloxacin and 57 completed treatment with moxifloxacin placebo in the first crossover part. During the first crossover part, 4 subjects discontinued the trial after completing the first period and 1 subject discontinued the trial after completing the second period. In the second crossover part, 48 subjects completed treatment with pramipexole and 50 subjects completed treatment with pramipexole placebo.

##### **4.2.8.2 Statistical Analyses**

###### **4.2.8.2.1 Primary Analysis**

Change of QTcI from baseline and placebo is considered as the primary endpoint for the study. The pair-wise comparison between pramipexole placebo and pramipexole of the QTcI at each time point on day 12 and day 21 was based on a repeated measurements analysis with fixed effects for treatment, period, sequence, time treatment\*time and period\*time and the random effect subjects within sequence. The highest upper limit of the two-sided 90% confidence interval was 1.6 ms on day 12 and 0.7 ms on day 21, less than 10 ms.

**Table 1: QTcI Comparison between Treatment and Placebo on Day 12 and 21**

Relative time	Day 12, difference of pramipexole 2.25 mg vs. placebo [ms]			Day 21, difference of pramipexole 4.5 mg vs. placebo [ms]		
	N	Mean (SE)	90% CI (lower, upper)	N	Mean (SE)	90% CI (lower, upper)
1:00	48	-2.7 (2.0)	(-6.1, 0.6)	48	-5.0 (1.7)	(-7.8, -2.3)
1:30	47	-2.0 (1.8)	(-5.0, 1.0)	48	-2.5 (1.6)	(-5.3, 0.3)
2:00	48	-2.2 (1.7)	(-5.0, 0.6)	48	-1.9 (1.5)	(-4.4, 0.7)*
3:00	47	-1.2 (1.7)	(-4.0, 1.6)*	48	-3.3 (1.5)	(-5.8, -0.7)
4:00	48	-4.4 (1.7)	(-7.3, -1.5)	47	-4.1 (1.7)	(-6.9, -1.3)
7:00	48	-3.0 (1.6)	(-5.8, -0.3)	48	-2.9 (1.8)	(-5.8, 0.0)

Source: sponsor's table 11.5.3.2:2

#### **4.2.8.2.2 Assay sensitivity**

Assay sensitivity was to be shown by a different test of moxifloxacin compared with placebo using an ANCOVA model with the factors described for the primary analysis. The same model used for pramipexole was applied on moxifloxacin and placebo during stage one. The unadjusted largest upper bound of  $\Delta\Delta\text{QTcI}$  is 17.4 ms at 2 hours after dose, greater than 5 ms.

#### **4.2.8.2.3 Categorical Analysis**

Overall, there was no occurrence of QTc interval >480 ms during the trial, and no increase of >60 ms. With moxifloxacin treatment, 3 subjects showed a new onset of QTcI >450 ms, 7 subjects showed a placebo-corrected change from baseline of QTcI >30 ms and 4 subjects showed a change from baseline of QTcI >30 ms. There were no notable changes of QTcI for either placebo or pramipexole treatments. Similar results were observed in QTcF and QTcB.

#### **4.2.8.3 Safety Analysis**

Overall, 48 subjects completed the total planned observation period, and 12 subjects discontinued treatment prematurely. Seven subjects withdrew consent due to private reasons (subjects no. 5, 6, 10, 18, 40, 52, and 58). Subject no. 57 was removed from the trial due to non-compliance with the trial protocol (positive drug test). Subjects n° 2, 34, 54 and 43 experienced an AE resulting in treatment discontinuation. Of the 4 subjects who discontinued the trial due to an AE, 1 was on treatment with pramipexole and 3 were on treatment with placebo at the time of onset. The number of subjects who discontinued the trial during the third period (first part of pramipexole crossover) was 5 during placebo treatment and 2 during pramipexole treatment. No subjects discontinued the trial after the third treatment period.

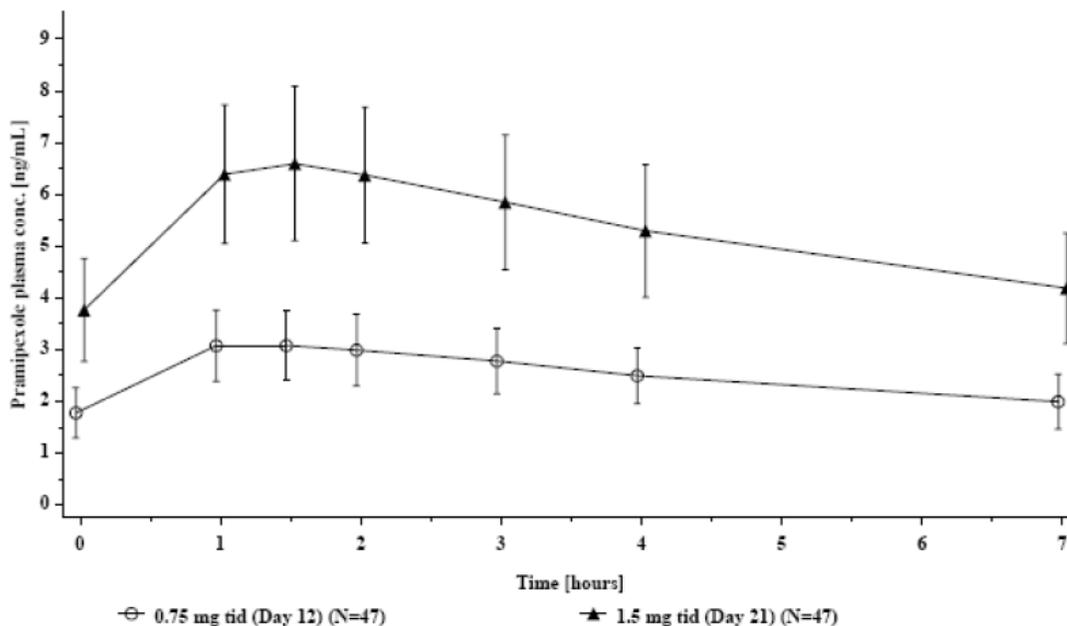
#### **4.2.8.4 Clinical Pharmacology**

##### **4.2.8.4.1 Pharmacokinetic Analysis**

The PK results are demonstrated in Figure 2 and summarized in Table 2 (pramipexole).  $C_{\text{max}}$  and  $\text{AUC}_{\tau, \text{ss}}$  in the thorough QT study were both 2.1-fold higher following

administration of 1.5 mg pramipexole compared with 0.75 mg, the intended clinical dose. No PK of moxifloxacin was reported.

**Figure 2: Mean plasma concentration-time profiles of pramipexole after multiple oral administration of pramipexole IR 0.75 mg t.i.d (day 12) or 1.5 mg t.i.d (day 21) to healthy male and female volunteers.**



Source: Figure 11.5.2.1:3 from page 74 of the Sponsor's Report

**Table 2: Comparison of key pharmacokinetic parameters of pramipexole after multiple administration of either 0.75 mg t.i.d or 1.5 mg t.i.d of pramipexole IR to healthy male and female healthy volunteers**

Treatment		0.75 mg t.i.d.		1.5 mg t.i.d.			
		N	gMean	gCV (%)	N	gMean	gCV (%)
AUC <sub>τ,ss</sub>	[ng·h/mL]	47	19.2	22.9	47	40.3	22.9
AUC <sub>0-7,ss</sub>	[ng·h/mL]	47	17.3	22.6	47	36.4	22.6
C <sub>max,ss</sub>	[ng/mL]	47	3.20	20.4	47	6.69	20.9
C <sub>pre,ss</sub>	[ng/mL]	47	1.71	29.6	47	3.64	27.6
t <sub>max,ss</sub> *	[h]	47	1.50	1.00-3.00	47	1.50	1.00-3.00

The asterisk (\*) indicates median and range

Source: Table 11.5.2.2:1 from page 75 of the Sponsor's Report

#### 4.2.8.4.2 Exposure-Response Analysis

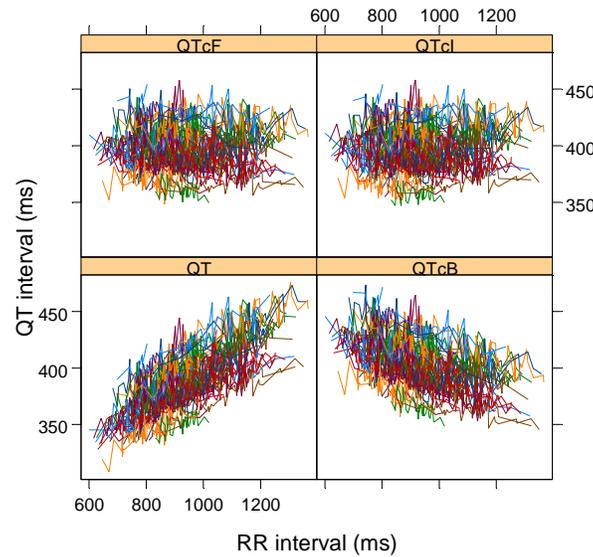
Reviewer's Comments: The sponsor did not evaluate the dose/concentration-QTcF relationship.

## 5 REVIEWERS' ASSESSMENT

### 5.1 EVALUATION OF THE QT/RR CORRECTION METHOD

The observed QT-RR interval relationship is presented together with the Bazett's (QTcB), Fridericia (QTcF) and individual correction (QTcI) in Table 3. Among all three correction methods, QTcF is obviously the least associated with heart rate as seen from the graph.

**Figure 3: QT, QTcB, QTcF, and QTcI vs. RR (Each Subject's Data Points are Connected with a Line)**



We also used the average sum of squared slopes as the criterion. The smaller this value is, the better the correction. Based on the results listed in the following table, QTcF is the best correction method with the lowest average sum of squared slope. Therefore, this statistical reviewer used QTcF as the primary outcome for the statistical analysis.

**Table 3: Average of Sum of Squared Slopes for Different QT-RR Correction Methods**

method	Treatment									
	Moxifloxacin 400 mg		Placebo (to Moxi)		Placebo (to Pramipexole)		Pramipexole		Z	
	N	MSSS	N	MSSS	N	MSSS	N	MSSS	N	MSSS
QTcB	59	0.0090	57	0.0090	50	0.0084	48	0.0082	60	0.0065
QTcF	59	0.0057	57	0.0029	50	0.0019	48	0.0027	60	0.0021
QTcI	59	0.0086	57	0.0042	50	0.0015	48	0.0062	60	0.0044

## 5.2 STATISTICAL ASSESSMENTS

### 5.2.1 QTc Analysis

#### 5.2.1.1 The Primary Analysis for Pramipexole

The statistical reviewer used mixed model to analyze the  $\Delta\Delta\text{QTcF}$  effect. The model includes treatment, time points and period as fixed effects and subject as a random effect. Interactions between treatment and time points were used to construct the LS means. Baseline values are also included in the model as a covariate. The analysis results are listed in the following tables.

**Table 4: Analysis Results of  $\Delta\text{QTcF}$  and  $\Delta\Delta\text{QTcF}$  for Treatment Group of Pramipexole on day 12**

	<b>Pramipexole day 12</b>	<b>Placebo</b>	<b><math>\Delta\Delta\text{QTcF}</math></b>	
<b>Time/(hr)</b>	<b>Mean</b>	<b>Mean</b>	<b>Mean</b>	<b>90% CI</b>
1	-8.4	-11.0	2.6	(0.3, 4.8)
1.5	-9.3	-12.4	3.1	(0.8, 5.4)
2	-9.3	-11.0	1.7	(-0.6, 3.9)
3	-8.6	-12.4	3.8	(1.6, 6.1)
4	-7.1	-9.2	2.1	(-0.2, 4.3)
7	-10.8	-13.8	3.0	(0.7, 5.2)

**Table 5: Analysis Results of  $\Delta\text{QTcF}$  and  $\Delta\Delta\text{QTcF}$  for Treatment Group of Pramipexole on day 21**

	<b>Pramipexole day 21</b>	<b>Placebo</b>	<b><math>\Delta\Delta\text{QTcF}</math></b>	
<b>Time/(hr)</b>	<b>Mean</b>	<b>Mean</b>	<b>Mean</b>	<b>90% CI</b>
1	-8.6	-9.6	1.0	(-1.3, 3.3)
1.5	-7.3	-10.0	2.7	(0.4, 5.0)
2	-7.7	-11.1	3.4	(1.1, 5.6)
3	-7.7	-10.6	2.8	(0.5, 5.1)
4	-5.9	-7.7	1.8	(-0.5, 4.1)
7	-9.1	-11.3	2.2	(-0.1, 4.5)

The largest upper bounds of the 2-sided 90% CI for the mean difference between pramipexole and placebo were 6.1 ms and 5.6 ms at 3 hours and 2 hours after dose on day 12 and day 21, respectively.

### 5.2.1.2 Assay Sensitivity Analysis

The statistical reviewer used the same model to analyze moxifloxacin and placebo data from half hour to 4 hours after dose. The whole time course for  $\Delta\Delta\text{QTcF}$  of ten time points after dose is displayed in Figure 3. The largest unadjusted 90% lower confidence interval is 13.1 ms at 2 hours after dose. By considering Bonferroni multiple endpoint adjustment, the largest lower confidence interval is 12.2 ms at 2 hours after dose, which indicates that an at least 5 ms  $\Delta\Delta\text{QTcF}$  effect due to moxifloxacin can be detected for Part 1 of the study. Table 7 shows the two placebo comparison results from Part 1 and Part 2. It can be seen that placebo effect at two different stages was significantly different at 5 out of 6 time points, indicating a possible period effect.

**Table 6: Analysis Results of  $\Delta\text{QTcF}$  and  $\Delta\Delta\text{QTcF}$  for Treatment Group of 400mg Moxifloxacin at Time Point 1 hour – 7 hours**

Time/(hr)	400 mg Moxifloxacin	Placebo	$\Delta\Delta\text{QTcF}$	
	Mean	Mean	Mean	90% CI*
1	3.1	-6.7	9.9	(6.9, 12.9)
1.5	6.7	-8.3	15.1	(12.0, 18.1)
2	6.9	-8.3	15.2	(12.2, 18.3)
3	7.8	-6.5	14.3	(11.2, 17.3)
4	9.4	-3.4	12.8	(9.8, 15.9)
7	3.0	-7.6	10.6	(7.6, 13.7)

Bonferroni method was applied for multiple endpoint adjustment for 6 time points.

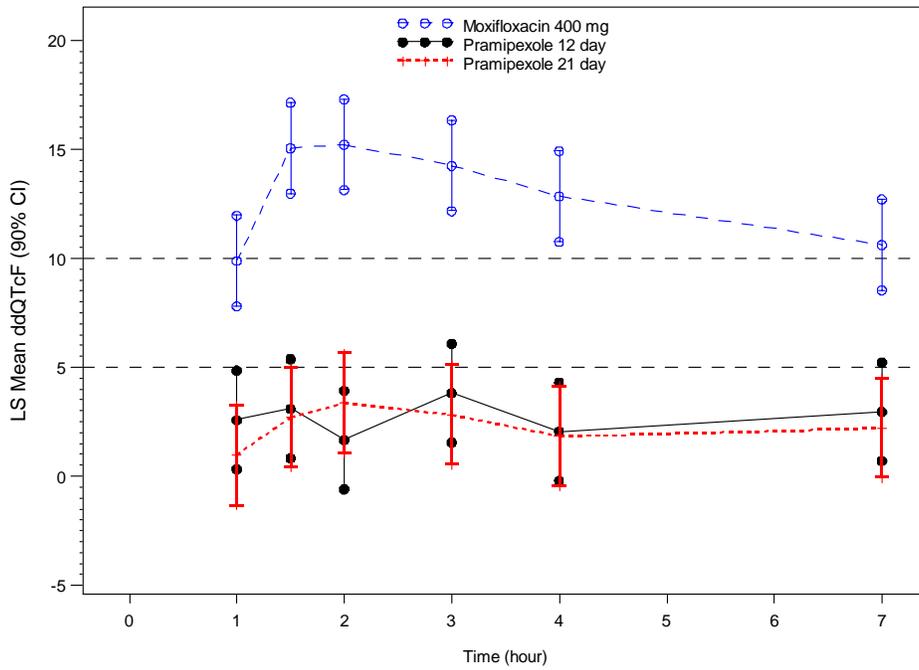
**Table 7: Pair-wise Comparison of  $\Delta\text{QTcF}$  between Placebos at Different Time Points**

Differences	Time 1	Time 1.5	Time 2	Time 3	Time 4	Time 7
Placebo (to Pramipexole) at day 12 - Placebo (to Moxi) (p-value)	-4.4 (0.005)	-4.2 (0.007)	-2.6 (0.09)	-5.8 (0.0006)	-5.5 (0.0016)	-5.8 (0.006)

### 5.2.1.3 Graph of $\Delta\Delta\text{QTcF}$ over Time

The following figure displays the time profile of  $\Delta\Delta\text{QTcF}$  for different treatment groups.

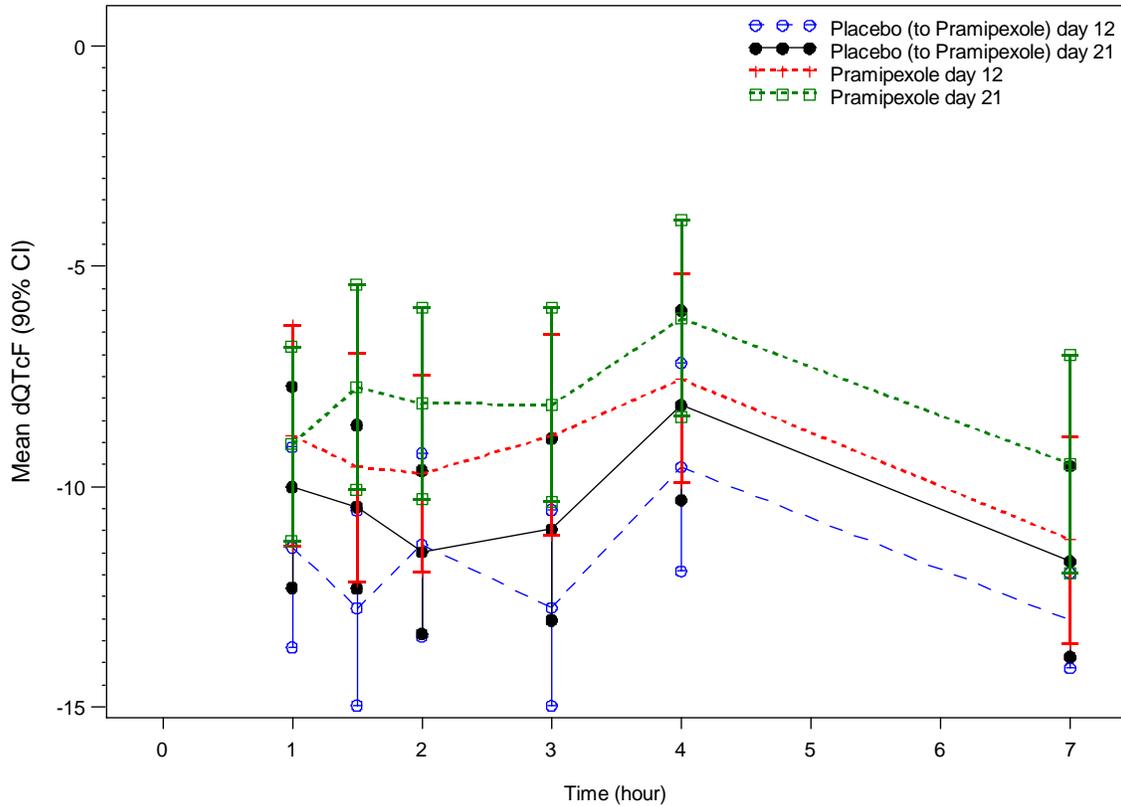
**Figure 4: Mean and 90% CI  $\Delta\Delta\text{QTcF}$  Timecourse**



Note: 1) Moxifloxacin is from the first cross-over period while drug treatments are from the second drug treatment period. 2) CIs are all unadjusted including moxifloxacin.

Figure 5 shows the  $\Delta$ QTcF of pramipexole at day 12 (2.25 mg/day) and day 21(4.5 mg/day) with matching placebos for each group. It indicates that  $\Delta$ QTcF for both drug treatments overlap with their placebos during the 7-hour time course.

**Figure 5: Mean and 90% CI  $\Delta$ QTcF Timecourse for Drug Treatment Groups**



#### 5.2.1.4 Categorical Analysis

Table 8 lists the number of subjects as well as the number of observations whose absolute QTcF values are  $\leq 450$  ms and between 450 ms and 480 ms. No subject's QTcF was above 480 ms.

**Table 8: Categorical Analysis of QTcF**

Treatment Group	Total N		Value $\leq 450$ ms		450 ms < Value $\leq 480$ ms	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Baseline	60	310	60 (100%)	310 (100%)	0 (0.0%)	0 (0.0%)
Moxifloxacin 400 mg	59	354	55 (93.2%)	347 (98.0%)	4 (6.8%)	7 (2.0%)
Placebo	57	930	57 (100%)	930 (100%)	0 (0.0%)	0 (0.0%)

Pramipexole	48	573	48 (100%)	573 (100%)	0 (0.0%)	0 (0.0%)
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**Table 9** lists the categorical analysis results for  $\Delta$ QTcF. No subject's change from baseline was above 60 ms.

**Table 9: Categorical Analysis of  $\Delta$ QTcF**

Treatment Group	Total N		Value $\leq$ 30 ms		30 ms<Value $\leq$ 60 ms	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Moxifloxacin 400 mg	59	354	58 (98.3%)	353 (99.7%)	1 (1.7%)	1 (0.3%)
Placebo	57	930	57 (100%)	930 (100%)	0 (0.0%)	0 (0.0%)
Pramipexole	48	573	48 (100%)	573 (100%)	0 (0.0%)	0 (0.0%)

### 5.2.2 PR Analysis

The same statistical analysis was performed based on PR interval. The point estimates and the 90% confidence intervals are presented in Table 10. The largest upper limits of 90% CI for the PR mean differences between pramipexole and placebo on day 12 and day 21 are 6.8 ms and 5.3 ms, respectively.

**Table 10: Analysis Results of  $\Delta\Delta$ PR by Treatment Group**

Time/(hr)	Pramipexole day 12		Pramipexole day 21	
	LS Mean	90% CI	LS Mean	90% CI
1	0.9	(-2.8, 4.6)	-0.9	(-4.6, 2.8)
1.5	3.1	(-0.6, 6.8)	1.6	(-2.1, 5.3)
2	3.1	(-0.5, 6.8)	0.7	(-3.0, 4.4)
3	2.4	(-1.3, 6.1)	1.6	(-2.1, 5.3)
4	1.5	(-2.2, 5.1)	-0.6	(-4.3, 3.1)
7	-0.6	(-4.2, 3.1)	-0.4	(-4.0, 3.3)

The outlier analysis results for PR are presented in Table 11.

**Table 11: Categorical Analysis for Observations PR >200 ms under Treatment**

Treatment Group	Total		Value<=200		Value>200	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Baseline	60	310	57 (95.0%)	302 (97.4%)	3 (5.0%)	8 (2.6%)
Moxifloxacin 400 mg	59	354	58 (98.3%)	348 (98.3%)	1 (1.7%)	6 (1.7%)
Placebo	57	930	52 (91.2%)	896 (96.3%)	5 (8.8%)	34 (3.7%)
Pramipexole	48	573	43 (89.6%)	547 (95.5%)	5 (10.4%)	26 (4.5%)

### 5.2.3 QRS Analysis

The same statistical analysis was performed based on QRS interval. The point estimates and the 90% confidence intervals are presented in Table 12. The largest upper limits of 90% CI for the QRS mean differences between pramipexole and placebo on day 12 and day 21 are 0.5 ms and 1.3 ms, respectively. There is no subject who experienced absolute QRS interval greater than 120 ms in any treatment group.

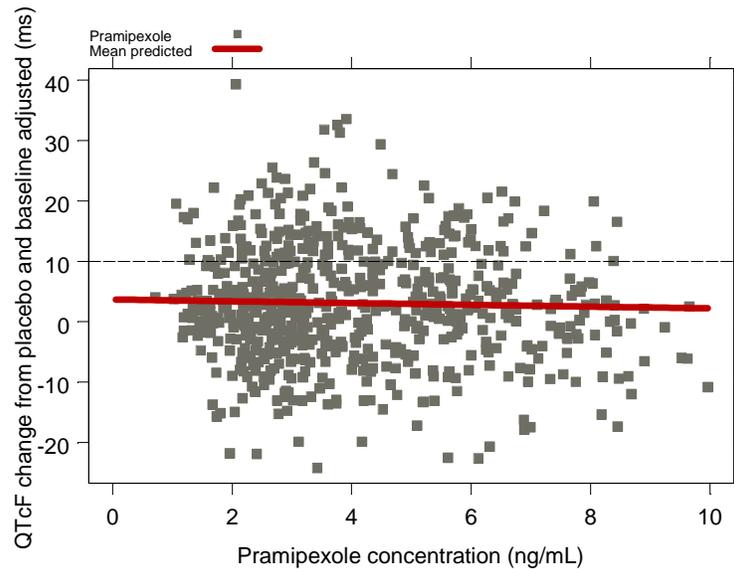
**Table 12: Analysis Results of  $\Delta\Delta$ QRS by Treatment Group**

Time/(hr)	Pramipexole day 12		Pramipexole day 21	
	LS Mean	90% CI	LS Mean	90% CI
1	-0.8	(-1.6, -0.1)	-0.2	(-0.9, 0.6)
1.5	-0.3	(-1.0, 0.5)	0.2	(-0.6, 0.9)
2	-0.3	(-1.1, 0.4)	-0.2	(-1.0, 0.5)
3	-0.6	(-1.3, 0.2)	0.2	(-0.6, 0.9)
4	-0.5	(-1.3, 0.2)	0.4	(-0.3, 1.2)
7	-0.4	(-1.2, 0.3)	0.5	(-0.2, 1.3)

### 5.3 CLINICAL PHARMACOLOGY ASSESSMENTS

The relationship between  $\Delta\Delta$ QTcF and Pramipexole concentrations is visualized in Figure 6. No evident exposure-response relationship was observed.

**Figure 6.  $\Delta\Delta$  QTcF vs. Pramipexole Concentration**



## 5.4 CLINICAL ASSESSMENTS

### 5.4.1 Safety assessments

None of the events identified to be of clinical importance per the ICH E 14 guidelines i.e. syncope, seizure, significant ventricular arrhythmias or sudden cardiac death occurred in this study.

### 5.4.2 ECG assessments

Waveforms from the ECG warehouse were reviewed. According to ECG warehouse statistics 99% of the ECGs were annotated in the primary lead II, with no ECGs reported to have significant QT bias, according to the automated algorithm. Overall ECG acquisition and interpretation in this study appears acceptable.

The largest upper bounds of the 2-sided 90% CI for the mean difference between pramipexole and placebo were 6.1 ms and 5.6 ms at 3 hours and 2 hours after dose on day 12 and day 21, respectively. No subject had a  $\Delta$ QTcF above 60 ms.

### 5.4.3 PR and QRS Interval

The largest upper limits of 90% CI for the PR mean differences between pramipexole and placebo on day 12 and day 21 are 6.8 ms and 5.3 ms, respectively.

The largest upper limits of 90% CI for the QRS mean differences between pramipexole and placebo on day 12 and day 21 are 0.5 ms and 1.3 ms, respectively. There is no subject who experienced absolute QRS interval greater than 120 ms in any treatment group.

### 5.4.4 MGPS Data Mining Analysis

The clinical reviewer conducted an MGPS (Multi-item Gamma Poisson Shrinker) data mining analysis of the AERS database for AE's related to QT prolongation and cardiac arrhythmias with pramipexole. There were no scores (EBGM value) > 2 for all AEs listed below under selection criteria, suggesting a weak signal similar to the background rate of the general population.

**Configuration:** CBAERS BestRep (S) **Run :** Generic (S) **Run ID:** 614  
**Dimension:** 2 **Selection Criteria:** Generic name(Pramipexole) + PT(...) **Where:** EBGM > 2.0  
**Zero rows selected**

Generic name	Level 1	Level 2	PT	HLT	HLGT	SOC	N	EBGM	EB05	EB95	PRR
<b>ID:</b>	614										
<b>Type:</b>	MGPS										
<b>Name:</b>	Generic (S)										
<b>Description:</b>	Generic; Suspect drugs only; Minimum count=1; Standard strata (Age, FDA Year, Gender); includes PRR and ROR; includes hierarchy information										
<b>Project:</b>	CBAERS Standard Runs										
<b>Configuration:</b>	CBAERS BestRep (S)										
<b>Configuration Description:</b>	CBAERS data; best representative cases; suspect drugs only; with duplicate removal										
<b>As Of Date:</b>	04/24/2009 00:00:00										
<b>Item Variables:</b>	Generic name, PT										
<b>Stratification Variables:</b>	Standard strata										
<b>Highest Dimension:</b>	2										
<b>Minimum Count:</b>	1										
<b>Calculate PRR:</b>	Yes										
<b>Calculate ROR:</b>	Yes										
<b>Base Counts on Cases:</b>	Yes										
<b>Use "All Drugs" Comparator:</b>	No										
<b>Apply Yates Correction:</b>	Yes										
<b>Stratify PRR and ROR:</b>	No										
<b>Fill in Hierarchy Values:</b>	Yes										
<b>Exclude Single Itemtypes:</b>	Yes										
<b>Fit Separate Distributions:</b>	Yes										
<b>Save Intermediate Files:</b>	No										
<b>Created By:</b>	(b) (4)										
<b>Created On:</b>	05/02/2009 22:17:46 EDT										
<b>User:</b>	Monica Fiszman										
<b>Source Database:</b>	Source Data: CBAERS data from Extract provided by CBER as of 04/24/2009 00:00:00 loaded on 2009-05-01 01:31:41.0										

**Dimension:** 2 **Selection Criteria:** Generic name(Pramipexole) + PT(Atrioventricular block, Atrioventricular block complete, Atrioventricular block first degree, Atrioventricular block second degree, Bifascicular block, Cardiac arrest, Convulsion, Electrocardiogram QRS complex prolonged, Electrocardiogram QT prolonged, Hypokalaemia, Hypomagnesaemia, Sudden cardiac death, Sudden death, Syncope, Torsade de pointes, Ventricular arrhythmia, Ventricular asystole, Ventricular fibrillation, Ventricular flutter, Ventricular tachyarrhythmia, Ventricular tachycardia) **Where:** EBGM > 2.0

These data do not, by themselves, demonstrate causal associations; they may serve as a signal for further investigation.

## 6 APPENDIX

### 6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

All dosages are given as the pramipexole dihydrochloride monohydrate. For the respective pramipexole base the conversion factor is 1.431.

The subject headings requested by the FDA are presented below in bold with underlining. The FDA comments and suggested units for the information are presented in italics. The data provided by Boehringer Ingelheim is presented in standard font.

References are provided in the text as:

(Pxx-xxxx) for published reports

(Uxx-xxxx) for unpublished reports

(xxx.xxx) for draft reports.

#### **Therapeutic dose**

*(Include maximum proposed clinical dosing regimen)*

- For treatment of Parkinson's disease
  - Immediate release (IR) tablets, maximum approved daily dose: 4.5 mg (administered 1.5 mg TID immediate release (IR) tablets)
  - Extended release (ER) tablets, maximum proposed daily dose: 4.5 mg (administered 4.5 mg QD)
  - Total daily dosages: 0.375 mg, 0.75 mg, 1.5 mg, 3.0 mg, 4.5 mg.
- For treatment of Restless Legs Syndrome (RLS)
  - IR tablets, maximum approved dose: 0.75 mg (administered 0.75 mg QD)

#### **Maximum tolerated dose**

*(Include if studied or NOAEL dose)*

- Healthy subjects, single oral dose (solution): 0.3 mg (U89-0039; U89-0478; P92-4118)

- Healthy subjects, multiple doses with gradual titration (ER tablets): 4.5 mg administered q.d.(highest daily dose tested) (U07-1551)
- Healthy subjects, multiple doses with gradual titration (IR tablets): 1.5 mg (administered t.i.d.) (U95-0470)

### **Principal adverse events**

*(Include most common adverse events; dose limiting adverse events)*

Dose-limiting adverse events in healthy subjects with IR tablets are gastro-intestinal adverse events (nausea and vomiting) and central nervous side effects.

The most common adverse events (> 10 %) in Early Parkinson's clinical trials with pramipexole (as described in the Labeling for MIRAPEX) were: nausea, dizziness, somnolence, insomnia, asthenia and constipation.

The most common adverse events (> 10 %) in Advanced Parkinson's clinical trials with pramipexole (as described in the labeling for MIRAPEX) were: postural hypotension, dyskinesia, extrapyramidal syndrome, insomnia, dizziness, accidental injury, hallucinations and dream abnormalities.

The most common adverse events (> 5%) in RLS clinical trials with pramipexole (as described in the Labeling for MIRAPEX) were: nausea, headache, fatigue and somnolence.

### **Maximum dose tested**

*(Specify dose)*

#### **Single Dose**

- Healthy subjects, oral solution: 0.4 mg (U89-0039)
- Healthy subjects, ER tablets: 0.375 mg (U06-1598)

#### **Multiple Dose**

*(Specify dosing interval and duration)*

- Healthy subjects, multiple doses with gradual titration (IR tablets): 4.5 mg (administered as 1.5 mg TID) (U95-0470)

- Healthy subjects, multiple doses with gradual titration (ER tablets): 4.5 mg (administered QD) (U07-1551)

**Exposures Achieved at Maximum Tested Dose**

**Single Dose**

*(Mean (%CV) Cmax and AUC)*

Dose	Cmax:	AUC0-∞:	Note
0.4 mg solution (N=6/9)	0.80 ng/mL (18.75%)	n/a	(U89-0039) one sample, taken at 1.75h after drug intake
0.3 mg solution (N=4/3)	2.29 ng/mL (18.77%)	7.35 ng·h/mL (20.27%)	( U89-0305)
0.25 mg solution (N=12/12):	0.401 ng/mL (19.95%)	5.82 ng·h/mL (21.82%)	(U95-0542)
0.375 mg ER tablet (N=15/15)	0.268 ng/mL (10.9%)	6.61 ng·h/mL (31.8%)	(U06-1598-01) Cmax given as gMean

**Multiple Dose**

*(Mean (%CV) Cmax and AUC)*

after 1.5 mg IR t.i.d. (N=19/19): (U95-0470)

Cmax,ss: 8.19 ng/mL (18.93%);

AUCτ,ss: 47.9 ng·h/mL (20.88%)

after 4.5 mg ER q.d. (N=24/24) given gMean (gCV%): (U07-1551)

Cmax,ss: 4.89 ng/mL (22.30%);

AUCτ,ss: 91.7 ng·h/mL (30.10%)

### **Range of linear PK**

*(Specify dosing regimen)*

Linear, dose proportional PK between 0.125 - 1.5 mg t.i.d. IR (U95-0499) and between 0.375 and 4.5 mg q.d.ER (U07-1551).

### **Accumulation at steady state**

*(Mean (%CV); specify dosing regimen)*

Accumulation of pramipexole has not been addressed in an individual study. For the IR formulation given orally t.i.d. and assuming a mean half-life of 8h, the accumulation factor  $R_A$  after multiple administrations is approximated from equation 1

$$(1) \quad R_A = 1/1 - e^{-\lambda z \tau}$$

with  $\lambda z$  = terminal elimination rate and  $\tau$  = dosing interval

A  $R_A$  of about 2 is calculated which is confirmed comparing 0.25 mg IR single dose vs. multiple dose.  $C_{max}$  after single dose (U95-542) = 0.401 ng/mL (19.95%);  $C_{max,ss}$  after multiple dose of 0.25 mg t.i.d. (U96-0068) = 0.931 ng/mL (17.08%).

For the ER formulation comparing  $C_{max}$  after 0.375 mg single (U06-1598-01) vs. multiple dose (U07-1551) = 0.268 ng/mL (10.9%) vs. 0.423 ng/mL (19.1%), respectively.

### **Metabolites**

*(Include listing of all metabolites and activity)*

Pramipexole is metabolized in man to less than 10% and no active metabolite has been identified (U92-0018; U96-0260)

### **Absorption Absolute/Relative Bioavailability**

*Mean (%CV)*

Pramipexole is rapidly and almost completely absorbed with an absolute bioavailability of oral form greater than 90% (U91-0026)

### **Tmax**

*(Median (range) for parent)*

The median Tmax after multiple dose of 1.5 mg IR t.i.d. was 1.00 (0.5 - 3.02) h; median Tmax after multiple dose of 4.5 mg ER q.d. was 6.0 (1.50 - 16.0) h (U07-1551)

*(Median (range) for metabolites)*

n.a.

### **Distribution Vd/F or Vd**

*Mean (%CV)*

Following 0.1 mg intravenous dose the mean Vss (%CV) was 401 L (27.2%) (U91-0026).

### **% bound**

*Mean (%SD)*

At plasma concentrations of 2.5 and 5.2 ng/mL, respectively, the percent bound was  $14.1 \pm 1.77\%$  and  $18.2 \pm 1.44\%$ , respectively. Albumin accounts for most of the plasma protein binding (P99-11399).

### **Elimination Route**

*Primary route;*

*(percent dose eliminated)*

Urinary excretion is the major route of elimination with, 90% of dose recovered in urine, almost exclusively as unchanged pramipexole (U96-0260).

*Other routes*

Less than 2 % is found in faeces (U92-0018).

**Terminal  $t_{1/2}$**

*Mean (%CV) for parent*

The terminal  $t_{1/2}$  has been reported between 8 and 12 h in a study using IR tablets (P99-11399).

*Mean (%CV) for metabolites.*

n.a.

**CL/F or CL**

*Mean (%CV)*

The total CL/F is 500 mL/min and the renal CL is about 400 mL/min in a study using IR tablets (P99-11399)

**Intrinsic Factors**

**Age**

*Specify mean changes in  $C_{max}$  and AUC*

After a single dose of 0.25 mg,  $AUC_{0-\infty}$  and  $C_{max}$  were 41 % and 7.8 % greater, respectively, in subjects aged 61 to 80 years compared with subjects aged 20 to 40 years in a study using IR tablets (U95-0541).

## **Sex**

*Specify mean changes in C<sub>max</sub> and AUC*

At the dose range between 0.125 and 1.5 mg IR tablets t.i.d. AUC<sub>τ,ss</sub> was 35 to 43 % greater and C<sub>max,ss</sub> was 28 to 32 % higher in females. In this trial the higher exposure in females was also attributed to the older age (mean 28.0 vs. 48.2 years) of the female subjects (U95-0499).

## **Race**

*Specify mean changes in C<sub>max</sub> and AUC*

In a PopPK analysis CL/F was compared between male and female Japanese Parkinson's disease patients and US Caucasian male and female patients (U02-3442). CL/F was estimated as 19.7 and 17.2 L/h in Japanese male and female patients and 20.2 and 17.6 L/h in Caucasian patients. The total exposure (AUC) at a given dose is, thus, also comparable between Asian and Caucasian patients. Since V/F in the Japanese patients was lower compared with Caucasians (483 vs. 605L) a slightly higher C<sub>max</sub> in Japanese subjects can be expected. Although otherwise no study were conducted comparing the PK of pramipexole in different races it seems justified to assume that other factors affecting the renal CL of pramipexole (age , body weight) are more determining the PK and thus exposure.

## **Hepatic & Renal Impairment**

*Specify mean changes in C<sub>max</sub> and AUC*

In renally impaired patients with a creatinine clearance below 30 mL/min, the AUC<sub>0-∞</sub> and C<sub>max</sub> were 208% and 22.7 % higher, respectively, compared to healthy subjects after a single oral dose of 0.25 mg IR pramipexole. For moderate renally impaired subjects (creatinine CL < 50 mL/min) AUC<sub>0-∞</sub> and C<sub>max</sub> were 124% and 15.9 % higher, respectively in studies with IR tablets (U96-0081; U96-0093)

No studies in hepatically impaired patients have been conducted.

## **Extrinsic Factors**

### **Drug interactions**

*Include listing of studied DDI studies with mean changes in C<sub>max</sub> and AUC*

The only drug interaction resulting in a significant change in exposure of pramipexole was observed after co-medication of multiple doses of 300 mg cimetidine given every 6 hours. AUC<sub>0-∞</sub> was increased by 46 and 52 % in male and female subjects, respectively. However, C<sub>max</sub> in males was increased by only 26.7 % and no effect was seen in females in a study conducted with IR tablets (U95-0540).

### **Food Effects**

*Specify mean changes in C<sub>max</sub> and AUC and meal type (i.e., high-fat, standard, low-fat)*

When 0.25 mg IR pramipexole tablets were taken after high fat meal the AUC<sub>0-∞</sub> was increased by about 6% while C<sub>max</sub> remained mainly unchanged. The time to peak exposure was reduced on average from 2.71 to 1.67 h (U95-0542).

When pramipexole ER was given at the highest dose of 4.5 mg after a high fat meal, AUC<sub>τ,ss</sub> was increased from (gMean) 92.83 ng·h/mL in the fasted state to 105.5 ng·h/mL. C<sub>max,ss</sub> was increased from 4.94 ng/mL to 5.942 ng/mL and median T<sub>max</sub> was prolonged from 6.0 h to 7.92 h. in fasted and fed states, respectively (U07-1551).

### **Expected High Clinical Exposure Scenario**

*Describe worst case scenario and expected fold-change in C<sub>max</sub> and AUC. The increase in exposure should be covered by the supra-therapeutic dose.*

Due to the pharmacokinetic and metabolic properties of pramipexole, only a limited potential for an increase in plasma level due to drug interaction exists. In case of renal insufficiency, and/or administration of concomitant drugs eliminated via renal excretion, the dose should be reduced and/or caution is advised. Therefore the dose of 4.5 mg, ER tablets, once daily, are expected to cover the exposure levels which are expected clinically. Over-dosage is not expected to remain undetected due to the profile of side effects. Since pramipexole is up-titrated based on therapeutic effect and side effects it is unlikely that patient with a lower CL (e.g. elderly) will ever receive the highest dose of 4.5 mg daily. Moreover, renally impaired patients will also receive a lower starting and maintenance dose.

The worst conceivable case would be a patient who required the highest daily dose of 4.5 mg pramipexole would start accidentally a high dose cimetidine co-medication. However, the possible increase in C<sub>max</sub>, which is the relevant parameter with respect to QT effects,

would be still in the range of interindividual variability. The highest daily dose of 4.5 mg given to steady state is therefore justified to cover the exposure under therapeutic conditions. In addition, dosages higher than 1.5 mg IR t.i.d or 4.5 mg ER q.d. will be hardly tolerated by healthy volunteers.

## References

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P99-11399 Pollentier S, Brecht HM. Pramipexole - preclinical and clinical data. *Aktuel Neurol* 1998; 25 (Suppl4): 300-304

U89-0039 Schilling C, Haeselbarth V. A Single Increasing Dose Tolerance Study in Healthy Volunteers after Oral Administration (Dosage: 25-400 mcg). 10 November 1988.

U89-0478 Schilling C, Leonard J. Dose and time response study of SND 919 CL 2 Y after single oral administration in healthy volunteers (Dosages: Placebo, 0.1 mg, 0.2 mg, 0.3 mg). 07 July 1989.

U91-0026 Haeselbarth V, Foerster HJ, Justus-Obenauer H, Peil H, Schilling C. Pharmacokinetics and bioavailability of SND 919 CL 2 Y, comparison of the plasma levels after intravenous (infusion, 100 mcg), oral (tablets, 300 mcg) and oral (solution, 300 mcg), administration in 12 healthy volunteers (3-fold cross-over).

U92-0018 Haeselbarth V, Koester J, Lohmann H, Justus-Obenauer H, Peil H. SND 919 CL 2 Y: Investigations on the pharmacokinetics and metabolism of SND 919 CL 2 Y after administration of single radioactive doses of 0.100 mg intravenously and 0.300 mg orally in 6 volunteers.

U95-0470 Häselbarth V., Adamus W.S., Neubacher D, Peil H. A study in healthy volunteers to compare the bioavailability after thrice daily repeated per oral administration of either the formulation used in the main clinical studies or the final formulation intended for marketing (at strengths of 0.125 and 1.5 mg). 24 August 1995.

U95-0499 Wright CE, Lasher Sisson T, Ichhpurani AK, Peters GR. Pramipexole steady-state pharmacokinetics in healthy male and female volunteers for doses between 0.375 mg/day and 4.5 mg/day (M/2730/0047).

U95-0540 Wright CE, Herman BD, Ichhpurani AK, Peters GR. Influence of probenecid and cimetidine on pramipexole pharmacokinetics 9M/2730/0061). 13 October 1995.

## 6.2 TABLE OF STUDY ASSESSMENTS

Visit 1 - Visit 3 and Visit 9					
Trial Phase	Screening (21 days before V2)	Cross-over Moxifloxacin - Placebo			End of study (max. 8 days after V8)
Visit	Visit 1	Visit 2	Visit 3	...	Visit 9
Day		1	1		
Informed consent, Randomisation	X				
Medical examination	X				X
Administration (Moxifloxacin or placebo)		X	X		
BP, PR after 5 min supine	X				X
12-lead ECG (single)	X				X
triple 12-lead ECG profile (ptm=before, 1, 1:30, 2, 3, 4, 7 h)		X	X		
Laboratory, before dosing, Electrolytes only		X	X		
Laboratory full + Preg.test for females	X <sup>1</sup>				X
PK blood sample (blank sample, before dosing)		X			
Meal		X <sup>2</sup>	X <sup>2</sup>		
Adverse Events, Concomitant Therapy	X	X	X		X

<sup>1</sup> including drug and virus screening

<sup>2</sup> small standardised meals 30 to 60 minutes before dosing, on ECG profile days also after ECG recording at 4:00 h (small meal) and 7:00 h (full meal) after dosing (cf. section 6.2: ECG profile days)

Visit 4 - Visit 8																										
Trial Phase	Cross-over Pramipexole - Placebo																									
Visit	Visit 4 / Visit 6												Visit 5 / Visit 7								Visit 8					
Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	1	2	3	4	
Administration PPX (ER tab) or Pbo (q.d.: ptm=0:00) <sup>2</sup>	X <sup>1</sup>	X <sup>1</sup>	X <sup>1</sup>	X <sup>1</sup>	X	X	X	X	X	X			X	X	X	X	X	X					X	X	X	X
Administration PPX (IR tab) or Pbo (t.i.d.: ptm=0:00, 8:00, 16:00) <sup>2</sup>											X	X								X						
Administration PPX (IR tab) or Pbo (b.i.d.: ptm=0:00, 12:00) <sup>2</sup>																					X					
BP, PR 5 min sup + 1 min standing (ptm = before, 4:00)	X			X			X			X			X			X			X			X			X	X
Triple 12-lead ECG profile (ptm = before, 1, 1:30, 2, 3, 4, 7 h)												X									X					
PK Profile (ptm=before, 1, 1:30, 2, 3, 4, 7 h)												X									X					
Laboratory, electrolytes only (ptm = before)												X														
Laboratory full + preg.test for females (ptm = before)																					X					
Meal <sup>2</sup>	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events, Conc. Therapy	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

<sup>1</sup> Down-titration of the treatment referring to Visits 4/5 will take place on days 1 to 4 on Visit 6, i.e., there will be a four-day overlap with up-titration of the treatment referring to Visit 6/7

<sup>2</sup> Small standardised meals 30 to 60 min before dosing, on ECG profile days also after ECG recording at 4:00 h (small meal) and 7:00 h (full meal) after dosing (cf. section 6.2: ECG profile days)

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/s/  
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Joanne Zhang

5/28/2009 12:58:29 PM

BIOMETRICS

Dr. Qianyu Dang was the primary statistical reviewer for  
this QT study.

Monica Fiszman

5/28/2009 02:39:43 PM

PHARMACOLOGIST

Fang Li

5/28/2009 04:28:34 PM

BIOPHARMACEUTICS

I did it. It's Christine's turn

Christine Garnett

6/2/2009 08:17:14 AM

BIOPHARMACEUTICS

Norman Stockbridge

6/2/2009 09:02:04 AM

MEDICAL OFFICER