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MEDICAL REVIEW(S)

CLINICAL REVIEW

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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 reviewer that Pramipexole Extended Release (MIRAPEX ER®) is effective for the treatment of the motor signs and symptoms of advanced Parkinson's disease (PD). It has a side effect profile consistent with its class (dopamine agonist) and its overall risk to benefit ratio is therapeutically acceptable.

1.1 Recommendation on Regulatory Action

Review of clinical data finds sufficient evidence to support MIRAPEX ER's use in the treatment of advanced Parkinson's disease. In this submission, the basis of approval is a single efficacy trial of 18 weeks duration in advanced Parkinson's disease using a well-accepted design and measures of outcome. The primary endpoint was the change from baseline of the sum of Part II (Activities of Daily Living) and Part III (Motor Function) scores of the Unified Parkinson's Disease Rating Scale (UPDRS) assessed at the week 18 visit.

This review finds that the mean improvement in UPDRS score from baseline was -6.7, -12.2 and -13.6 for placebo, extended release pramipexole (PPX ER) and immediate release pramipexole (PPX IR), respectively. The p-value is less than 0.0001 for both PPX ER vs. placebo and PPX IR vs. placebo. This finding is independently supported by the Statistical Review and Evaluation for this NDA. To place this change in clinical perspective, untreated PD worsens at a rate of about 3 UPDRS points per year of disease. The improvement seen in the placebo arm is consistent with regression to the mean seen over the course of a PD clinical trial using this measure.

Because MIRAPEX ER has been previously approved for use in early Parkinson's disease (NDA 22421, February 19, 2010), it is recommended that a global indication for the treatment of PD be granted.

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 compiled and reviewed from two completed 33 week placebo controlled blinded trials: the efficacy trial in advanced Parkinson's disease as well as the earlier trial in early Parkinson's disease.

1.3 Recommendations for Postmarket Risk Management Activities

No recommendations for postmarket risk management are made.

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

MIRAPEX ER (NDA 22421) was approved by the US FDA for the treatment of the signs and symptoms of early Parkinson's disease on February 19, 2010. This was investigated under IND 75,961.

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 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 Anti-Parkinson drugs currently marketed in the US.

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 nausea and vomiting, 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 regulatory meetings related to the clinical evaluation of NDA 22514 (MIRAPEX ER in advanced PD) were extensively summarized in the final clinical review for NDA 22421 (MIRAPEX ER in early PD) which is available in DARRTS. Their summary for this review is limited to clinically relevant points. For example, the extensive discussion concerning the acceptability of interim data from confirmatory trials for NDA 22421 is omitted as it is irrelevant to this submission now that these studies are complete. FDA comments and discussion regarding clinical pharmacology, NDA Modules 3 and 4 are omitted here due to their review by respective disciplines in NDA 22421, without newly submitted information in this application. Requests concerning the physical structure of the electronic submission and datasets are also omitted.

2.5.1 Pre-IND Meeting 2002

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 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 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.

2.5.2 Pre-IND Meeting 2007

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.

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 Phase 3 trial in early Parkinson's disease patients.

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 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). The extent of safety data from interim data for NDA 22421 was agreed upon.

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).

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.

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 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 (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).

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-submission Meeting for NDA 22421

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)

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)

FDA made several comments in relation to the Sponsor's planned conduct of Study 248.525 in Advanced PD: The division reiterated its position that approval of the late PD indication is not a given based on the results of the early PD trial, and strongly suggested that the Sponsor complete the late PD trial. That trial could be of 3 months duration. The Sponsor inquired if the late PD trial could be submitted during the review cycle as a separate application, independent of the early PD trial, while referencing the previously submitted early PD application. The Division was not aware of any reason why the Sponsor could not reference the previously submitted electronic early PD application, and the pharmacokinetic data could be cross referenced.

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.)

FDA found the following pharmacokinetic analysis acceptable pending review of the data submitted: a population PK analysis based on the subset of approximately 100 patients treated with the ER formulation used for the 18 week efficacy analysis of Study 248.524 (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.

NDA 22421 was submitted to the Agency for review on October 27, 2008 and acted upon August 24, 2009, in compliance with the PDUFA requirement (see Section 2.5.7, below).

2.5.6 Pre-submission Meeting for NDA 22514

Written questions from the Sponsor were answered on February 3, 2009. It was agreed that because all relevant CMC information for MIRAPEX ER was submitted to NDA 22421 there was no need to duplicate that information in this NDA. Similarly, nonclinical information and clinical pharmacology data relevant to pramipexole IR and ER would not be duplicated in Modules 2.4, 2.6, and 4, and Modules 2.7.1 and 2.7.2, respectively.

Interim reports of the trials in early and advanced PD (248.524 and 248.525) included in NDA 22421 may be referenced by location in that submission. Complete safety data from these two trials and from all ongoing trials will be submitted to the Summary of Clinical Safety. Safety data would identify the source of each designated pool, and where the individual study reports may be found if submitted previously in NDA 22421.

(b) (4)

2.5.7 Complete Response Letter Issued Following NDA 22421 Review

On August 24, 2009, a CR letter was issued after regulatory review of NDA 22421, for reasons other than clinical efficacy.

Following assessment of the clinical data, it was the opinion of the clinical 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 only. It has a side effect profile consistent with its class (dopamine agonist) and its overall risk to benefit ratio is therapeutically acceptable.

The basis of this opinion of effectiveness was 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.

The primary statistical review demonstrated that 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 was 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.) Clinical Pharmacology review provided support of pharmacokinetic and pharmacodynamic equivalence to the immediate release product.

No clinical trial efficacy data for the treatment of advanced disease was submitted for consideration, and this indication was not supportable. The reasons for this were detailed in the Agency's CR letter:

"In part, our decision is based on our view that the data do not establish that the demonstrated beneficial effects of pramipexole in patients with early PD are independent of the pattern of absorption. For example, we cannot know from Study 524 that the effects of the ER and immediate release formulations are truly equivalent (the study was not designed to address this question). Because we cannot know that these formulations produce equivalent clinical effects, we cannot conclude that similar extents of absorption are guaranteed to produce identical clinical results. In particular, we also cannot be certain that even the same pattern of absorption will produce similar results in patients with early and late PD, given

the differences in the underlying brain states in the two conditions. In short, we are not prepared, at this time, to conclude that plasma levels of pramipexole known to be associated with effectiveness in patients with early PD must also be associated with effectiveness in patients with late PD.”

In addition, a safety concern exists in that adverse events may be more prevalent in patients with advanced disease and the safety experience with this formulation in later stages of PD was limited.

The basis of the Complete Response to NDA 22421 was the safety concern emanating from the physical similarity of the MIRAPEX ER tablets and related packaging among the different ER dosage strengths as well as to the IR product. As described in the letter the key factors likely to contribute to medication errors were as follows:

1. *Similarities between the carton and container labels for the ER and IR formulations,*
2. *Similarities in tablets*
 - A. *the lack of a uniform shape within specific formulations,*
 - B. *the size, shape, and color of ER and IR tablets,*
 - C. *similarities in the size and shape of several of the strengths within the ER formulation itself (for example, the ER 1.5 mg and 3 mg tablet are almost identical in appearance, and very similar to the 4.5 mg tablet),*
 - D. *overlapping strengths of the ER and IR formulations (0.75 mg and 1.5 mg),*
 - E. *the presence of symbols debossed on the ER tablets that are not readily meaningful to either pharmacists or patients.*

Proposed possible solutions included changes in trade dress and color scheme, more distinct NDC numbers, debossing the ER tablets with the letters “ER” and the strength, and color differentiation of the tablets. It was also pointed out the necessary CMC requirements would have to be fulfilled for any proposed changes in the physical structure of the table.

2.5.8 Sponsor’s Response to the NDA 22421 CR Letter and Approval

The Sponsor proposed a tentative package for response to the CR letter on September 2, 2009 and the Division issued written responses concerning agreement (subject to regulatory review) for tablet appearance, revisions to carton and container, and requirements for chemistry, manufacturing, and controls information. Because efficacy of PPX ER in early PD had been reviewed and was not at issue, no further clinical information was needed for that NDA. The Sponsor’s complete response to the CR letter was received and accepted for filing as a Class I resubmission. Upon review it was deemed that the Sponsor’s resubmission, including changes in the appearance of the pills and packaging, fulfilled the requirements for approval of MIRAPEX ER for the treatment of early PD. The label for MIRAPEX ER was completed for this early PD indication. NDA 22421 was approved on February 19, 2010, and its approval obviated

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the need for an obligatory CR letter to NDA 22514 (PDUFA action date March 22, 2010) for the same reasons of safety.

2.6 Other Relevant Background Information

The MIRAPEX immediate release label (NDA 20667) is currently in old format and the last approved version of the label dates to December 31, 2008. There are pending CBEs in review for that NDA (and now NDA 22421 as well):

(b) (4)

The most significant of these is labeling concerning Impulse Control Disorder in PD. A separate safety review of clinical data has been completed by Gerard Boehm MD, MPH, and this will be incorporated into final label decisions for both formulations. A preliminary conversion of the IR label to PLR format has been performed and extensive ER label discussion took place with the Sponsor in the final review period of NDA 22421.

Assuming, following review, the agency approval of the Sponsor's response to the CR letter, as well as approval of the efficacy indication for PPX ER in advanced PD, the following steps have been proposed in order to update the pramipexole label:

(b) (4)

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

Clinical review of NDA 22421 (PPX ER in early PD) revealed deficiencies in the presentation of data in the application and these were pointed out to the Sponsor at that time. The datasets were audited and corrected by the Sponsor and these corrections were carried through by the Sponsor in the datasets submitted to this NDA. The nature of this problem and more detailed descriptions of difficulties arising from the datasets and requests made to the Sponsor may be found in the clinical review of NDA 22421 in DARRTS. The reviewer's conclusion was 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. The integrity of the trial was not affected.

The Sponsor's application was well organized and generally compliant with eCTD and CDISC SDTM standards. Results of clinical site audits by the Office of Compliance, Division of Scientific Investigations for this submission are reviewed in 3.2, below. The reviewer concludes that the data appears to be of good quality and there are no other questions related to the integrity of the data submitted.

3.2 Compliance with Good Clinical Practices

The Sponsor affirms that all studies in the clinical development program of pramipexole ER in PD were approved by ethics committees or institutional review boards, in line with Good Clinical Practice guidelines, the Sponsor's Standard Operating Procedures (SOPs) and according to the Declaration of Helsinki, version 1996. Written informed consent was obtained from all patients prior to any study related procedure.

The Sponsor certifies that it did not use any debarred investigators.

Trial 248.525 Advanced PD:

Three foreign sites were selected for inspection by the Division of Scientific Investigations, once again on the basis of having the largest number of enrolled subjects in their respective countries. This trial in advanced Parkinson's disease was performed in Europe and the Far East. These three sites were requested on the basis of their high enrollment of 76 sites in this NDA's pivotal efficacy/safety trial. The site chosen in the Philippines represents 20 % of all patients entered in that country. The two clinical sites chosen in Barcelona represent almost half of that country's contribution to the trial.

All three sites have well qualified investigators but the Agency has not had previous experience with these sites' performance. There was no indication in our preliminary analysis to suggest that any site in the study had a disproportionate effect on study outcome, question of scientific misconduct, or disproportionate number of protocol

violations or safety issues. However the Philippines site did have a different response profile for the major outcome variable in the placebo arm of the trial (when compared to the performance of patient groups from other sites in the trial).

On inspection of these sites by the Division of Scientific Investigations, no actions were indicated for any violation of GCP. Data was considered reliable. There were found to be some irregularities in the recording of data in patient diaries for on-off states – a patient reported outcome. (It is supposed to be completed by the patient or caregiver). In the two Barcelona sites it is not clear how this was implemented. However, this was a minor protocol violation and there was no appearance of a pattern of malfeasance. This finding had no influence on the interpretation of the results of the confirmatory trial.

Trial 248.524 Early PD:

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 indicates that the Sponsor found substantially the same deviations 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 as reported in the clinical review for NDA 22421. Data relating to any adverse events were included in the safety analysis. This site did not participate in the confirmatory trial in advanced PD (Trial 248.525) or any other trials submitted in this NDA.

3.3 Financial Disclosures

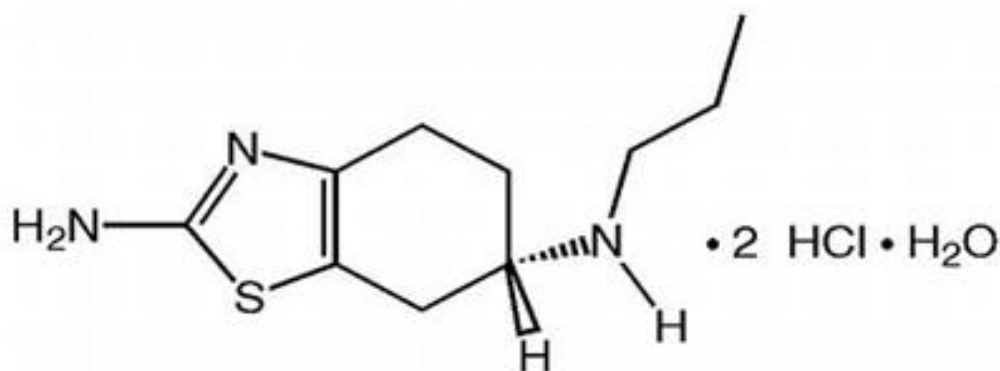
The Sponsor provided required information regarding financial disclosure. These were reviewed and there were no findings of conflicts of interest in the investigators participating in the confirmatory trial; the consultants receiving funds above the threshold for reporting did not enter patients or act as clinical investigators.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

None have been identified; however, final reviews from related disciplines have not been incorporated into this clinical review at the time of its writing. It should be noted however that non-clinical ancillary issues were addressed and resolved for this entity during the approval process for PPX ER in early PD (NDA 22421).

4.1 Chemistry Manufacturing and Controls

Figure 1 Chemical structure of pramipexole (source: Sponsor)



While no chemistry or manufacturing concerns have been identified previously, the newly debossed ER tablet has not undergone final CMC review.

4.2 Clinical Microbiology

No investigations of clinical microbiology are submitted.

4.3 Preclinical Pharmacology/Toxicology

No pharmacological toxicology concerns have been identified.

4.4 Clinical Pharmacology

No new clinical pharmacology studies have been submitted with this NDA, which references material reviewed for NDA 22421.

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 2 Receptor binding affinities Ki (nM)

	D1	D2	D3	D4	α 1 Adreno	α 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. This information is accessible via Global Submit Review (version 4.2) and may be found in the CDER Electronic Document Room via the path:

\\CDSESUB1\EVSPROD\NDA022514

5.1 Tables of Studies/Clinical Trials

The following table, found in Module 5.2 of the eCTD, is a listing of clinical studies contributing efficacy and safety data. There are a total of 11 trials with the PPX ER formulation in support of the PD indication. Two other studies used immediate release formulation in support of the ER application (studies of QT safety and renal impairment). The contributions of all these trials to either safety and / or efficacy analysis are defined further in **Section 5.2 Review Strategies** and other review sections to follow.

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 3 Pramipexole development program: trial listing (source: Sponsor)

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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
BA	248.529 (U05-2046)	5.3.1.1 Report included in NDA 22-421	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 Report
BE	248.530 (U07-1551)	5.3.1.2 Report included in NDA 22-421	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 Report
BE	248.607 (U07-3136)	5.3.1.2 Report included in NDA 22-421	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 Report
BA	248.560 (U06-1598-01)	5.3.1.3 Report included in NDA 22-421	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 Report

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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
PK	248.545 (U08-1652-01)	5.3.3.1 Report included in NDA 22-421	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 Report
PK	7215-96-006 248.113 (U96-0093)	5.3.3.3 Report included in NDA 22-421	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 Report
Efficacy	248.524 (U08-1826-01)	5.3.5.1 Interim Report included in NDA 22-421	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	Up to 33 weeks, with confirmatory efficacy analysis at week 18	Complete; Interim Report
Efficacy	248.524 (U09-1232-01)	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 (non-inferiority test of PPX ER vs. PPX IR)	Complete; Full Report

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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
PK	248.524 (U08-1904-01)	5.3.3.5 Report included in NDA 22-421	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	PPX ER: 75 PPX IR: 72 (147)	PD patients	13 weeks	Complete; Full (pop PK) Report
Efficacy	248.525 (U08-1962-01)	5.3.5.1 Interim Report included in NDA 22-421	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	Up to 33 weeks	Complete; Interim Clinical Safety Report
Efficacy	248.525 (U09-1270-01)	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 : 165 PPX IR: 175 PBO: 178 (518)	PD patients	33 weeks, with confirmatory efficacy analysis at week 18	Complete; Full 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: 56 PPX IR: 56 (112)	PD patients	Up to 64 weeks, with descriptive analysis at week 26	Ongoing; None

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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
Efficacy	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: 511	PD patients	Up to 81 weeks	Ongoing; None
Efficacy	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: 391	PD patients	Up to 81 weeks	Ongoing; None
Efficacy	248.636 (U08-1964-01)	5.3.5.4 Full Report included in NDA 22-421	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 Report
Efficacy	248.637	5.3.5.1 (Fibromyalgia)	Efficacy and safety in fibromyalgia patients	Double-blind, double-dummy, randomized, placebo-controlled	Tablets; 0.375 to 4.5 mg QD (PPX ER)	PPX ER: 30 Placebo: 31 (61)	Fibromyalgia patients	Up to 29 weeks (13 weeks titration followed by 16 weeks maintenance)	Ongoing; None

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 PD?
 - Efficacy data from two confirmatory Phase III trials: Advanced PD (248.525) and Early PD (248.524). The Advanced PD trial is the source of efficacy data for this application's indication for the treatment of advanced PD. It is reviewed in Sections 5.3.1. *(The efficacy analysis of the Early PD trial was presented in the clinical review for NDA 22421. This is summarized in Section 5.3.2, but safety data from the completed trial is assessed further in this clinical review.)*
- Do the IR and ER formulations of pramipexole have comparable pharmacokinetic and pharmacodynamic properties? *(These reports were submitted with NDA 22421 and were reviewed at that time. These findings are summarized in Section 4.4.3 and are covered more fully in the primary review from Clinical Pharmacology for that application)*
 - 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 Phase III trial in early PD (248.524)
- Is ER formulation of pramipexole safe? *(These trials are individually described in Section 5.3. except for the QTc safety trial which may be found in Section 7.4.5)*
 - Safety data from blinded comparisons:
 - ◆ QTc trial (248.545, review reproduced from NDA 22421)
 - ◆ Safety data from the Phase III trial in early PD (248.524)
 - ◆ Safety data from the Phase III trial in advanced PD (248.525)
 - Safety data from active comparator, unblinded or terminated trials:
 - ◆ Safety and comparability of overnight switch from PPX IR to PPX ER (248.636)
 - ◆ Safety data from the ongoing open label extension trials (248.633 and 248.634)
 - ◆ Safety data from the combined active comparator trial and PK study in advanced PD (248.610)
 - ◆ Safety data from Phase II trial in fibromyalgia (248.637). This trial has been discontinued prior to completion because the indication was dropped by the Sponsor

Three open label trials are ongoing and are collecting long term safety data on PPX ER. Their cut-off dates for their data are as follows:

Open label, long term extension Trial 248.633 contain patients who completed the double blind portion of the early PD trial (248.524). The overnight switch trial in early PD (248.636) also entered patients into 248.633. (data cut-off date: November 3, 2008).

Open label, long term extension Trial 248.634 contain patients who completed the double blind portion of the advanced PD trial (248.525), (data cut-off date: November 3, 2008).

Open label, long term extension Trial 248.610 is collecting open label safety data in patients from the double blind portion of this advanced PD active control trial in Japan (DB portion completed November 4, 2008; data cut-off date: November 28, 2008).

The 120 day safety update was submitted September 22, 2009 and included data up to its cut off on April 20, 2009 from the three ongoing open label trials: 248.610, 248.633 and 248.634.

5.3 Discussion of Individual Clinical Trials

5.3.1 Confirmatory Trial in Advanced PD (248.525)

Trial

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

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. By amendment, the endpoint analysis was moved to the 18th week of the maintenance period. At the end of the maintenance, subjects either entered an open label extension or tapered off medication over 1 week. Trial began May 9, 2007, the last patient enrolled July 4, 2008 and it ended November 19, 2008.

Primary endpoint:

- UPDRS (Unified Parkinson's Disease Rating Scale) parts II+III score (change from baseline to week 18. Originally to end of the maintenance period, but this was changed: see Amendments, below).

Key secondary criteria:

- Percentage of off-time during wakefulness –change from baseline (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 (“good on-time”)
 - 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)
- Responder rate for Patient Global Impression of Improvement (PGI-I) of early morning symptoms
- 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 Criteria

- Idiopathic Parkinson's disease diagnosed by UK Brain Bank criteria 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 Criteria

- Atypical parkinsonian syndromes
- Dementia with MMSE < 24 at baseline
- Psychosis except drug induced hallucinations
- History of deep brain stimulation
- Significant ECG abnormality or clinically significant hypotension
- Any dopamine blocking concomitant treatments within 4 weeks of the baseline visit.
- Patients with a creatinine clearance < 50 mL/min (estimated by the Cockcroft and Gault formula and calculated by the central lab on screening lab test).

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 of the trial:
anticholinergics, MAO B inhibitors, amantadine, entacapone or other COMT-inhibitor, and beta-blockers (when used to treat Parkinson's disease).

There was no rescue medication strategy for Parkinson symptoms in this trial.

Trial Visits

Table 4 Advanced PD Trial: Study checklist (source: Sponsor)

Clinical Review
Kenneth Bergmann, MD, FAAN
NDA 22-514
Mirapex ER / pramipexole dihydrochloride extended-release tablets

Table 9.5: 1 Trial Flow Chart

Trial period	S ¹	B ¹	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 ²	V12 ²	
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 ⁷													X ⁷			
BP, Pulse, Weight, Height ⁴	X	X		X		X		X		X	X	X	X	X	X	X	
Check for abnormal behaviour ^{8, 10}				X		X		X			X		X	X			
Modified MIDI ¹⁰		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 ¹	B ¹	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 ²	V12 ²	
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 ³	
Serum pregnancy test (if applicable)	X																
12-lead ECG	X														X	X ³	
Dispense/ re-dispense trial medication		X		X		X		X		X	X	X	X	X	X ⁵		

Trial period	S ¹	B ¹	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 ²	V12 ²
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 ⁶
Concomitant therapy	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events ⁹	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.

Treatment is given three times a day. In the PPX ER arm active drug would only be present in the first AM dose. In the IR arm there is active drug in each of the three daily doses. Tablets were administered in double dummy format.

Doses were taken with water, with or without food.

Predetermined criteria for the removal of subjects were specified in the trial protocol, including medication compliance in the 80-120% range.. Patients withdrawn prematurely were not replaced.

Randomization and Controls

The treatment allocation was determined according to the randomization code provided by Boehringer Ingelheim Pharma GmbH & Co. KG. The commercial program PMX CTM Release 3.3.0, Propack Data GmbH, was used for creation of the code listing. Randomization was stratified by study center. There is a 1:1:1 randomization to PPX ER, PPX IR or placebo in this trial. The block size was 3 subjects.

Access to the randomization schedule was restricted to the Sponsor's Clinical Trial Support and Clinical Trial Supplies Unit. The CRO handled the blinded assignment of subjects to intervention. However to keep the trial blinded the CRO was also involved in

the interim analysis for safety which was submitted earlier to NDA 22421, keeping the trial team from access to any results of that interim analysis.

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).

Subject Enrollment

76 sites in 14 countries (11 in Europe, 3 in Asia) enrolled 618 patients, beginning May 9, 2007. The trial ended November 19, 2008 with the last patient enrolling July 4, 2008.

Trial Populations / Patient Disposition

Of 618 enrolled subjects, 518 were entered into the study and were randomly assigned to active treatment IR or ER or placebo, in a ratio of 1:1:1.

Table 5 Advanced PD Trial: Subject enrollment

	Entered	Treated	Analyzed by Sponsor for primary endpoint.
PPX ER	165	164	161
PPX IR	175	175	172
Placebo	178	178	174
Total	518	517	507

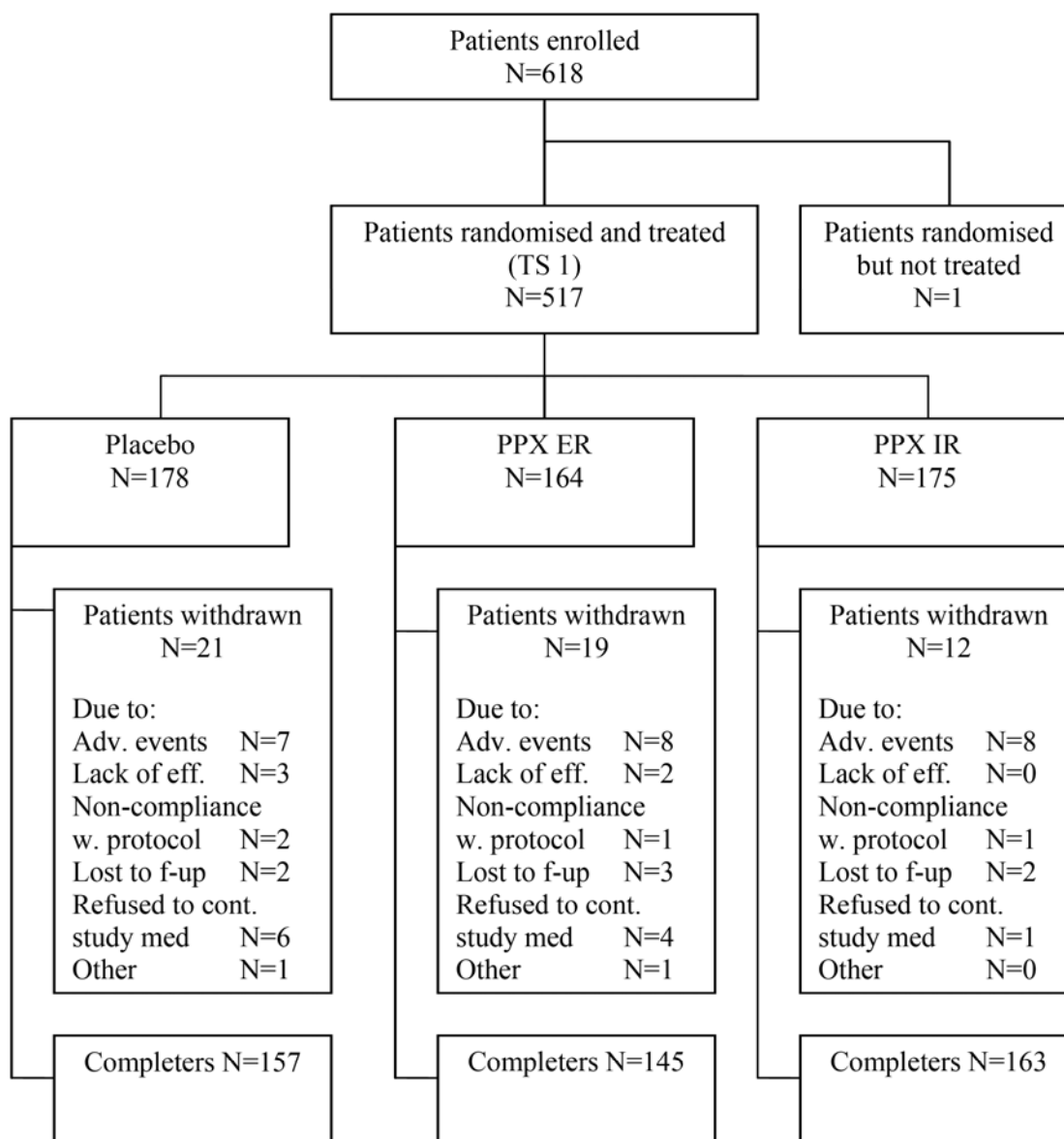


Figure 2 Advanced PD Trial: Patient flow (source: Sponsor)

The Sponsor indicates that “of the 518 randomized patients, 517 patients were treated and 507 have been analyzed in FAS 1. Four hundred and sixty five (465) patients completed the study until week 18. A total of 52 (10.1%) patients prematurely discontinued the study, 21 patients (11.8%) in the placebo group, 19 patients (11.6%) in the PPX ER group and 12 patients (6.9%) in the PPX IR group. The most common reasons for premature discontinuation of the study were AE and consent withdrawn, not

due to AE.” This group had data censored due to not reaching Visit 8 (week 18) treated in LOCF fashion. This is the cohort chosen by the reviewer for efficacy analysis.

The Sponsor also has designated a second TS group (TS 2), defined as all patients who were dispensed study medication, were documented to have at least one dose of study medication and completed Visit 11 (were treated for 33 weeks or had discontinued treatment prior to week 33) comprised of the 395 subjects who reached week 33, the original endpoint of the study. A subset of these (FAS 2) has at least one post treatment evaluation for efficacy. This group was analyzed for the evaluation of maintenance of effect, but the Sponsor’s statistical plan did not adjust *a priori* for analysis of multiple time points for efficacy.

The Sponsor also defined a third TS group (TS 3): all patients who were dispensed study medication and were documented to have at least one dose of study medication whatever the treatment duration. According to the Sponsor, “of the 517 randomized and treated patients in TS 3, 450 patients (87.0%) completed the study and 67 (13.0%) were discontinued during the titration-maintenance period. Of the 67 patients who prematurely discontinued the study during the titration-maintenance period, 31 patients (17.4%) were in the placebo group, 23 patients (14.0%) in the PPX ER group and 13 patients (7.4%) in the PPX IR group. The most common reasons for premature discontinuation (all groups pooled) of the study were AE (27 patients, 5.2%) and consent withdrawn, not due to AE (18 patients, 3.5%)”. This group was used for safety analysis by the reviewer.

The statistical reviewer, Jingyu (Julia) Luan, Ph.D., and I reviewed the individual subject’s line listing in the datasets relating to the primary outcome and confirmed the accuracy of the LOCF value for UPDRSII+III and membership of the subject to the appropriate analysis cohort. We found the Sponsor’s exclusion of a subject from the efficacy analysis to be accurate and based upon predefined criteria related solely to the availability of a pre- and single post-treatment evaluation.

To summarize:

TS1: all patients restricted to a treatment period of 18 weeks.

TS3: all data from all treated patients.

TS2: a subset of TS3 containing those subjects who had the chance to be treated for 30 weeks

Table 6 Advanced PD Trial: Summary of analysis sets (source: Sponsor)

	Placebo N (%) [*]	PPX ER N (%) [*]	PPX IR N (%) [*]	Total N (%) [*]
Treated set 1 (TS 1)	178 (100.0)	164 (99.4)	175 (100.0)	517 (99.8)
Full analysis set 1 (FAS 1)	174 (97.8)	161 (97.6)	172 (98.3)	507 (97.9)
Per protocol set (PPS 1)	160 (89.9)	149 (90.3)	161 (92.0)	470 (90.7)
Treated set 2 (TS 2)	140 (78.7)	120 (72.7)	135 (77.1)	395 (76.3)
Full analysis set 2 (FAS 2)	136 (76.4)	117 (70.9)	132 (75.4)	385 (74.3)
Treated set 3 (TS 3)	178 (100.0)	164 (99.4)	175 (100.0)	517 (99.8)

^{*} percentages based on randomised patients

Ten treated patients who were missing either a baseline or a treatment evaluation of UPDRS II + III were removed from TS1 to become FAS1, the efficacy analysis set. The reasons given are as follows:

Table 7 Advanced PD Trial: Patients excluded from FAS 1 (Source: Sponsor)

Country	Site No.	Pat. No.	Sex/ Age	Treatment	Treatment Duration (days)	UPDRS Part II+III at baseline	Reason for discontinuation
Russia	07007	6525	F/67	Placebo	8	46	Consent withdrawn
Korea	82003	7257	F/44	PPX ER	8	8.5	Consent withdrawn
Korea	82006	7327	F/59	Placebo	13	16.5	AE: Bradykinesia / Tremor
Korea	82006	7328	M/45	PPX IR	6	4.5	Consent withdrawn
Korea	82007	7350	M/54	PPX IR	236	.*	Completer
India	91005	7528	M/55	PPX ER	11	43	Lost to Follow-up
Philippines	63204	7996	M/63	PPX IR	7	60	AE: Agitation/ Hallucination/Insomnia
Philippines	63205	8024	F/78	PPX ER	10	71	Other (patient did not meet EX13 for creatinine clearance)
Philippines	63207	8082	F/65	Placebo	4	13	AE: Dizziness/Palpitations/ Nausea/Contusion
Philippines	63210	8174	M/41	Placebo	6	12.5	Non compliance

^{*} Patient 7350 had UPDRS II off-scale missing at baseline, leading to an incomplete UPDRS II+III at baseline
Source data: Appendix 16.2, Listing 1.1.1, 7.1.2.3

Three-quarters of subjects went on to enter the open label follow-up trial.

Method for determining the outcome of efficacy analysis (Source: Sponsor's protocol)

Planned analyses on efficacy and safety were based upon three predefined populations. The Treated Set (TS) was defined as all subjects who had at least one dose of investigational treatment. The Full Analysis Set (FAS) was defined as all patients who were randomized and received at least one dose of study drug and have

any post baseline efficacy assessment. The Per Protocol Set (PPS) is the set of the FAS who completed 18 weeks with baseline and end-of-study efficacy data with no major protocol violations.

Efficacy endpoints were analyzed in the FAS population while safety was investigated in the TS population.

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. It is appropriate, in this reviewer's opinion, to use these two adjustments in the efficacy model. UPDRS scoring has a much higher *intra*-observer as opposed to *inter*-observer reliability. It is also sensitive to the training and experience of the rater, which was largely the same person in each center. In addition, as is discussed below in subgroup response, the degree of improvement is related to severity of illness, i.e.: baseline UPDRS II + III score.

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

Demographics and Concomitant Medication

Each continent contributed roughly half the patients enrolled. The 76 trial sites randomized 518 subjects (mean 7 subjects / site; range 1 – 22). No site contributed more than 4% of all subjects.

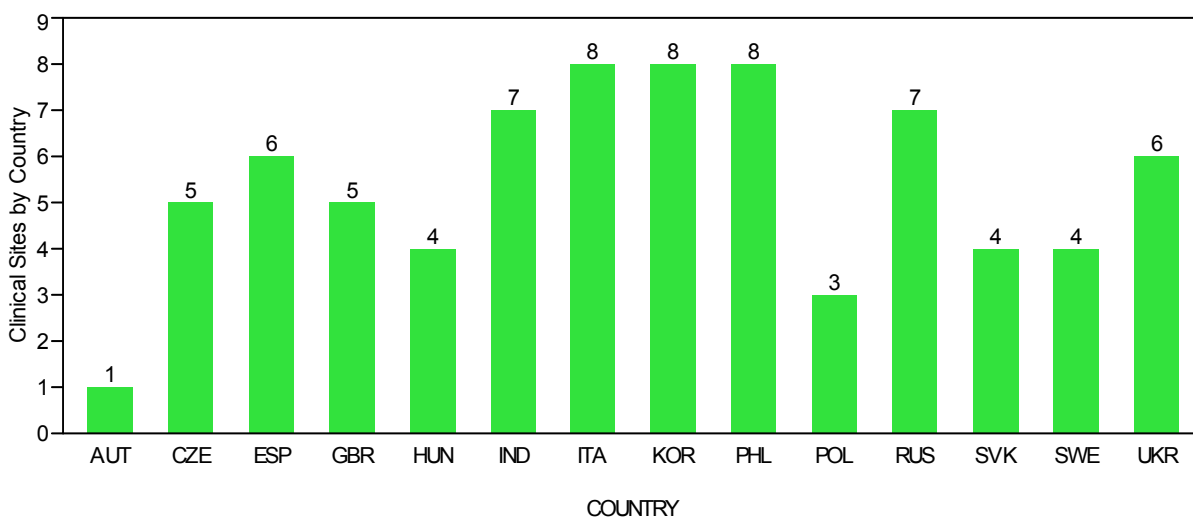


Figure 3 Advanced PD Trial: Numbers of clinical trial sites by country

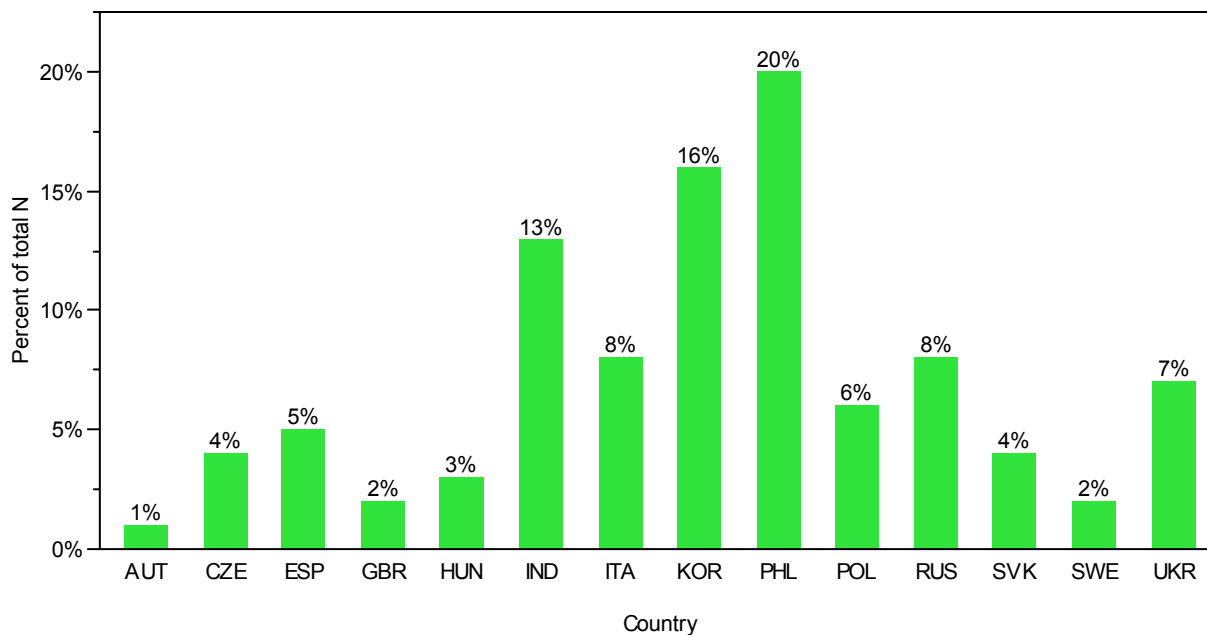


Figure 4 Advanced PD Trial: Contribution to enrollment by country

The demographic characteristics (age and gender distribution) for the group of enrolled subjects were equivalent among the treatment arms and typical of disease cohorts found in the clinic setting. The racial mix reflected the locations of the clinical sites and no black persons were treated. As illustrated below, the reviewer confirms that the study cohort contained the typical characteristics of a population characterized as having advanced PD with motor fluctuations in response to drug therapy.

Table 8 Advanced PD Trial: Demographic data for TS1 (source: Sponsor)

	Placebo	PPX ER	PPX IR	Total
Number of patients	178	164	175	517
Gender [N (%)]				
Male	94 (52.8)	92 (56.1)	98 (56.0)	284 (54.9)
Female	84 (47.2)	72 (43.9)	77 (44.0)	233 (45.1)
Age [years]				
Mean (SD)	60.9 (9.7)	61.6 (9.7)	62.0 (10.3)	61.5 (9.9)
Age classes [N (%)]				
<65 years	104 (58.4)	94 (57.3)	100 (57.1)	298 (57.6)
>=65 years	74 (41.6)	70 (42.7)	75 (42.9)	219 (42.4)
Race [N (%)]				
White	92 (51.7)	81 (49.4)	87 (49.7)	260 (50.3)
Black	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Asian	86 (48.3)	83 (50.6)	88 (50.3)	257 (49.7)
BMI [kg/m²]				
Mean (SD)	25.0 (4.6)	24.7 (3.9)	24.5 (4.2)	24.7 (4.3)

Source data: [Table 15.1.4.1: 1](#)

The profile of clinical characteristics of PD at baseline was representative of patents with moderately advanced disease and fluctuations in control of motor symptoms. The TS1 cohort was equivalent across the treatment arms.

Table 9 Advanced PD Trial: Baseline disease characteristics (source: Sponsor)

	Placebo	PPX ER	PPX IR	Total
PD duration [years]				
Duration mean(SD) or median (IQR)	5.9 (3.8)	6.1 (4.0)	6.6 (4.4)	6.2 (4.1)
PD known since				
0-< 2 [y] N (%)	1 (0.6)	1 (0.6)	3 (1.7)	5 (1.0)
2-< 5 [y] N (%)	90 (50.6)	82 (50.0)	76 (43.4)	248 (48.0)
>= 5 [y] N (%)	87 (48.9)	81 (49.4)	96 (54.9)	264 (51.1)
UPDRS Part II+III total score				
Number of Patients	178	164	174	516
Mean (SD)	39.6 (18.2)	41.7 (17.9)	40.7 (17.6)	40.6 (17.9)
Percentage off-time				
Number of Patients	178	164	175	517
Mean (SD)	38.6 (15.6)	36.0 (15.7)	37.7 (13.2)	37.5 (14.9)
Off-time in hours				
Number of Patients	178	164	175	517
Mean (SD)	6.0 (2.5)	5.8 (2.8)	6.0 (2.2)	5.9 (2.5)
UPDRS Part I total score				
Number of Patients	178	164	175	517
Mean (SD)	1.9 (1.9)	2.1 (1.8)	1.9 (1.7)	1.9 (1.8)
UPDRS Part II total score (average on and off-period)				
Number of Patients	178	164	174	516
Mean (SD)	11.9 (6.1)	12.7 (6.5)	12.3 (5.7)	12.3 (6.1)
UPDRS Part III total score				
Number of Patients	178	164	175	517
Mean (SD)	27.7 (13.6)	29.0 (12.9)	28.3 (13.3)	28.3 (13.2)
PDSS				
Number of Patients	178	164	175	517
Mean (SD)	101.7 (25.3)	96.8 (27.7)	101.1 (26.2)	100.0 (26.4)

Source data: [Table 15.1.4.1: 2](#), [15.1.4.1: 3](#), [15.1.4.1: 4](#)

This was confirmed by the reviewer by tabulating baseline Hoehn and Yahr Stage across treatment arms (There are no H-Y Stage I patients; this would be inconsistent with advanced disease).

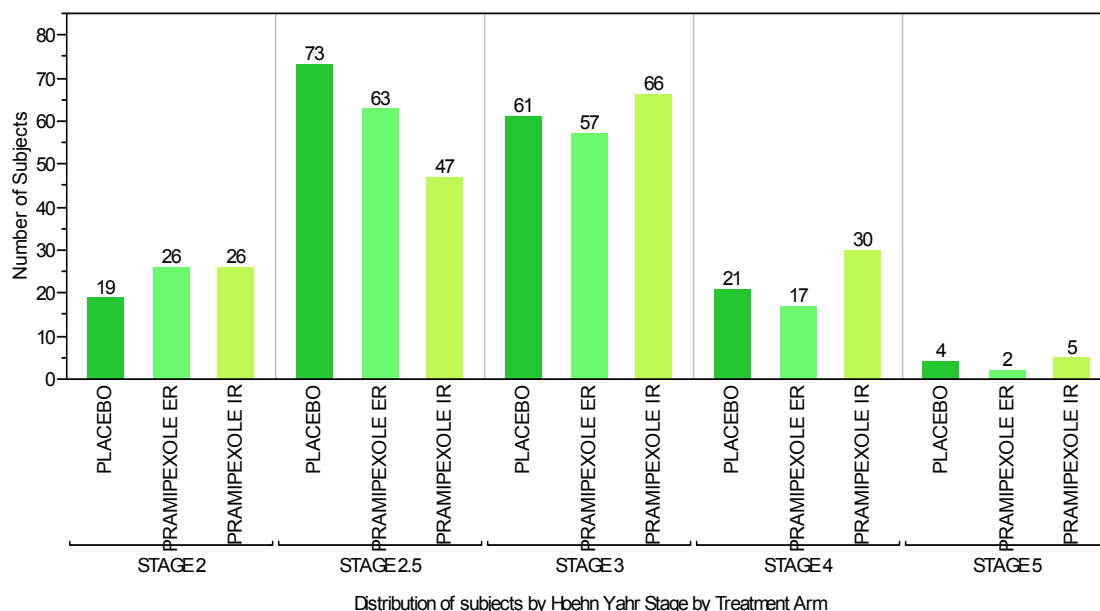


Figure 5 Advanced PD Trial: Hoehn-Yahr Stage in "off" period at baseline

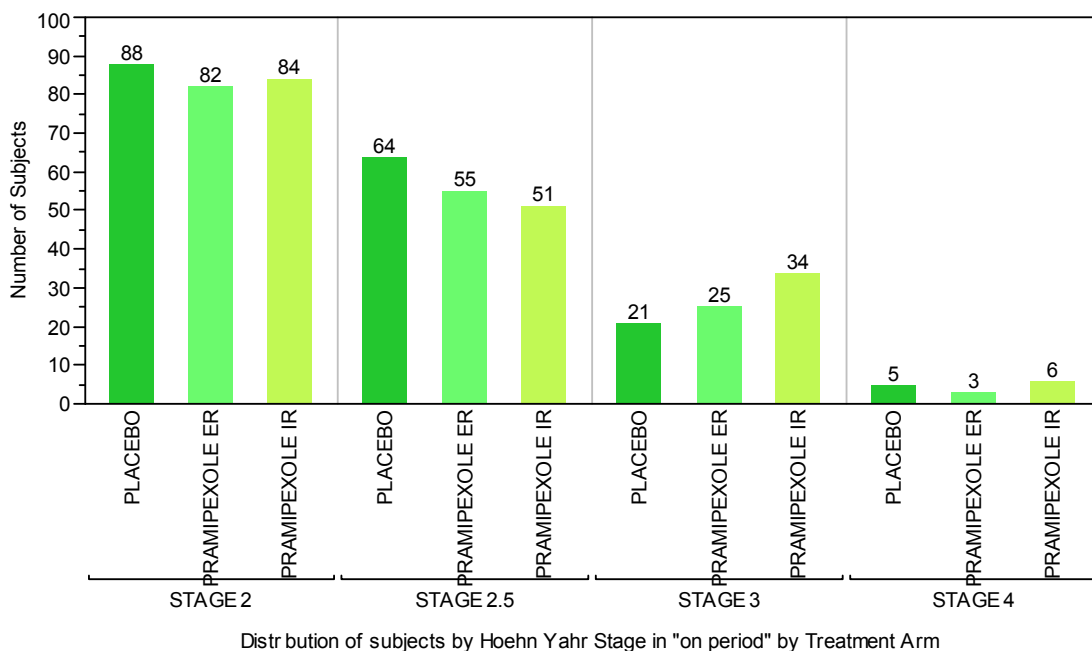


Figure 6 Advanced PD Trial: Hoehn-Yahr Stage in "on" period at baseline

By categorical analysis, there is no maldistribution of severity of disease among the treatment arms in either the "on" or "off" state (Pearson $\chi^2 = 0.4823$ and 0.1385 , respectively). The same is true for age of the subjects across treatment arms.

Depression, which has been shown to impact greatly the perception of treatment success in PD, was measured at baseline using the Beck Depression Inventory (BDI). With a mean score of 10 for the cohort as a whole, this finding did not correlate with age; best fit of a line to the data is virtually horizontal:

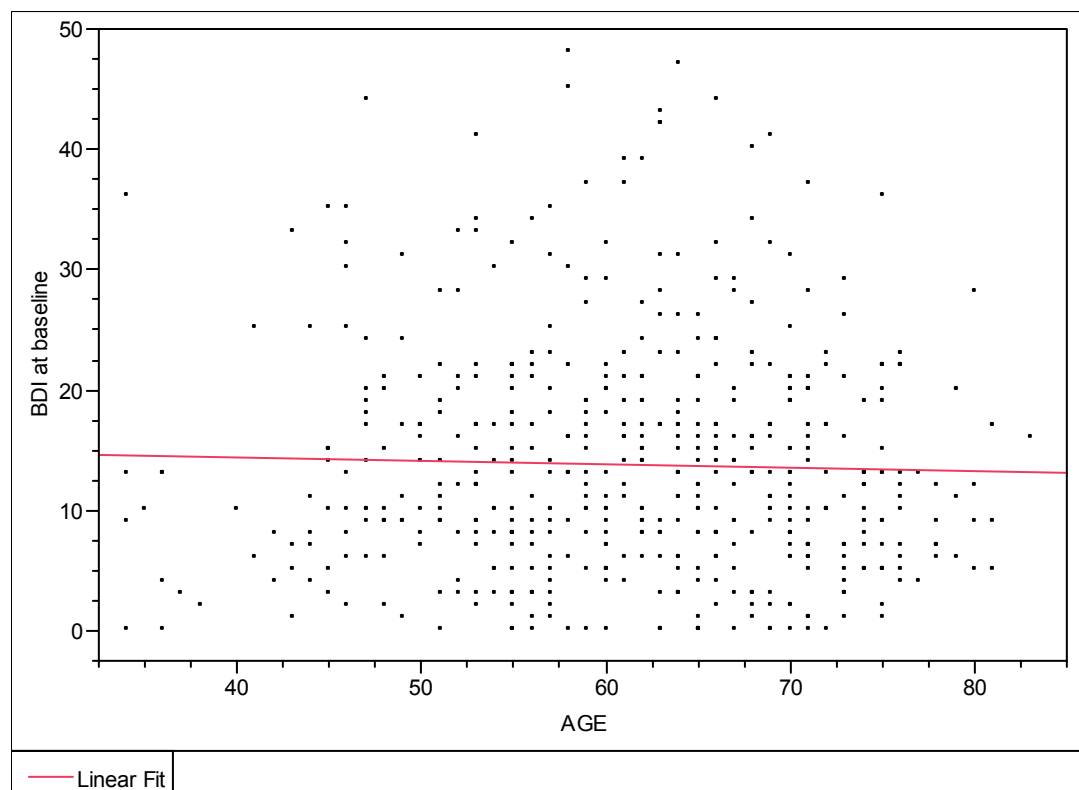


Figure 7 Advanced PD Trial: Baseline Beck Depression Inventory by age

There was no quantitative difference in baseline depression score among the treatment arms, though each arm contained subjects who were significantly depressed by this measure (ANOVA, $p = 0.0926$)

	N	Mean	Std Error	Lower 95%	Upper 95%
PLACEBO	178	12.5843	0.71586	11.178	13.991
PRAMIPEXOLE ER	164	14.7744	0.74579	13.309	16.240
PRAMIPEXOLE IR	175	14.1143	0.72197	12.696	15.533

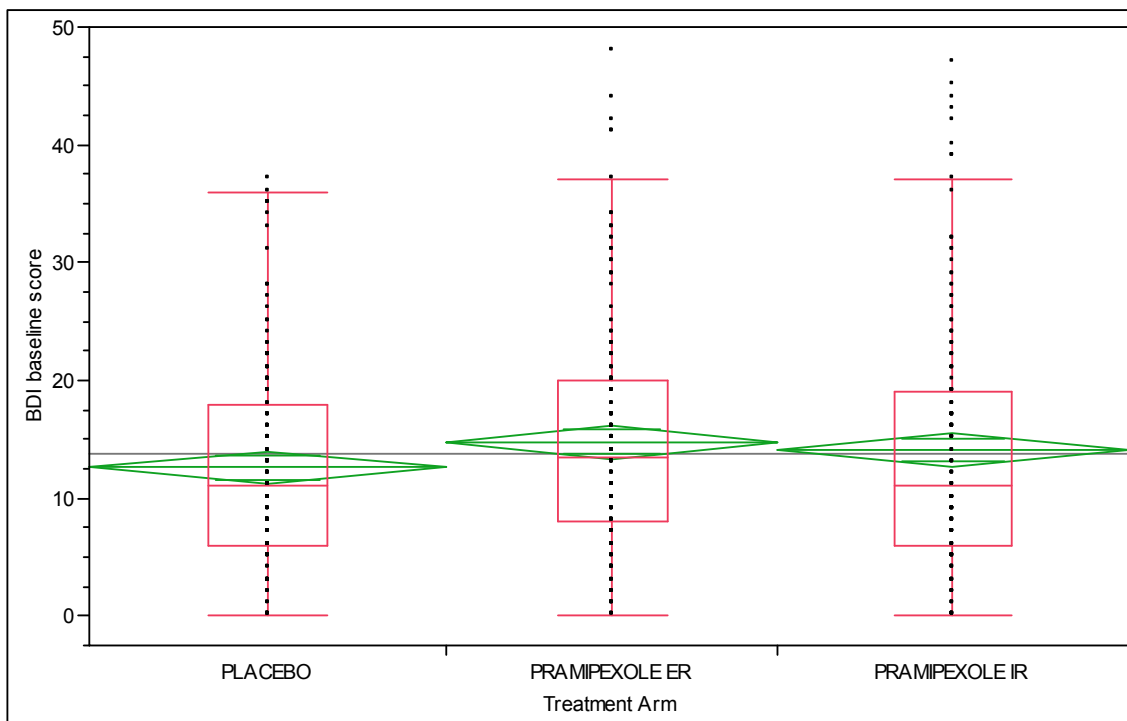
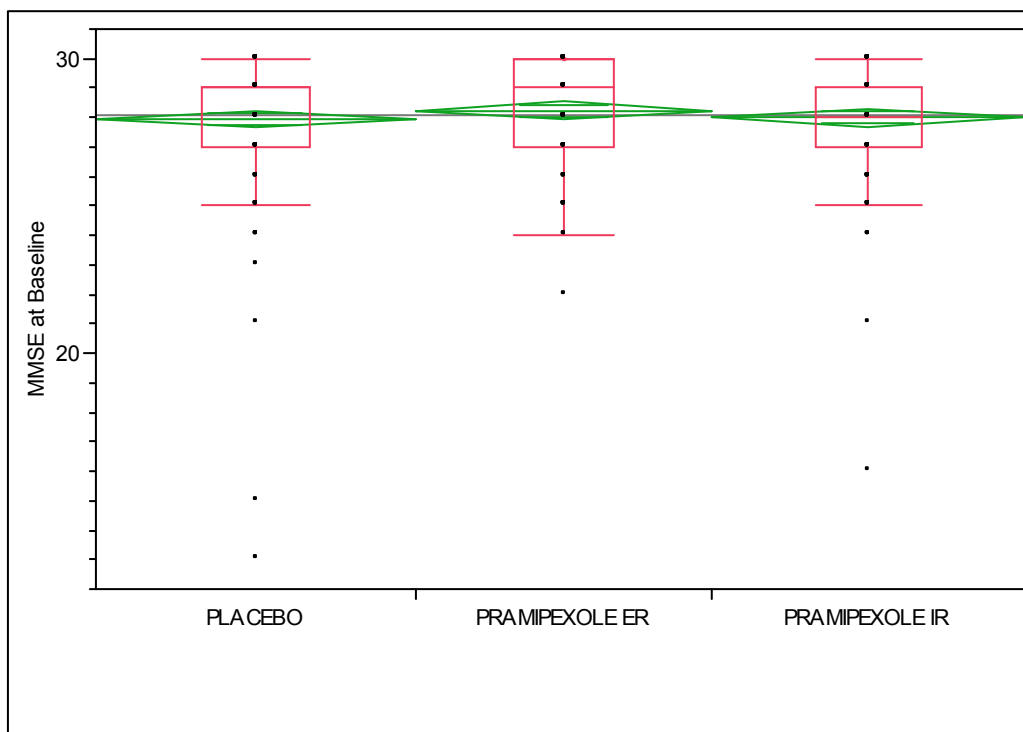


Figure 8 Advanced PD Trial: BDI baseline distribution, means and confidence interval

Baseline mental status evaluation was performed using the Folstein “Mini Mental Status Examination” (MMSE). There were no differences among the treatment arms (ANOVA, $p = 0.3871$). It should be noted that a score less than 24 was an exclusion criteria for the trial but 7 subjects (aged 51 to 69) scoring below this threshold were enrolled (PBO = 4, PPX ER = 1, PPX IR = 2). Given that the MMSE is relatively insensitive to frontal cognitive decline of the sort seen in PD, these individuals were likely fairly impaired.



Arm	N	Mean	Std Error	Lower 95%	Upper 95%
PLACEBO	178	27.9438	0.14944	27.650	28.237
PRAMIPEXOLE ER	165	28.2242	0.15521	27.919	28.529
PRAMIPEXOLE IR	175	27.9943	0.15071	27.698	28.290

Figure 9 Advanced PD Trial: Mini Mental Status Exam baseline distribution, mean and confidence interval

Four fifths of patients had concomitant medical diagnoses reflecting an aging population and these were distributed equally across the treatment arms. Most common were ocular disorders (cataracts and retinal vasculopathy), vascular disorder (hypertension, cardiac disorders and myocardial ischemia, hypercholesterolemia), diabetes mellitus, depression, constipation, gastritis and arthritis.

Concomitant Medications

The cohort had a typical exposure to antiparkinson medication at enrollment. By definition, all subjects were taking levodopa + peripheral decarboxylase inhibitor in some form. The next most common treatment given in addition was amantadine (27% of the cohort), MAO-B inhibitors (16%) and anticholinergics (15%). A number of patients (N=69, 13%) had anti PD medications added to their regimen during the active treatment portion of the study: Placebo (26, 15%) PPX ER (18, 11%), PPX IR (25,

14%). For most patients (64 of 69), this was represented by levodopa containing therapies.

The presence of a concomitant medication reduces the potential magnitude of motor response to the investigational agent. The net effect, if any, would be to reduce the trial's ability to reject the null hypothesis.

Compliance with trial medication

Measurement of compliance was effected through physical count of returned trial medication. The standard was between 80 and 120% of mg dose prescribed at every visit. For the efficacy population compliance was 97%; eleven patients had compliance below 80%.

Dosing information and Exposure

This is considered more fully in the review of safety, **Section 7.2.1, Overall Exposure at Appropriate Doses/Durations**. In brief, the average length of exposure to treatment in the 18 week efficacy study was 118 days (as compared to the safety i.e.: 33 week, population: 198 days). These exposures were consistent across treatment arms. 90% of patients in the efficacy analysis were exposed between 16 and 20 weeks.

With the flexible dose titration schedule, the distribution of dosing in the efficacy portion of the trial was as follows:

Table 10 Advanced PD Trial: Dose distribution at 18 weeks (source: Sponsor)

Table 12.1: 3 Dose distribution at 18 weeks, TS 1

Distribution of daily dose	Treatment group	
	PPX ER N (%)	PPX IR N (%)
Number of patients (%)	164 (100.0)	175 (100.0)
Low dose	64 (39.0)	64 (36.6)
0.375mg	8 (4.9)	7 (4.0)
0.75mg	14 (8.5)	18 (10.3)
1.5mg	42 (25.6)	39 (22.3)
Medium dose	37 (22.6)	42 (24.0)
2.25mg	12 (7.3)	17 (9.7)
3.0mg	25 (15.2)	25 (14.3)
High dose	63 (38.4)	69 (39.4)
3.75mg	12 (7.3)	19 (10.9)
4.5mg	51 (31.1)	50 (28.6)

Source data: [Table 15.3.1.1: 2](#)

Protocol Deviations and Violations

Protocol violations (PV) were evaluated before unblinding but the criteria used to classify a PV as important or not are vague. The Sponsor judges these to be “related to entrance criteria, informed consent, trial conduct, concomitant medication, or missing primary endpoint data which may have an impact on efficacy or safety assessment.” The Sponsor found that there were 47 subjects (9%) with any PV deemed “important” (Placebo = 18 (10%), PPX ER = 15 (9%), PPX IR = 14 (8%)). All of these were related to efficacy evaluation and none due to safety.

- The largest number (n = 22) was related to stopping treatment prior to Visit 7, i.e.: 5 weeks into the maintenance phase and the first visit after stable dose maintenance treatment was begun (Placebo = 10 (6%), PPX ER = 9 (6%) and PPX IR = 3 (2%)).
- Ten subjects were missing efficacy data for the main outcome measure and were excluded from the FAS I analysis group as a result (Placebo = 4, (2%) PPX ER = 3 (2%) and PPX IR = 3 (2%)).
- Eleven subjects were outside of drug compliance parameters (< 80% - >120% of daily PPX dose) (Placebo = 5, (3%) PPX ER = 2 (1%) and PPX IR = 4 (2%)).

Outcome of Efficacy Assessment

Primary Efficacy Endpoint

- UPDRS (Unified Parkinson’s Disease Rating Scale) parts II+III score (change from baseline to week 18.)

The Sponsor found that PPX ER was superior to placebo by the pre-specified statistical analysis plan, using the efficacy outcome UPDRS II + III at 18 weeks (11 weeks of maintenance treatment) using the LOCF FAS 1 population:

Table 11 Advanced PD Trial: Efficacy outcome at Week 18 (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	174	161	172		
Mean Baseline (SD)	40.0 (18.1)	41.7 (17.7)	40.8 (17.4)		
Mean week 18 (SD)	33.2 (17.4)	29.5 (17.3)	27.2 (16.4)		
LS Mean Change (SE) – ANCOVA*	-6.1 (0.9)	-11.0 (1.0)	-12.8 (0.9)	0.0001	<.0001
LS Mean Change (SE) – MMRM*	-6.4 (0.8)	-11.4 (0.9)	-12.6 (0.8)	<.0001	<.0001

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

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

Source data: [Table 15.2.1.1: 1](#)

The reviewer duplicated this analysis using an analysis of fit model in JMP using the change from baseline UPDRS II+III to Visit 8 (Week 18) among the treatment arms, using the baseline UPDRS as covariate and adjusting for site. This model closely fit the Sponsor's results:

Table 12 Advanced PD Trial: Efficacy analysis by least squares means

Level	Least Sq Mean	Std Error	Mean
PLACEBO	-6.25014	0.88894527	-6.787
PRAMIPEXOLE ER	-11.01461	0.92068157	-12.193
PRAMIPEXOLE IR	-12.57371	0.88354932	-13.580

Table 13 Advanced PD Trial: Efficacy analysis by analysis of covariance

Source	DF	Sum of Squares	Mean Square	F Ratio
Model	78	43238.355	554.338	5.2053
Error	428	45580.053	106.495	Prob > F
C. Total	506	88818.408		<.0001

Table 14 Advanced PD Trial: Efficacy analysis by Student's t for fit model

$\alpha = 0.050$, $t = 1.96552$

LSMean[i] By LSMean[j]

Mean[i]-Mean[j] Std Err Dif Lower CL Dif Upper CL Dif	PLACEBO	PRAMIPEXOLE ER	PRAMIPEXOLE IR
PLACEBO	0 0 0 0	4.76447 1.15338 2.49748 7.03146	6.32357 1.1282 4.10607 8.54107
PRAMIPEXOLE ER	-4.7645 1.15338 -7.0315 -2.4975	0 0 0 0	1.5591 1.1568 -0.7146 3.83281
PRAMIPEXOLE IR	-6.3236 1.1282 -8.5411 -4.1061	-1.5591 1.1568 -3.8328 0.71461	0 0 0 0

Level		Least Sq Mean
PLACEBO	A	-6.25014
PRAMIPEXOLE ER	B	-11.01461
PRAMIPEXOLE IR	B	-12.57371

Levels not connected by same letter are significantly different.

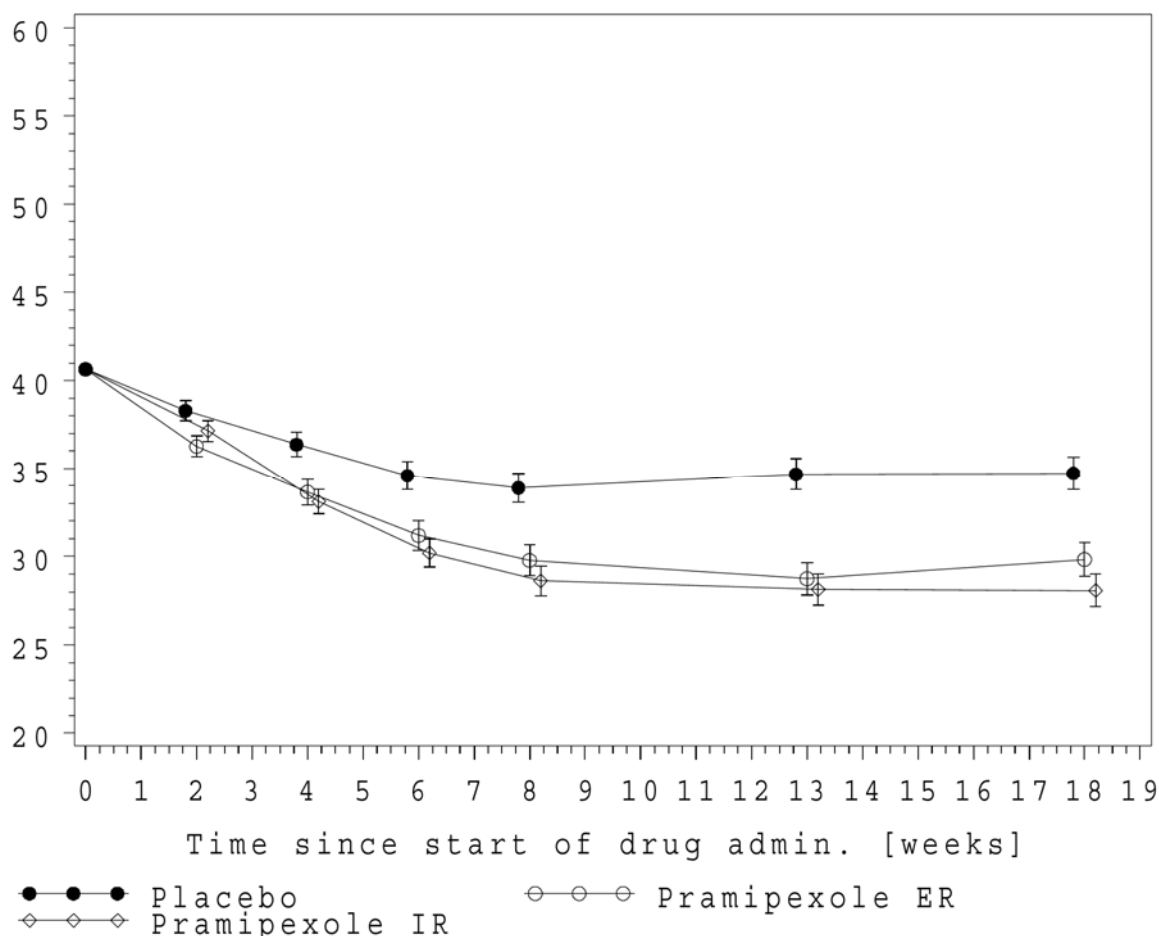


Figure 10 Advanced PD Trial: Improvement in UPDRS II+III in the FAS1 LOCF cohort (source: Sponsor)

While the PPX IR was also effective against placebo, this study was not designed for comparison of the two treatments to each other, nor was this pre-specified in the analysis plan. No claims on this point are able to be supported.

Sponsor's clarification of the UPDRS evaluation: It should be noted that the UPDRS Part II is a scale recording the patient's own assessment of their activities of daily living in the past week. It was performed asking the patient to recall their function while in both the "on" and "off" period. The Sponsor was queried as to which of these Part II scores was used in the analysis. Their response (**bold**) to the reviewer's request (*italics*) is as follows:

For the primary outcome variable (UPDRS Part II + Part III), which UPDRS Part II score was used to derive this measure: the "on" state or "off" state?

For the primary outcome (UPDRS II+III) in Study 248.525 we used the average UPDRS Part II during “on” and “off” state as described in section 1.3 of the trial protocol:

"the primary efficacy endpoint used to evaluate the patient's treatment response will be the UPDRS Parts II and III combined. The sum of the UPDRS Part II items (averaged for on-periods and off-periods) will be added to the sum of the UPDRS Part III items, to calculate the total UPDRS II+III score".

This is the same approach that was used in Phase III trials of advanced Parkinson's disease for the development of immediate-release pramipexole tablets (NDA 20-667).

Please note that in NDA 22-514, UPDRS II scores are usually qualified in the text and tables as “on”, “off”, or (average of “on” and “off”). However, wherever UPDRS II is presented without further qualification, it refers to the UPDRS II (average “on” and “off”) to avoid excessive redundancy in the text.

Likewise, Part III the motor examination of the UPDRS is subject to variation related to fluctuations of motor response to medication in advanced PD. Clarification was also sought from the Sponsor in this regard:

Please clarify what the trial protocol specified with regard to the time of day when the UPDRS Part III motor examination was performed.

The protocol for study 248.525 was designed to ensure that the UPDRS Part III was assessed during “on” time. See answer to [next question] below.

Please clarify what the trial protocol specified with regard to when, in relation to the time of the previous dose of levodopa, the UPDRS Part III motor examination was to be performed.

The protocol for study 248.525 indicated the preferred time (morning) and relation to previous dose of levodopa (1 hour post levodopa dose). The following instructions were given in the protocol regarding UPDRS Part III evaluation:

"At all visits, every effort should be done to see the patient always at on-periods. If possible, the UPDRS Part III evaluation has to be done 1 hour after the first morning dose of the L-Dopa+ or L-Dopa+/entacapone treatment".

These instructions were emphasized to the investigators during the International Investigators' Meetings before trial initiation and during the initiation visit.

Reviewers comment: The Sponsor has chosen a conservative path for the use of UPDRS in the evaluation of the efficacy of MIRAPEX ER. Trials of anti-parkinson drugs and devices such as subthalamic nucleus deep brain stimulation have generally found that the magnitude of effect of the agent or device in question upon the motor state (and resultant activities of daily living) differs depending upon the phase in which the patient is observed: “on” or “off” state. The comparison of the patient’s motor and ADL function in the “on” state before and after drug treatment is likely to show a smaller effect (even with the baseline score taken as a covariate) than comparison of improvement of the “off” state before and after drug treatment. This is due to a floor effect of the UPDRS: if you have a low (favorable) score at your best time, then there is little room for further improvement regardless of the treatment added. The “off” state however can benefit further and this low period is not as low as in the pretreatment time period. The Sponsor’s own analyses of secondary outcomes bear this out (see below).

The Sponsor, in averaging the “on” and “off” ADL scores, and using the motor ratings performed at a time of peak drug effect (1 hour after a morning levodopa dose) reduces the trial’s potential to demonstrate the full potential of extended release pramipexole. As a result, a finding of efficacy in this protocol could be considered quite robust.

Maintenance of treatment effect:

This analysis looked at whether the treatment effect was maintained over the 33 weeks period of treatment originally planned in the study. 122 subjects did not make it to this cut point and were not included in this analysis.

Given this caveat about the numbers of subjects included in this analysis, the efficacy reached at 18 weeks was largely maintained over the 33 week trial. There was also no evidence for a need for increasing the daily dose of PPX:

Table 15 Advanced PD Trial: Maintenance of effective drug dose (source: Sponsor)

Table 12.1: 4 PPX doses after 33 weeks compared to PPX doses after 18 weeks, TS 2

Distribution of daily dose	Placebo	PPX ER	PPX IR
Number of patients [N (%)]	111 (100.0)	102 (100.0)	123 (100.0)
Reduced	2 (1.8)	2 (2.0)	1 (0.8)
Unchanged	108 (97.3)	96 (94.1)	119 (96.7)
Increased	1 (0.9)	4 (3.9)	3 (2.4)

Source data: [Table 15.3.1.2: 3](#)

Table 16 Advanced PD Trial: Maintenance of efficacy by UPDRS (source: Sponsor)

Table 11.4.1.1.4: 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		100	94	114
Baseline	Mean (SD)	41.3 (18.5)	42.3 (18.9)	41.3 (17.9)
Week 18	Mean (SD)	32.0 (15.9)	27.3 (17.6)	26.4 (17.0)
Change from baseline	Mean (SD)	-9.2 (15.0)	-15.0 (13.2)	-14.9 (12.0)
Week 33	Mean (SD)	31.0 (16.2)	28.1 (19.2)	27.9 (19.1)
Change from baseline	Mean (SD)	-10.3 (14.9)	-14.2 (15.3)	-13.4 (15.8)

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

Source data: [Table 15.2.1.3: 8](#)

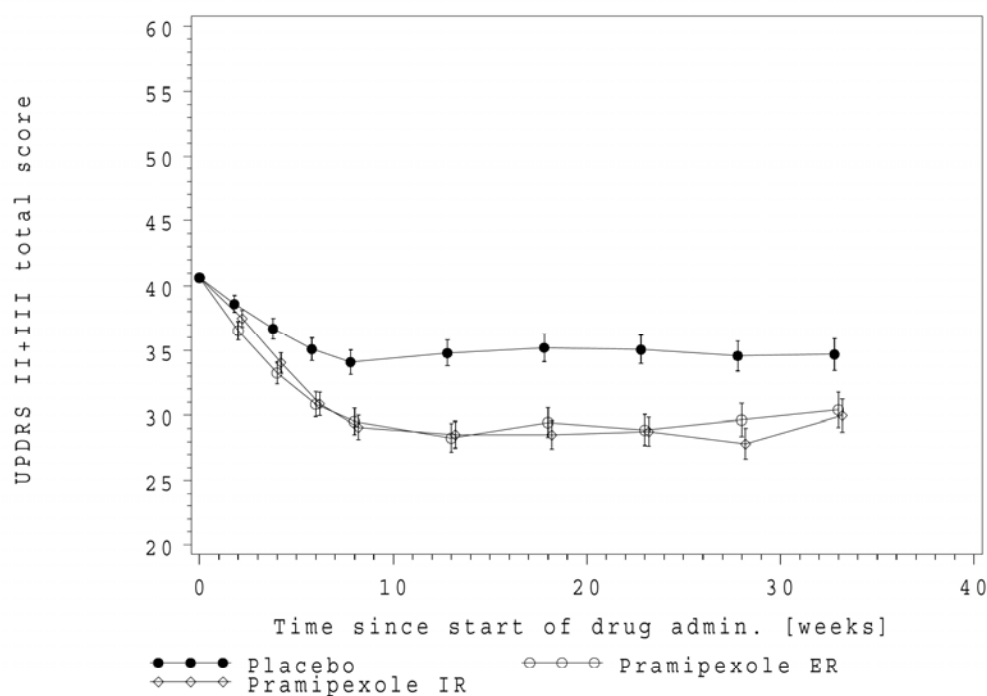


Figure 11.4.1.1.4: 1 Adjusted mean change (SE) from baseline in UPDRS Part II+III score, FAS 2 (LOCF)

Figure 11 Advanced PD Trial: Maintenance of UPDRS improvement (source: Sponsor)

Key Secondary Endpoint

- Percentage of off-time during wakefulness – change from baseline (diary based patient reported outcome).

Patients were instructed to complete a diary (covering a 24-hour period from midnight to midnight) indicating their status for each half-hour time period. The diary responses were supposed to be those of the patient, but a caregiver might have marked the diary as instructed by the patient (i.e. assisting with the physical task of marking the diary). The patient was instructed to place one check mark on the diary to indicate the patient's predominant state during the majority (i.e. > 15 min) of the half-hour time period. The diary category choices were: "asleep", "off", "on without dyskinesia", "on with non-troublesome dyskinesia", and "on with troublesome dyskinesia". The patient or caregiver was trained for this task at screening.

While the improvement was significant at 18 weeks by both analysis of covariance and a mixed model for repeated measures, it loses its support at 33 weeks over the course of the trial. Note however, a considerable loss in evaluable subjects at that point and the fact that an LOCF method would have brought in favorable outcomes from earlier evaluations in the trial. It is not clear whether this result represents tachyphylaxis or methodological shortcomings, but the UPDRS scores and dose requirements of the patients at 33 weeks do not support the notion of tachyphylaxis as a reason for this finding.

Table 17 Advanced PD Trial: Improved off-time at 18 weeks (source: Sponsor)

Table 11.4.1.2.1: 1 Percentage off-time, 18 weeks treatment, FAS 1 (LOCF)

Key secondary Endpoint	Placebo	PPX ER	PPX IR	PPX ER vs. placebo	PPX IR vs. placebo
Percentage off-time					
Number of Patients	174	160	171		
Mean Baseline (SD)	38.7 (15.6)	36.3 (15.8)	37.8 (13.1)		
Mean week 18 (SD)	29.6 (19.5)	24.1 (17.8)	22.3 (16.4)		
LS Mean Change (SE) – ANCOVA*	-8.8 (1.3)	-13.3 (1.4)	-15.9 (1.3)	0.0122	<.0001
LS Mean Change (SE) – MMRM*	-8.5 (1.1)	-13.9 (1.1)	-15.7 (1.1)	0.0004	<.0001

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

Negative changes imply improvement

Source data: [Table 15.2.2.1.1: 1](#)

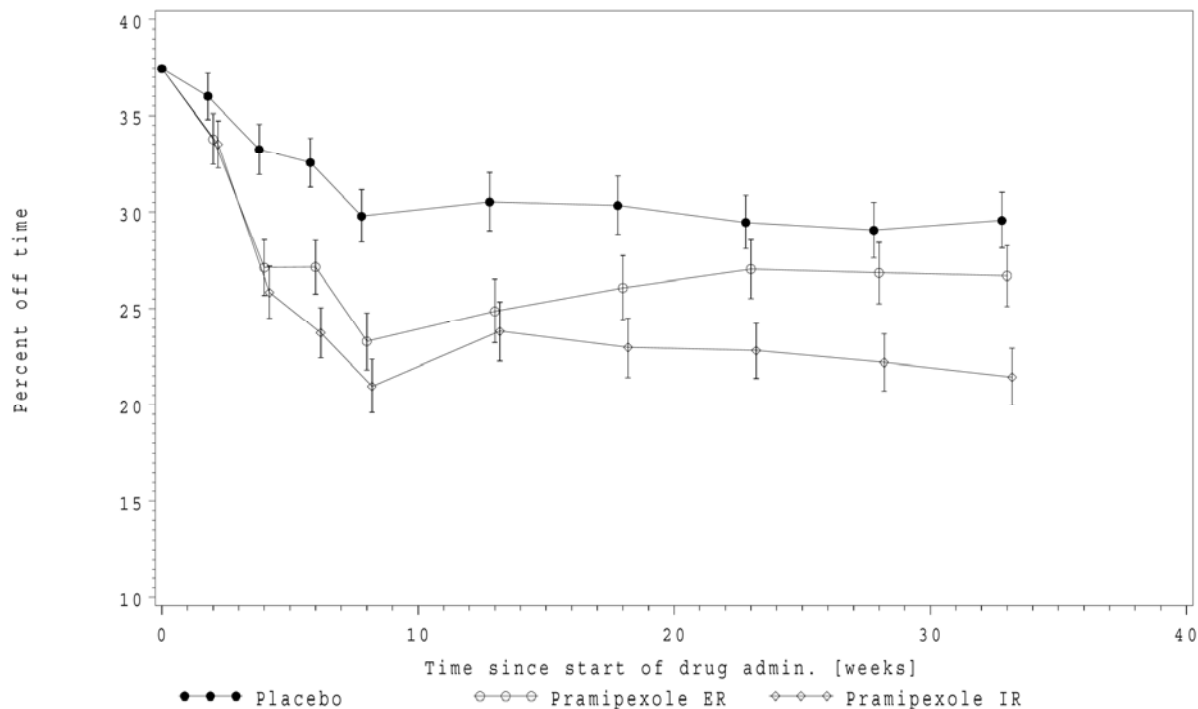


Figure 15.2.2.1.3: 1 Adjusted mean change(SE) from baseline in Percentage off time during waking hours,, FAS2 (LOCF)

Source data: Appendix 16.1.9.2, Statdoc 6.2.1.3.2

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Figure 12 Advanced PD Trial: Maintenance of off-time improvement at 33 weeks (source: Sponsor)

Table 18 Advanced PD Trial: Maintenance of off-time improvement at 33 weeks (source: Sponsor)

Table 15.2.2.1.3: 1 Percentage off time during waking hours, 33 weeks, FAS2 (LOCF)

Secondary Endpoint	Placebo	Pramipexole ER	Pramipexole IR	PPX ER vs.Placebo	PPX IR vs.Placebo
% off time during waking hours					
Number of patients	136	116	131		
Baseline, Mean (SD)	39.1 (16.1)	37.3 (16.5)	38.8 (13.3)		
Week 33, Mean (SD)	29.9 (18.8)	26.0 (19.2)	21.7 (14.7)		
Change from Baseline, Mean [95% CI]	-9.2 [-12.4, -6.0]	-11.3 [-14.9, -7.7]	-17.1 [-19.8,-14.4]		
LS Mean Change [95% CI] - ANCOVA*	-8.9 [-11.7, -6.1]	-11.8 [-14.9, -8.7]	-17.0 [-19.9,-14.1]	0.1537	<.0001
LS Mean Change [95% CI] - MMRM**	-8.7 [-11.1, -6.3]	-12.7 [-15.3,-10.1]	-16.1 [-18.5,-13.7]	0.0184	<.0001

Negative change implies improvement

* ANCOVA with factors treatment and pooled country and covariate baseline

** LS means per treatment group over visits 6 7 and 8 (maintenance)

Important Secondary Endpoints

The secondary endpoints Clinical Global Impression of Improvement (CGI-I) and Patient Global Impression of Improvement (PGI-I) responder rates were analyzed by the Sponsor using the Cochran-Mantel- Haenszel (CMH) test with pooled country stratification on the FAS populations.

The two items 'very much improved' (CGI-I) or 'very much better' (PGI-I) and 'much improved' (CGI-I) or 'much better' (PGI-I) were pooled by the Sponsor and these patients were considered as responders for CGI-I and PGI-I.

Table 19 Advanced PD Trial: CGI responder rate (source: Sponsor)

Table 11.4.1.2.2: 6 CGI-I responders, 18 weeks treatment, FAS 1 (LOCF)

Secondary Endpoint	Placebo	PPX ER	PPX IR	PPX ER vs. placebo	PPX IR vs. placebo
CGI-I Responders				CMH	CMH
Number of Patients	171	160	169		
Responder [N (%)]	56 (32.7)	78 (48.8)	88 (52.1)	0.0037	0.0002
% Responder [95% CI]	[25.8, 40.3]	[40.8, 56.8]	[44.3, 59.8]		

Source data: [Table 15.2.2.6.1: 1](#)

Table 20 Advanced PD Trial: PGI responder rate (source: Sponsor)

Table 11.4.1.2.2: 7 PGI-I responders, 18 weeks treatment, FAS 1 (LOCF)

Secondary Endpoint	Placebo	PPX ER	PPX IR	PPX ER vs. placebo	PPX IR vs. placebo
PGI-I Responders				CMH	CMH
Number of Patients	174	161	172		
Responder [N (%)]	47 (27.0)	60 (37.3)	76 (44.2)	0.0554	0.0005
% Responder [95% CI]	[20.6, 34.3]	[29.8, 45.2]	[36.6, 51.9]		

Source data: [Table 15.2.2.7.1: 1](#)

While this is a fairly commonly accepted confirmatory measure, there is good reason to suspect that they are not independent measures. Indeed, the concordance between the patient's and investigator's opinion of their clinical state is striking ($p < 0.0001$) and suggests that it is driven by conversation between the two at the visit where it is performed.

This matrix looks at the agreement between the patient's and investigator's impression at Visit 8 (Week 18) for 487 subjects, regardless of treatment arm:

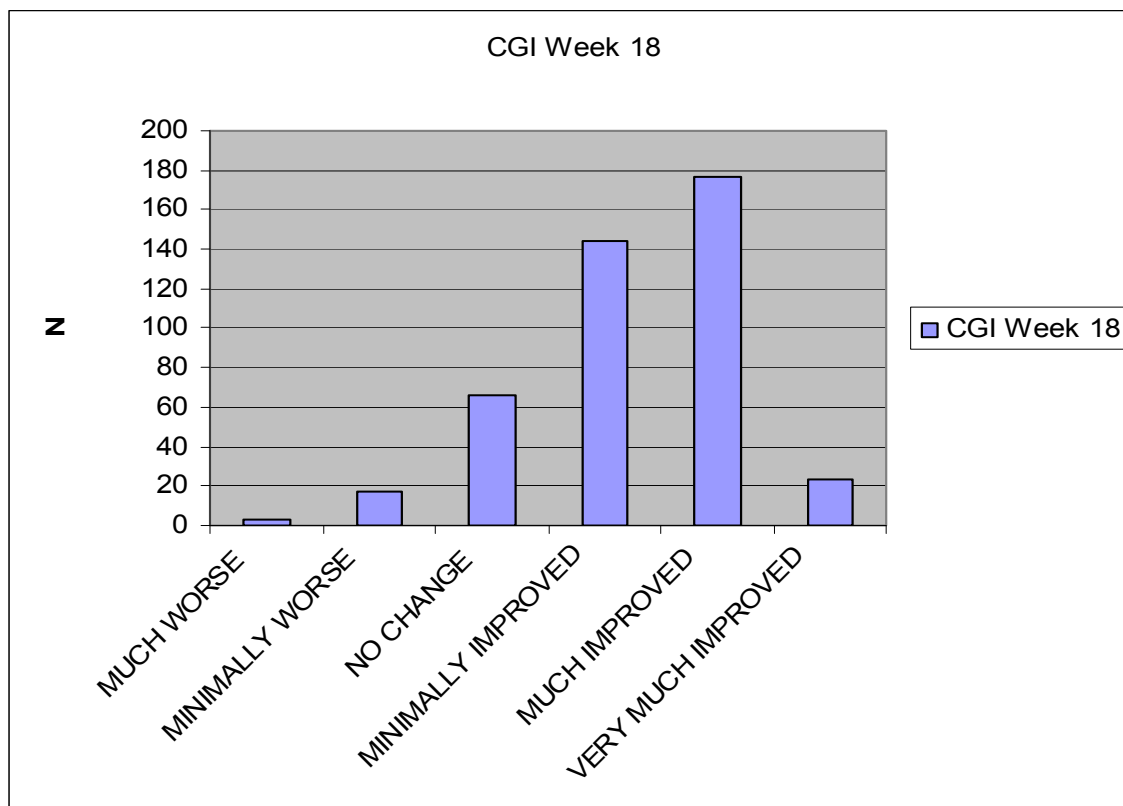
Table 21 Advanced PD Trial: Contingency table PGI by CGI at Visit 8 (week 18)

Count	MINIMALLY IMPROVED	MINIMALLY WORSE	MUCH IMPROVED	MUCH WORSE	NO CHANGE	VERY MUCH IMPROVED	
A LITTLE BETTER	93	2	42	0	19	8	164
A LITTLE WORSE	3	6	6	1	7	0	23
MUCH BETTER	25	2	113	0	2	6	148
MUCH WORSE	0	2	0	2	0	0	4
NO CHANGE	22	5	10	0	38	1	76
VERY MUCH BETTER	1	0	6	0	0	8	15
	144	17	177	3	66	23	430

	N	DF	-LogLike	RSquare (U)
	430	25	138.66959	0.2410
Test			ChiSquare	Prob>ChiSq
Likelihood Ratio			277.339	<.0001
Pearson			477.149	<.0001

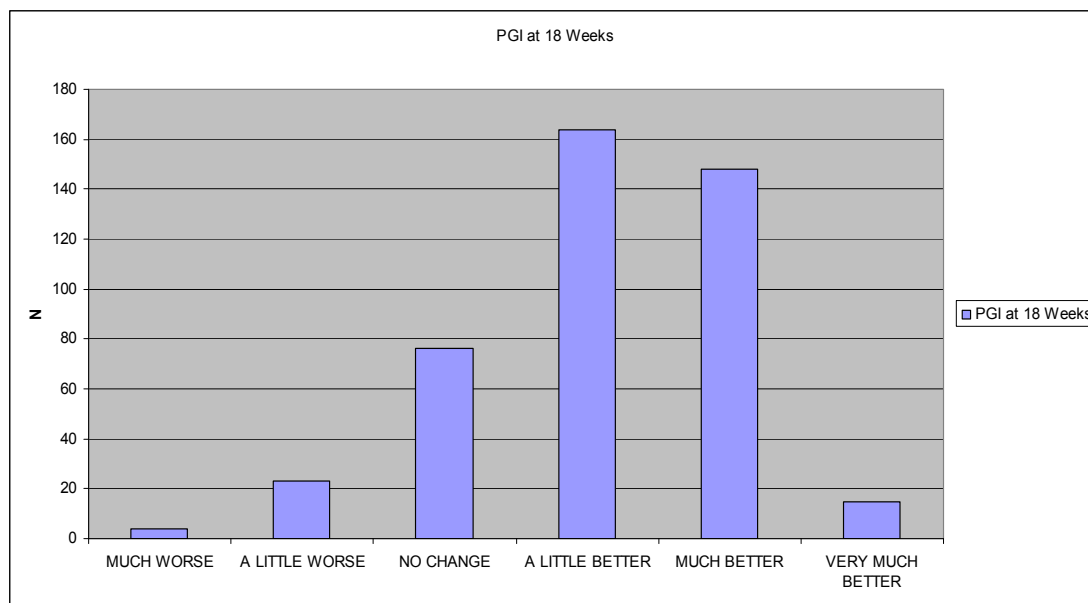
The first thing this reviewer noted was that evaluations are not randomly distributed: i.e. some categories are used less than expected and this lower frequency is consistent for both the patient and reviewer:

Table 22 Advanced PD Trial: Distribution of CGI responses at Week 18



Level	Count	Frequency
MUCH WORSE	3	0.00698
MINIMALLY WORSE	17	0.03953
NO CHANGE	66	0.15349
MINIMALLY IMPROVED	144	0.33488
MUCH IMPROVED	177	0.41163
VERY MUCH IMPROVED	23	0.05349
Total	430	1.00000

Table 23 Advanced PD Trial: Distribution of PGI responses at week 18



Level	Count	Frequency
MUCH WORSE	4	0.00930
A LITTLE WORSE	23	0.05349
NO CHANGE	76	0.17674
A LITTLE BETTER	164	0.38140
MUCH BETTER	148	0.34419
VERY MUCH BETTER	15	0.03488
Total	430	1.00000

While this is a commonly used secondary outcome measure of efficacy, there is good reason to think that these judgments are not independently made.

Other Secondary Efficacy Analyses

The nature of dyskinesia in advanced PD patients treated with PPX ER is discussed in **Section 7.3.5 Submission Specific Primary Safety Concerns**. Because only a single UPDRS item rates dyskinesia and because subjects with mild dyskinesia are often unaware of its presence, severity ratings derived from this scale are quite unreliable. In any case, the Sponsor did not discern significant differences among the treatment arms for the percentage of on-time without dyskinesia. Nor did they find differences among the arms with regard to percentage on-time with troublesome dyskinesia.

Responder rates were defined as patients with at least a 20% improvement from baseline at 18 weeks in the FAS 1 (LOCF) cohort. The Sponsor's result for the primary efficacy outcome is as follows:

Table 24 Advanced PD Trial: Responder rate by UPDRS II+III (source: Sponsor)

Table 11.4.1.2.2: 9 UPDRS II+III Response ($\geq 20\%$ improvement), 18 weeks treatment, FAS 1 (LOCF)

Secondary Endpoint	Placebo	PPX ER	PPX IR	PPX ER vs. placebo CMH	PPX IR vs. placebo CMH
UPDRS II+III Responders ($\geq 20\%$ improvement)					
Number of Patients	174	161	172		
Responder [N (%)]	70 (40.2)	103 (64.0)	118 (68.6)	<.0001	<.0001
% Responder [95% CI]	[32.9, 47.9]	[56.0, 71.4]	[61.1, 75.5]		

Source data: [Table 15.2.1.1: 4](#)

UPDRS Part I (Mentation, Behavior and Mood during the past week) showed no differences among the treatment arms. UPDRS Part II (activities of daily living) scores were averaged from evaluations performed in the on and off period. Differences from placebo were significant in both treatment arms though one could argue whether these represent clinically meaningful differences:

Table 25 Advanced PD Trial: UPDRS Part II ADL outcome (source: Sponsor)

Table 11.4.1.2.2: 11 UPDRS II total score (average at on and off-period), 18 weeks treatment, FAS 1 (LOCF)

Secondary Endpoint	Placebo	PPX ER	PPX IR	PPX ER vs. placebo ANCOVA	PPX IR vs. placebo ANCOVA
UPDRS II total score					
Number of Patients	174	161	172		
Baseline, Mean (SD)	11.9 (6.1)	12.8 (6.5)	12.3 (5.6)		
Week 18, Mean (SD)	9.8 (6.0)	9.6 (6.0)	8.4 (5.2)		
Change from baseline LS mean (SE)*	-1.9 (0.3)	-2.7 (0.3)	-3.6 (0.3)	0.0455	<.0001

*ANCOVA with factors treatment and pooled country and covariate baseline

Source data: [Table 15.2.2.10.3.1:1](#)

Consistent with the previous discussion about the timing of evaluations to dose, these differences disappear when only the on-period scores are used, and become stronger when evaluations performed in the off-period are used (Sponsor's ANCOVA PPX ER $p=0.019$; PPX IR $p<0.0001$).

It is evident (and not surprising) that UPDRS Part III (motor examination) is the major contributor to the significance of the primary outcome result:

Table 26 Advanced PD Trial: UPDRS Part III Motor Exam outcome (source: Sponsor)

Table 11.4.1.2.2: 12 UPDRS III total score, 18 weeks treatment, FAS 1 (LOCF)

Secondary Endpoint	Placebo	PPX ER	PPX IR	PPX ER vs. placebo ANCOVA	PPX IR vs. placebo ANCOVA
UPDRS III total score					
Number of Patients	174	161	172		
Baseline, Mean (SD)	28.1 (13.4)	29.0 (12.7)	28.5 (13.2)		
Week 18, Mean (SD)	23.4 (12.9)	20.0 (12.4)	18.8 (12.3)		
Change from baseline LS mean (SE)*	-4.3 (0.7)	-8.3 (0.7)	-9.2 (0.7)	<.0001	<.0001

*ANCOVA with factors treatment and pooled country and covariate baseline

Source data: [Table 15.2.2.11.1:1](#)

In advanced PD, motor improvement does not always translate to functional improvement in a robust fashion and that is evident in this trial as well.

No treatment effects were found for the Beck Depression Inventory, Likert Scale for Pain, Quality of Life scales (PDQ-39 and EQ-5D).

Total daily L-dopa dose did not change during the course of the study, consistent with the protocol's direction that it was only to be altered in the case of a "dopaminergic AE".

Table 27 Advanced PD Trial: Mean concomitant daily levodopa dose

Daily L-DOPA Dose			
Trial 248.525 Advanced PD	PLACEBO	PPX ER	PPX IR
Observed Cases in FAS1	(N=145)	(N=133)	(N=151)
Dose at baseline, Mean	569 mg	568 mg	610 mg
Dose at week 18, Mean	596 mg	565 mg	619 mg
Dose decreased over trial, N	4 (3%)	14 (11%)	12 (8%)
Dose increased over trial, N	3 (2%)	9 (6%)	14 (10%)

Exploration of Subgroup Effects

Subgroups analysis was performed by the Sponsor in exploratory fashion for the effect of age (above and below 65 years), race (Asian vs. white), gender, the use of MAO-B

inhibitors, amantadine, anticholinergics, baseline UPDRS II+III (above and below 37), hours of off-time at baseline, baseline L-dopa dose, and final pramipexole dose.

Differences noted were not of a magnitude to suggest clinical or statistical significance for these parameters. However, patients who were younger, male, more severely affected, took more medication (MAO B inhibitors and L-dopa), and had more off-time, had greater change in UPDRS II+III from baseline.

There was no relationship between motor improvement as measured on the UPDRS II+III and the final PPX ER dose.

Safety Assessment

*Reviewer's note: Because this trial contains the only group of advanced PD patients in a blinded placebo controlled trial, their tolerance of medication is analyzed and presented in **Section 7, Review of Safety**.*

Conclusion:

After review of the Sponsor's data and further analysis of the effect of MIRAPEX ER on a population of patients with advanced PD, I find substantial and consistent evidence to support the conclusion that MIRAPEX ER is effective as an adjunctive treatment for the motor symptoms and fluctuations in disease control which occur in advanced PD. The treatment effect appears to extend to 33 weeks without evidence of tachyphylaxis.

5.3.2 Confirmatory 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

(Reviewer's note: The structure of the trial is presented here in order to provide a framework for safety review and adverse event analysis. A synopsis of the efficacy analysis from NDA 22421 is provided but the full analysis is not repeated here.)

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 analyses submitted to NDA 22421 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.

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
- 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

Clinical Review
Kenneth Bergmann, MD, FAAN
NDA 22-514
Mirapex ER / pramipexole dihydrochloride extended-release tablets

- 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 in NDA 22421.

Table 28 Early PD Trial Checklist (source: Sponsor)

Trial period	S ¹	B ¹	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 ²	V12 ²			
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			
			±2	±2	±2	±2	±2	±2	±2	±3	±3	±3	±3	±3	±3	±3			
Written informed consent	X																		
Demographics	X																		
Baseline conditions	X																		
Inclusion/ Exclusion criteria	X	X																	
Physical exam.	X														X				
Ophthalmologic monitoring	X ⁷													X ⁷					
BP, Pulse, Weight, Height ⁴	X	X		X		X		X		X	X	X	X	X	X	X			
Check for abnormal behaviour ⁹				X		X		X			X		X						
Modified MID1		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				
CGI-I						X				X	X ⁸	X	X ⁸	X ⁸	X				
PGI-I			X	X	X	X	X	X	X	X	X ⁸	X	X ⁸	X ⁸	X				
ESS		X				X				X		X			X				
BDI		X				X				X		X			X				
PDSS		X				X				X		X			X				

Trial period	S ¹	B ¹	Flexible up-titration phase								Maintenance phase								Down-titration phase
	V1	V2	TC1	V3	TC2	V4	TC3	V5	TC4	V6	V7	V8	V9	V10	V11 ²	V12 ²			
Visit number	V1																		
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		±2	±2	X	X	X			X				
PDQ-39		X										X			X				
EQ-5D		X										X			X				
Safety lab tests	X									X					X	X ³			
PK samples ¹⁰	X									X	X								
Serum pregnancy test (if applicable)	X																		
12-lead ECG	X														X	X ³			
Dispense/re-dispense trial medication		X		X		X		X		X	X	X	X	X	X ³				
Check medication compliance			X	X	X	X	X	X	X	X	X	X	X	X	X	X ⁶			
Concomitant therapy	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Adverse events ¹¹	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 CG-I and PGI-I should be done before starting L-Dopa.
- 9 In case the patient experiences any abnormal behaviour, then the Modified MMID 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 MMID 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 daytime sleepiness or any episodes of unexpected falling asleep?" In case of a positive answer, it should be reported as an Adverse Event.

Treatments, randomization 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 (total daily pramipexole dose): 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 daily. Patients were titrated up if they reported that they were not “at least a little bit better”: Trial medication was administered in double blind fashion with double dummy dosing. 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.

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

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 analyses performed in this early PD trial were:

A. 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. 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 was 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 however remains the primary efficacy analysis for this trial.

Summary of the Trial Efficacy Assessment

Review of clinical data found sufficient evidence for MIRAPEX ER's use in the treatment of early Parkinson's disease. 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. This clinical reviewer found similar results:

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.

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 29 Early PD Trial: 248.524 reviewer's efficacy analysis for FAS1 at 18 weeks

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 30 Early PD Trial: Primary outcome efficacy analysis (source: Sponsor)

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

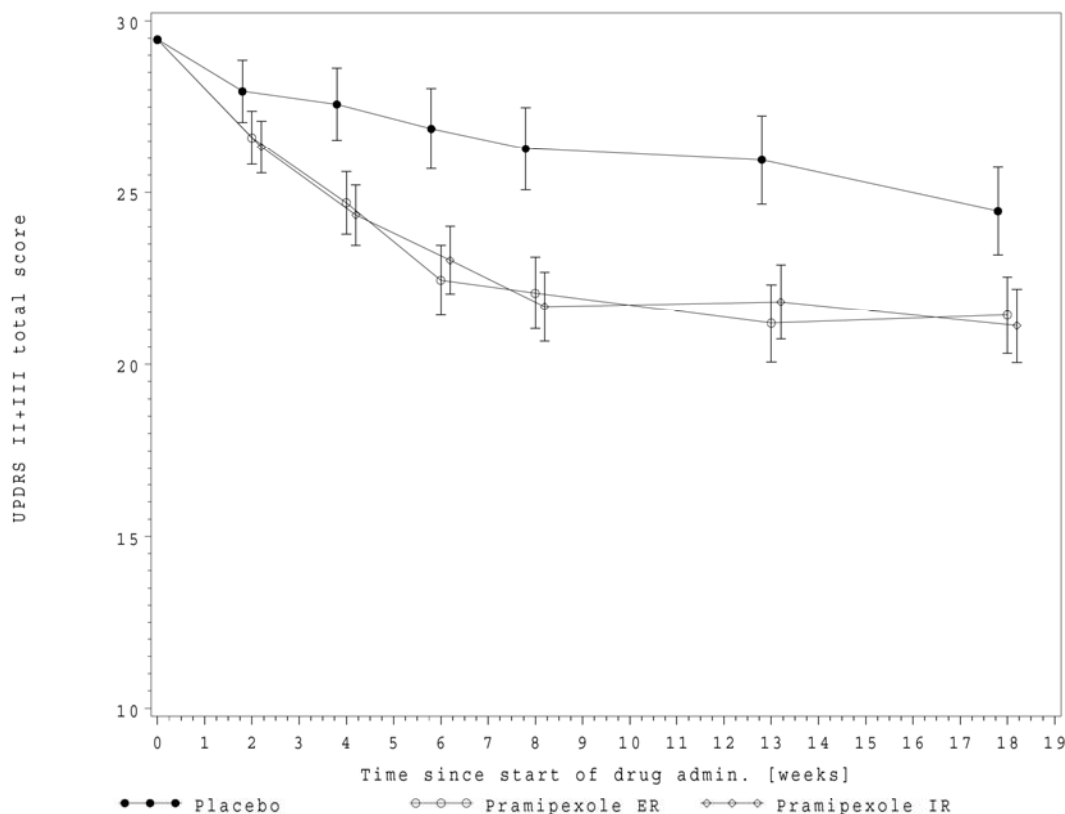
Primary Endpoint	Placebo	PPX ER	PPX IR	PPX ER vs. placebo	PPX IR vs. placebo
UPDRS Part II+III total score					
Number of Patients	50	102	101		
Baseline, Mean (SD)	30.1 (17.0)	30.5 (13.6)	28.3 (12.0)		
Week 18, Mean (SD)	24.0 (14.9)	21.3 (14.0)	19.3 (9.8)		
LS Mean Change (SE) – ANCOVA*	-5.1 (1.3)	-8.1 (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 13 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)

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 31 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
Total	6	101	45	152
Chi Square	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
Total	2	92	57	151
Chi Square	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.

- 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 32 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
Total	8	102	42	152
Chi Square	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
Total	1	120	30	151
Chi Square	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.

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 was presented in the clinical review of NDA 22421. Mood, pain, quality of life and of sleep showed no change over the course of the study.

Analysis of subjects reaching 33 weeks

Originally, this analysis was performed by the Sponsor as a demonstration of “maintenance of effect”. However, only 84 patients had completed the trial, reaching week 33 (6 months of treatment), at the time of the submission of NDA 22421. The Sponsor’s data for the completed study is presented below. (A flow chart of the final disposition of enrolled subjects at completion of the trial may be seen in the next section on Safety Assessments.)

Maintenance was defined as no worsening greater than 15% in the mean change of UPDRS II + III total score from baseline to week 18. Most subjects in fact had no appreciable change in dose requirement for MIRAPEX ER or change in the primary outcome variable between Week 18 and Week 33.

Table 33 Early PD Trial: maintenance of efficacy at 33 weeks (source: Sponsor)

Table 11.4.1.1.6: 1 Maintenance of efficacy in UPDRS Part II+III total score at week 18 and week 33, FAS (OC)

	Placebo	Pramipexole ER	Pramipexole IR
Number of patients	90	173	174
Baseline, mean (SD)	29.4 (15.0)	29.6 (12.9)	29.1 (12.4)
Week 18, mean (SD)	23.4 (14.3)	18.6 (11.3)	18.2 (10.9)
Change from baseline	-5.9 (8.9)	-11.0 (9.3)	-10.9 (8.9)
Week 33, mean (SD)	24.5 (15.2)	18.5 (11.2)	18.2 (11.3)
Change from baseline	-4.9 (9.8)	-11.1 (9.9)	-10.9 (10.5)

Source data: Appendix 16.1.9.2 Table 6.3.9

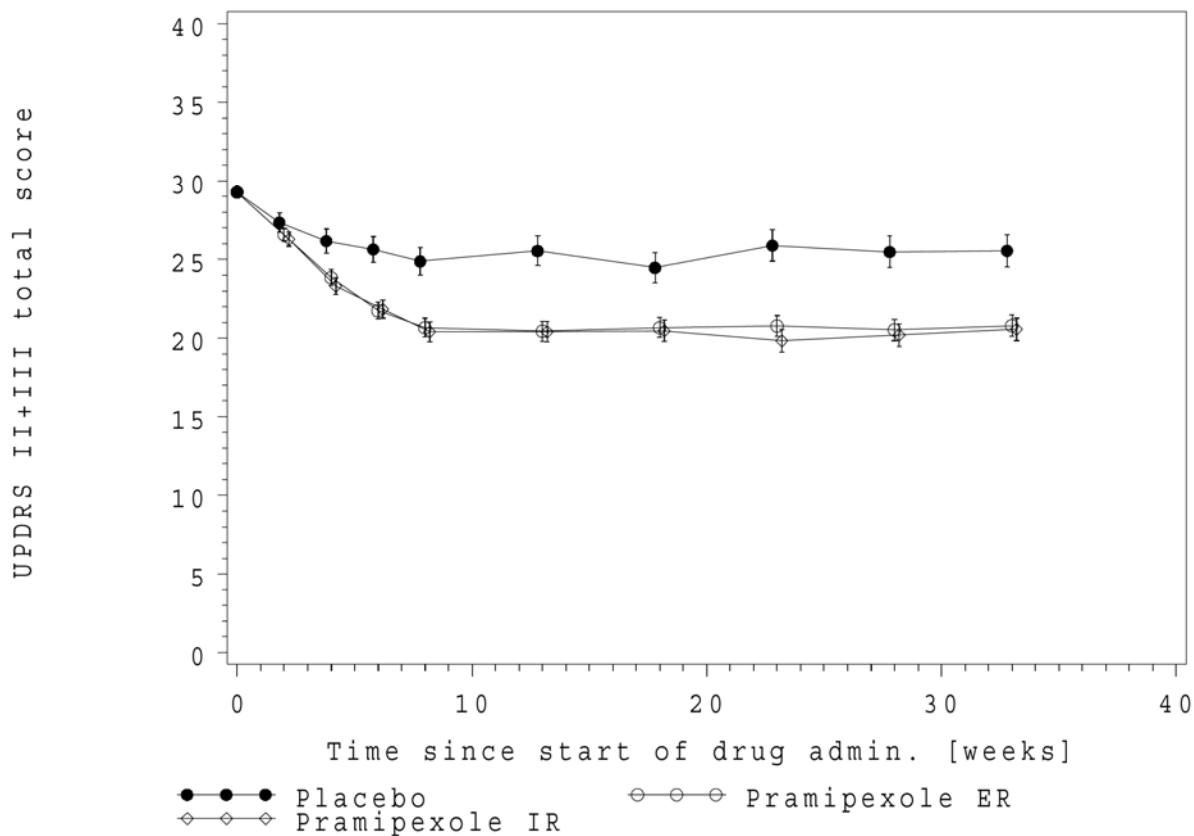


Figure 11.4.1.1.1: 1 Adjusted mean change (SE) from baseline in UPDRS Part II+III score, FAS (LOCF)

Figure 14 Early PD Trial: UPDRS improvement at 33 weeks (source: Sponsor)

Table 34 Early PD Trial: Maintenance of dose at 33 weeks (source: Sponsor)

Table 12.1: 3 Changes in pramipexole doses after 33 weeks compared to pramipexole doses after 18 weeks, TS

	Placebo N (%)	Pramipexole ER N (%)	Pramipexole IR N (%)
Number of patients treated	91 (100.0)	173 (100.0)	176 (100.0)
Distribution of daily dose			
Reduced	1 (1.1)	2 (1.2)	3 (1.7)
Unchanged	88 (96.7)	167 (96.5)	169 (96.0)
Increased	2 (2.2)	4 (2.3)	4 (2.3)

Source data: [Table 15.3.1: 4](#)

Safety Assessment

*Reviewer's note: Because this trial contains the only group of double blinded early PD in a placebo controlled trial, they are considered as a whole in **Section 7, Review of Safety**.*

The safety population:

A total of 599 patients were enrolled into Trial 248.524. Of these 60 failed the screening and 539 subjects were entered and randomized. Reasons for screen failures included not meeting inclusion or exclusion criteria (n = 44), withdrawal of consent (n = 11), and lost to follow up (n = 2). Half the subjects came from European sites; one third came from Asia and the remainder from North and South America.

441 patients (82%) completed the study, participating to week 33. The Sponsor's table showing the disposition of participants and the study flow chart follow below. The cohort of 539 subjects who were randomized and received at least one dose of medication were designated by the Sponsor as the treated set (TS):

Table 35 Early PD Trial: Disposition of the subjects (source: Sponsor)

	Placebo N (%)	Pramipexole ER N (%)	Pramipexole IR N (%)	Total N (%)
Enrolled				599
Not entered/randomised				60 (10.0)
Entered/randomised	103	223	213	539
Treated	103 (100.0)	223 (100.0)	213 (100.0)	539 (100.0)
Completed (33 weeks)	91 (88.3)	174 (78.0)	176 (82.6)	441 (81.8)
Prematurely discontinued	12 (11.7)	49 (22.0)	37 (17.4)	98 (18.2)
Adverse event	4 (3.9)	24 (10.8)	20 (9.4)	48 (8.9)
AE study disease worse	1 (1.0)	2 (0.9)	2 (0.9)	5 (0.9)
AE other disease worse	0 (0.0)	4 (1.8)	1 (0.5)	5 (0.9)
AE other	3 (2.9)	18 (8.1)	17 (8.0)	38 (7.1)
Lack of efficacy	4 (3.9)	2 (0.9)	2 (0.9)	8 (1.5)
Non compliance with protocol	1 (1.0)	2 (0.9)	1 (0.5)	4 (0.7)
Lost to follow-up	1 (1.0)	1 (0.4)	1 (0.5)	3 (0.6)
Refused to continue study medication ¹	2 (1.9)	16 (7.2)	10 (4.7)	28 (5.2)
Other	0 (0.0)	4 (1.8)	3 (1.4)	7 (1.3)

¹ Informed consent withdrawn not due to AE

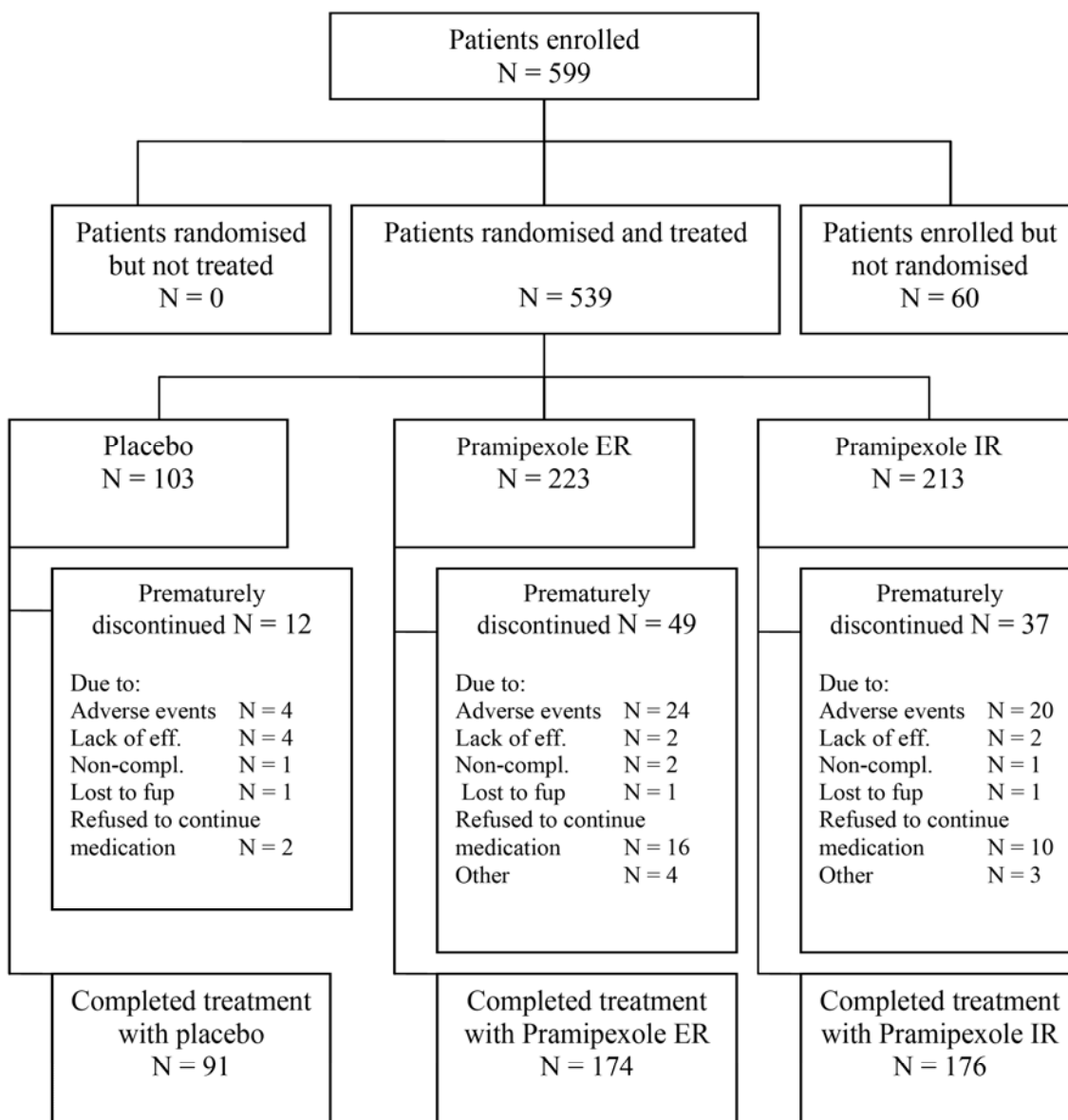


Figure 15 Early PD Trial: Disposition of subjects (source: Sponsor)

Demographics and Concomitant Medications

This patient population was typical of an early PD population. The cohort consisted of 56% males, and 57% were above the age of 65. Most patients had had their PD less than two years (82%) and 99% were less than 5 years of disease. All patients were Hoehn and Yahr Stage III or less (bilateral symptoms and signs of PD without loss of postural stability).

It should be noted that most were on a concomitant anti-parkinson drug treatment during the trial. It is not clear whether this contributed to side effects when PPX was added, but in any case, it represents a typical clinical situation seen in general neurological practice where polypharmacy for PD is the rule.

Table 36 Early PD Trial: Demographic data (source: Sponsor)

Table 11.2: 1 Demographic data, TS

	Placebo	Pramipexole ER	Pramipexole IR	Total
Number of patients treated	103	223	213	539
Gender (N [%])				
Male	51 (49.5)	127 (57.0)	121 (56.8)	299 (55.5)
Female	52 (50.5)	96 (43.0)	92 (43.2)	240 (44.5)
Age, mean (SD) (years)	62.0 (9.6)	61.3 (9.8)	61.7 (9.6)	61.6 (9.7)
Age categories (N [%])				
<65 years	55 (53.4)	131 (58.7)	119 (55.9)	305 (56.6)
≥65 years	48 (46.6)	92 (41.3)	94 (44.1)	234 (43.4)
Race (N [%])				
White	66 (64.1)	143 (64.1)	133 (62.4)	342 (63.5)
Black	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Asian	37 (35.9)	80 (35.9)	80 (37.6)	197 (36.5)
BMI, mean (SD) (kg/m ²)	26.9 (4.5)	26.6 (5.0)	26.2 (4.5)	26.5 (4.7)

Source data: [Table 15.1.4: 1](#)

Table 37 Early PD Trial: Concomitant medication (source: Sponsor)

Table 11.2: 5 Concomitant antiparkinsonian therapy by ATC4 class, TS

	Placebo N (%)	Pramipexole ER N (%)	Pramipexole IR N (%)	Total N (%)
Number of patients treated	103 (100.0)	223 (100.0)	213 (100.0)	539 (100.0)
Any PD therapy	70 (68.0)	135 (60.5)	133 (62.4)	338 (62.7)
Anticholinergic	21 (20.4)	48 (21.5)	43 (20.2)	112 (20.8)
Levodopa ¹	23 (22.3)	15 (6.7)	11 (5.2)	49 (9.1)
Amantadine	31 (30.1)	66 (29.6)	67 (31.5)	164 (30.4)
Dopamine agonist	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Monoamine oxidase B inhibitor	26 (25.2)	60 (26.9)	62 (29.1)	148 (27.5)

¹ Levodopa with or without catechol-O-methyl transferase (COMT) inhibitors.

Discussion

In conclusion, the reviewer finds that analysis of the completed enrolled population in Trial 248.524 supports the finding of efficacy originating in the interim analysis at 18

weeks. This interim analysis was accepted in NDA 22421 as supportive of the indication for the use of MIRAPEX ER in the treatment of early PD. The treatment effect appears to extend to 33 weeks without evidence of tachyphylaxis. More importantly, the completed cohort provides a larger safety population with a longer exposure allowing for a more robust review of safety in this application.

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, patients on stable PPX IR treatment were randomized to continued therapy on IR or crossed over to ER for four weeks (first maintenance period). Then a period of dose adjustments could take place and observation followed 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

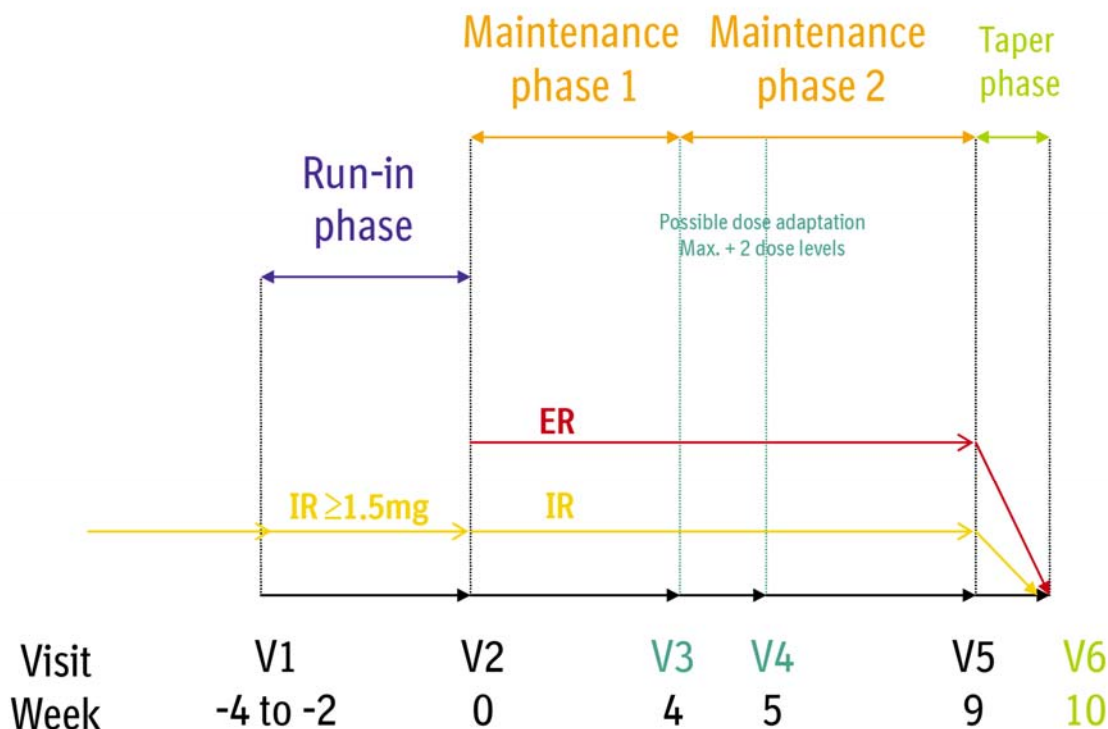
A concomitant treatment with one or more of the following drugs will be allowed (at a stable dose for at least 4 weeks prior to baseline and provided the investigator does not intent to change this treatment during the trial): L-Dopa+ (i.e. standard and/or controlled release Levodopa/DDC inhibitor), 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 16 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 38 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
Visit number	V1	V2	V3	V4	V 5 ² 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 ⁷	X				X	
Check for any other abnormal behaviour ⁷	X		X	X	X	
Check for specific abnormal behaviour ⁶			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 ⁴					
12-lead ECG	X					

Period	Run-in Phase	Maintenance Phase 1	Maintenance Phase 2			Tapering Phase
Visit number	V1	V2	V3	V4	V 5 ² 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 ¹	
Adjust trial medication, if needed			X	X		
Check medication compliance		X	X	X	X	X ⁵
Concomitant therapy	X	X	X	X	X	X
Adverse events	X	X ³	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 39 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)

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.

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

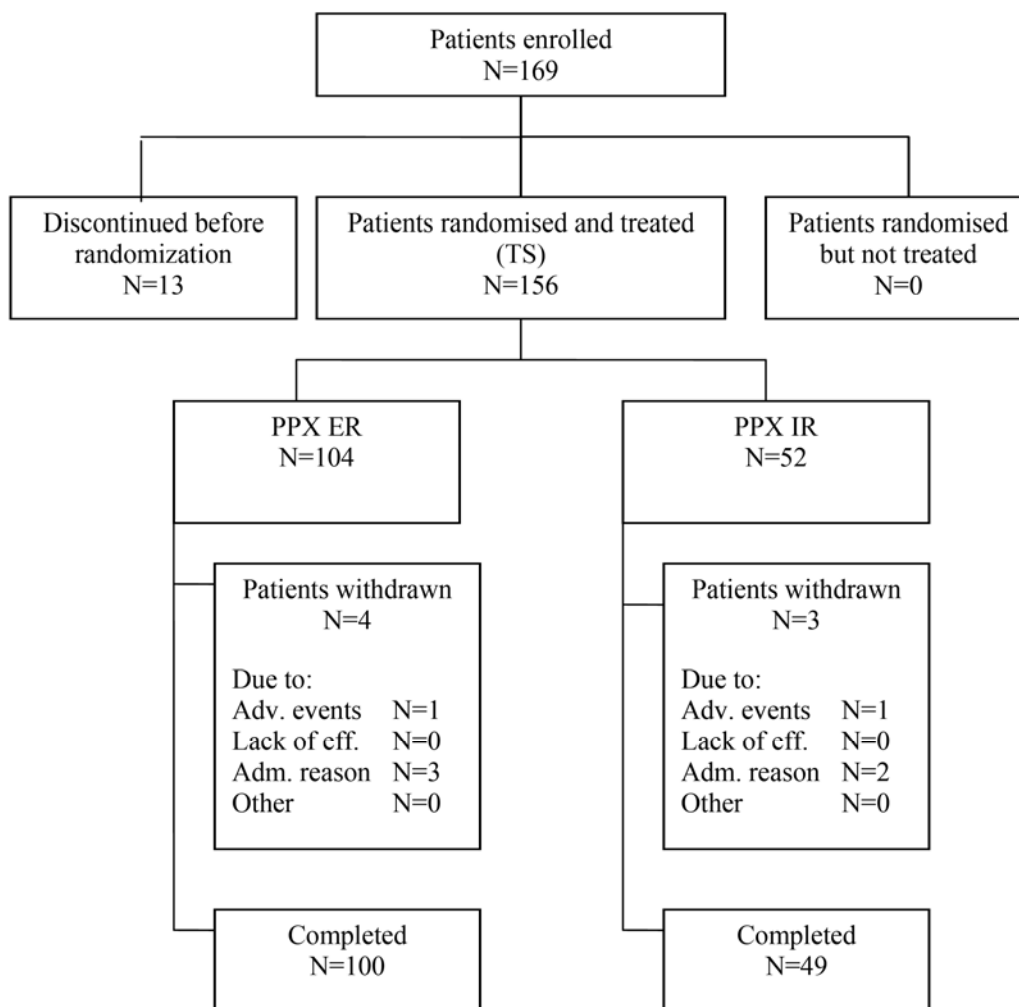
Amendment 1 (September 20, 2007) added the modified Minnesota Impulse Disorder Interview (mMIDI) and in the case of a new positive response, referral would be made to a psychiatrist for evaluation.

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 17 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 40 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 41 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.

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 42 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 43 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 from 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 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, i.e. approximately the same number of patients needed dose adjustments of some type in both treatment arms.

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; no placebo arm was present. Treatment emergent adverse events from this trial contribute to the discussion of overall safety of MIRAPEX ER found in Section 7.

5.3.4 Active Control Trial in Japanese Advanced 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 was 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 and the double blind phase has been completed.

Trial design and visit checklist

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.

Table 44 Active Control Trial visit checklist (source: Sponsor)

FLOW CHART (DOUBLE-BLIND PERIOD)

Trial period		S ¹	B ¹	Double-blind period									
Visit (V)	V1	V2	V3	TC1	V4	TC2	V5	TC3	V6	TC4	V7	V8 ²	
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 ³	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	
UPDRS part I, II, III, IV		X	X		X		X		X		X	X	
CGI-I			X ³		X ³		X ³		X ³		X ³	X ³	
PGI-I			X ³		X ³		X ³		X ³		X ³	X ³	
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 ⁴	
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	

- Abbreviations: S=Screening, B=Baseline
- 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.
- Height will only be measured at Screening (Visit 1)
- At Visit 8, dispense trial medication for open label pramipexole ER according to the switching rule.
- 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 ⁶
	TC5 13	V9 14	TC6 15	V10 16	V11 18	V12 22	V13 26	V14 30/34	V15 38	V16 42/46	V17 50	V18 54/58 /60	V19 64
Visit number⁹													
Week													
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
Physical examination													
BP, Pulse and weight													
Medication FAX													
Instruct and supply patient diary													
Review patient diary													
UPDRS part I, II, III, IV													
CGI-I													
PGI-I													
ESS													
Safety lab													
ECG													
Dispense trial medication													
Check medication compliance	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant therapy	X	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	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 was escalated to maximum dose (PPX 4.5 mg per day) unless any adverse event occurred, and even if the investigator or sub-investigator found significant efficacy with lower doses.

In the open label period, open-label PPX ER was to 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 is an uncontrolled trial with regard to safety; no placebo arm was present. No report of efficacy parameters is submitted in this NDA. Treatment emergent adverse events from this trial contribute to the discussion of overall safety of MIRAPEX ER found 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 ER 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 45 Follow up Trial: Double blind visit checklist (source: Sponsor)

FLOW CHART (DOUBLE-BLIND PERIOD)

Trial period	S ¹	B ¹	Double-blind period									
	V1	V2	V3	TC1	V4	TC2	V5	TC3	V6	TC4	V7	V8 ²
Visit (V)												
Telephone Contact (TC)												
Week												
Day												
Written informed consent	-4 to -1	0	1	2	3	4	5	6	7	8	9	12
Demographics	-28 to -7	0	7±2	14±2	21±2	28±2	35±2	42±2	49±2	56±2	63±4	84±4
Baseline conditions	X											
Inclusion/ Exclusion criteria	X											
Physical examination Weight, Height ³	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
UPDRS part I, II, III, IV		X	X		X		X		X		X	X
CGI-I			X ⁵		X ⁵		X ⁵		X ⁵		X ⁵	X ⁵
PGI-I			X ⁵		X ⁵		X ⁵		X ⁵		X ⁵	X ⁵
ESS		X	X		X		X		X		X	X
Safety lab tests	X						X					
Pregnancy test	X											
Trough PK sampling	X		X		X		X					
12-lead ECG	X											
Dispense trial medication		X	X		X		X		X		X	X ⁴
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

- Abbreviations: S=Screening, B=Baseline
- 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.
- Height will only be measured at Screening (Visit 1)
- At Visit 8, dispense trial medication for open label pramipexole ER according to the switching rule.
- CGI-I and PGI-I must be evaluated compared with those at Visit 2 (baseline)

Table 46 Open Follow up Trial: Open label visit checklist (source: Sponsor)

FLOW CHART (OPEN-LABEL PERIOD)

Trial period	Dose adjustment phase				Maintenance phase							Down-titration	
	TC5	V9	TC6	V10	V11	V12	V13	V14	V15 ⁶	V16 ⁶			
Visit number ⁹	13	14	15	16	18	26	30/34	42/46	50	54/58/60		64	65
Week													
Day	91±2	98±2	105±2	112±2	126±7	182±7	210±7/ 238±7	294±7/ 322±7	350±7	378±7/ 406±7/ 420±7		448±7	455±2
Physical examination						X						X	X
BP, Pulse and weight		X		X	X	X			X			X	X
Medication FAX													X ¹¹
Instruct and supply patient diary		X		X	X	X			X				
Review patient diary		X		X	X	X			X			X	
UPDRS part I, II, III, IV		X		X	X	X			X			X	
CGI-I		X ¹⁰		X ¹⁰		X ¹⁰							
PGI-I		X ¹⁰		X ¹⁰		X ¹⁰							
ESS		X		X	X	X			X			X	
Safety lab						X			X			X	X ⁸
ECG						X			X			X	X ⁸
Dispense trial medication		X		X	X	X			X			X	
Check medication compliance	X	X	X	X	X	X			X	X		X	X ⁷
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. Enrollment numbers at the time of the data cutoffs are discussed in the safety analysis in Section 7.

Protocol Amendments

None.

Results and Safety Assessment

No clinical report or efficacy data files of the double blinded entry period are provided. The open label extension trial is ongoing. Available exposure and safety data for deaths, discontinuations and SAEs are 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 were deemed necessary by the Sponsor in order to maintain the blinding for patients still being treated in 248.525, as this trial was still be on-going when the open-label extension trial 248.634 began. The Sponsor also wished 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 47 Advanced PD Trial: Open follow up visit checklist (source: Sponsor)

FLOW CHART

Trial periods	B ¹	Transfer phase						OL phase						EOT-Taper-down phase
	V1	V2	TC1	V3	TC2	V4	TC3	V5	V6	V7	V8	V9 ³	V10 ⁵	
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	
Days	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 ²										X ⁷	X		
Ophthalmologic monitoring														
BP, Pulse, Weight	X ²	X		X		X		X	X	X	X	X	X	
Instruct and supply patient diary	X	X		X		X		X	X	X	X			
Review patient diary	X ²	X		X		X		X	X	X	X	X		
Hoehn and Yahr	X													
UPDRS part I, II, III, IV	X ²	X		X		X		X	X	X	X	X		
CGI-I		X		X		X		X	X	X	X	X		
PGI-I		X	X	X	X	X	X	X	X	X	X	X		
PGI-I for early morning off-symptoms								X						
ESS	X ²			X				X				X		
PFS-16	X											X		
Safety lab tests	X ⁸											X		
Urinary pregnancy test ⁴ (if applicable)	X													
12 lead-ECG	X ⁸													
Dispense/ re-dispense trial medication	X	X		X		X		X	X	X	X	X ⁵		
Check medication compliance		X	X	X	X	X	X	X	X	X	X	X	X ⁶	
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 fundoscopy). 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. Enrollment 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

No clinical report or efficacy data files of this double blinded period are provided. The open label extension trial is ongoing. Available exposure and safety data for deaths, discontinuations and SAEs are 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.

Conducted in the USA, this trial was terminated when the Sponsor made the decision to no longer pursue this indication. There were 61 patients enrolled (PPX ER 30; PCB 31) and none had reached maintenance phase. It does not contribute efficacy data to

this submission. Dose exposure in this trial to PPX ER was brief (mean 1.1 mg /d for mean 28 days).

Available exposure and safety data for deaths, discontinuations and SAEs are discussed in Section 7.

6 Review of Efficacy

In this application, a single efficacy trial was submitted by the Sponsor: Study 248.525 *A double-blind, double-dummy, placebo-controlled, randomized, three parallel groups study comparing the Efficacy, Safety and Tolerability of Pramipexole ER versus placebo and versus Pramipexole IR administered orally over a 26-week maintenance phase in L-Dopa+ treated patients with advanced Parkinson's disease (PD).*

In a previous application NDA 22421, a single efficacy trial was submitted by the Sponsor in support of treatment in early PD: 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 Review of Efficacy summarizes the advanced PD confirmatory trial submitted in this NDA. These trials in advanced and early PD are detailed in **Section 5.3** above. Analyses of these therapeutic outcome measures at 18 weeks were submitted in support of efficacy. In brief, the Sponsor satisfactorily demonstrates that MIRAPEX ER has the ability to reverse the motor signs and symptoms and disability in early and advanced PD as demonstrated by significant improvement as rated by the UPDRS Parts II + III. These findings were corroborated by the global impressions of investigators and patients in both trials and the general direction of secondary measures toward improvement was consistent.

The therapeutic effect of PPX ER appears sustained in both early and advanced disease states over the full course of the 33 week trials. It also appears to be tolerable to most patients to switch from the immediate release formulation to the once a day ER tablet on a 1 to 1 mg basis overnight.

6.1 Indication

The Sponsors proposed labeling for this NDA is for the treatment of the signs and symptoms of advanced Parkinson's disease. Given that the therapeutic effect in early PD has already been established, this reviewer finds that there is no reason to not consolidate the claims to an approved indication for "treatment of the signs and symptoms of Parkinson's disease", consistent with the approved indication for immediate release pramipexole.

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 advanced PD was performed. After an initial titration period to usual therapeutic doses, an efficacy analysis was performed using the 18th week evaluation thought the trial continued to completion at 33 weeks. 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 as well as taking into account a center effect for the rating scales (intra-rater reliability for the UPDRS is greater than inter-rater reliability for the UPDRS). In addition, the percent of time during the day in which the patient lacked control of motor symptoms (off-time) was recorded using a patient diary. 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 62 years, gender (M 55%; F 45%), and racial distribution (Caucasian 50%, Asian 50%, blacks were not studied). The severity of illness was also consistent with the naturally occurring illness in a clinic population.

6.1.3 Subject Disposition

618 subjects were screened and 517 subjects were enrolled, randomized and treated with at least one dose of medication in this efficacy cohort. Ten subjects were excluded due to lack of either a pre or post treatment observation for the primary outcome variable. At the end, 507 were suitable for this reviewer’s analysis set.

6.1.4 Analysis of Primary Endpoint

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. This review finds that the mean improvement in UPDRS score from baseline was -6.7, -12.2 and -13.6 for placebo, PPX ER and PPX IR, respectively. The p-value is less than 0.0001 for both PPX ER vs. placebo and PPX IR vs. placebo. This finding is independently supported by the Statistical Review and Evaluation. To place this change in clinical perspective, untreated PD worsens at a rate of about 3 UPDRS points per year of disease. The improvement seen in the placebo arm is consistent with regression to the mean seen over the course of a PD clinical trial using this measure.

6.1.5 Analysis of Secondary Endpoints(s)

The key secondary endpoint for the advanced PD trial measures that, in addition to improving motor function, fluctuations in the control of motor symptoms are also improved. The amount of time with poor motor control (“off-time”) taken as a percentage of the time the patient is awake, is important measure of the general function of the advanced PD patient. At the Week 18 endpoint, PPX ER improved off-time (as measured as change from the baseline percentage off time) in the treated vs. placebo group. ER patients reduced off time from 36% to 24%, while placebo group reduced from 39% to 30% (ANCOVA $p = 0.0122$). However, this effect was statistically weakened and no longer significant by the end of the trial, with fewer subjects having reached that 33 week time point.

The other important secondary criteria were the Clinical Global Impression of Improvement (CGI-I) and Patient Global Impression of Improvement (PGI-I) responder rates. Investigators felt that 78 of 160 subjects taking PPX ER were “very much improved” or “much improved”, while 56 of 171 placebo subjects were so characterized (χ^2 , $p = 0.0037$).

Patients rated themselves similarly; 60 of 161 taking PPX ER called themselves “very much better” or “much better”, while 47 of 174 placebo subjects considered themselves better (χ^2 , $p = 0.0554$).

This concordance is not surprising to the reviewer. In clinical trial process, the CGI and PGI are often discussed and evaluated together during the research visit as the investigator and patient go 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 this review indicates that these measures are very much inter-related, duplicating a consensus between them.

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. The effect of this drug in the African American population has not been studied.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

As suggested by the overnight switch trial (248.636: *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*), there is a close enough therapeutic effect to suggest that it is possible to convert a patient on a 1:1 mg for mg basis. This was well tolerated in a majority of patients and most did not require further adjustment over the following month of observation. This is purely a clinical observation; no measure of pharmacokinetic/pharmacodynamic efficacy has been established. It is reasonable to extend current dosing guidelines for the IR product in the general PD population to the ER product.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

In this submission, for both the early and advanced PD trials, the Sponsor included data comparing the improvement in UPDRS Parts II+III at 18 and 33 weeks, as well as the daily dose of PPX ER administered at those two time points. As discussed in **Section 5.3**, in neither population did there appear to be any loss of therapeutic effect over this time span or an indication that higher doses of medication were needed to maintain therapeutic effect. While this was not a stated goal of the trials, it is fair to say that there is no evidence of any important tachyphylaxis of therapeutic effect over the 24 week maintenance period of these trials.

7 Review of Safety

Safety Summary

It is this reviewer's opinion that MIRAPEX 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, orthostasis and dyskinesia. These are discussed more fully in **Section 7.3.5 Submission Specific Primary Safety Concerns**, below.

No significant risk of injury to the cardiovascular, liver, kidney, or the hematopoietic system was identified. No signals suggesting rare events were observed.

It is noted that the periods of active treatment that contribute to the safety analysis in the double blind placebo controlled trials are short (about 24 weeks at maintenance dose). This reviewer's concern is that an inadequate period of exposure has been observed and it is difficult to fully determine the true incidence of treatment emergent adverse events, especially behavioral ones. It is also likely that the forced titration schema used in the confirmatory trials increased the incidence of adverse gastrointestinal events such as nausea and vomiting over that which might be encountered in a more naturalistic setting.

Analysis of the safety data indicates that there is no need to consider a postmarketing risk evaluation and mitigation strategy at this time.

7.1 Methods

The original data cut off date in November, 2008 was extended by the 120 day safety update to April 20, 2009 for all SAEs and deaths. At the time of the 120 day safety update, updated analysis datasets for remaining open label trial extensions were submitted with relevant 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 serious adverse events which were generated electronically reveals a paucity of detail. The narratives were adequate.

1107 subjects have been exposed to at least a single dose of PPX ER in the Sponsor's development program. Subjects who were in the PPX ER arm of double blinded studies and then were entered into open label extensions for PPX ER were double counted, accounting for the smaller number of unique patients exposed to PPX ER in this review.

Safety assessments in individual clinical trials were adequate and in general, adequately coded in MedDRA. Specific examples of inappropriate splitting of adverse events are commented upon in the relevant sections below.

Relative rates of treatment emergent adverse events were compiled by comparison of the analyses of datasets by JMP and MedDRA Adverse Events Diagnostic Service (MAEDService). Any event occurring at 1% or greater in any treatment arm was the basis for inclusion in the event tables below.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

It is noted below where PPX studies relevant to this application were performed using the IR formulation and not repeated using the ER dosage form. Existing 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 data from the Phase III trial in advanced PD (248.525)
- Safety data from the Phase III trial in early PD (248.524)
- Safety and comparability of overnight switch from PPX IR to PPX ER (248.636)
- QTc trial (248.545): see **Section 7.4.5**

- Safety data from open label extensions of Trials 248.633, 248.634 and 248.610.
- Safety data from Phase II trial in fibromyalgia (248.637)

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. Safety data from Phase I and 2 trials are also described.

This table indicates the sum of all prospectively collected safety data from blinded trials for this submission.

Table 48 Early and Advanced PD Trials: Double blind placebo controlled subjects contributing to safety data

	Early PD 248.524	Advanced PD 248.525	Total N
PPX ER	223	165	388
PPX IR	213	175	388
Placebo	103	178	281

Table 49 Subject exposure to PPX ER in Phase III trials (N = 1107)

	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	165	104	242	233	109	31
PPX IR	213	175	52			56	
Placebo	103	178					30

#Reviewers Note: The Sponsor double-counted PPX ER subjects from the Advanced PD, Early PD, and Overnight Switch trials who went on to enter into open label safety extensions. The numbers in this table represent unique subjects exposed to PPX ER.

*53 of 56 subjects from the IR arm of the blinded study were entered into the open label extension of 248.610

Table 50 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 Versions 11.0 and 11.1 were used by the Sponsor for coding of adverse events in the Advanced and Early PD trials, respectively. 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 ½ life of the drug of about 12 hours (versus 8 h in healthy volunteers). AEs outside of this time frame were assigned to screening or post-treatment assessment periods by the Sponsor.

The Sponsor's coding exhibited occasional lapses in the quality of 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 inexperienced 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

The reviewer looked at adverse events in the double blind trials in advanced and early PD both individually and together in order to investigate the possibility of increasing vulnerability to certain side effects with age and/or advancing disease.

The long term open trials are pooled for review. Events were ascertained in similar fashion in these trials. Observations in this population yield a more "naturalistic" portrait

of what adverse events may occur in a diverse spectrum of PD patients which might be found in a typical neurological clinic.

7.2 Adequacy of Safety Assessments

An adequate population was exposed to PPX ER for an adequate time period of observation. Safety assessments were performed using methods accepted in confirmatory and open PD trials of dopamine agonists. Protocols for standardized inquiry and observation of special interest adverse events such as sudden onset of sleep, orthostatic hypotension, and impulse control disorder were implemented in accordance with recommendations from the Division.

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

The dose of PPX ER and the total exposure in the PD population is sufficient for evaluation of common adverse events. The population exposure is indicated in the Sponsor's tables below. These indicate an appropriate distribution of dose and duration across the treatment groups.

Table 51 Advanced PD Trial: Dose and duration of exposure (source: Sponsor)

Table 1.2.5.1: 2 Number (%) of patients exposed to pramipexole ER by treatment duration and final dosage level and overall - placebo-controlled Trial 248.525, 18-week analysis / TS 1 (18 weeks treatment)

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 (%)	64 (38.1)	37 (22.6)	63 (38.4)	164 (100.0)
Duration of exposure, in days				
Mean (SD)	106.9 (38.1)	119.4 (20.9)	123.3 (11.0)	116.0 (27.6)
Median	125.0	125.0	125.0	125.0
Exposure in weeks N (%)				
N	64 (100.0)	37 (100.0)	63 (100.0)	164 (100.0)
< 1 week	3 (4.7)	0 (0.0)	0 (0.0)	3 (1.8)
1 - < 4 weeks	3 (4.7)	0 (0.0)	0 (0.0)	3 (1.8)
4 - < 8 weeks	3 (4.7)	2 (5.4)	0 (0.0)	5 (3.0)
8 - <13 weeks	2 (3.1)	1 (2.7)	2 (3.2)	5 (3.0)
13 - <18 weeks	39 (60.9)	18 (48.6)	35 (55.6)	92 (56.1)
18 - <23 weeks	14 (21.9)	16 (43.2)	26 (41.3)	56 (34.1)

Source data: [Appendix 7, Table 1.2.4.5](#)

Table 52 Early PD Trial: Dose and duration of exposure (source: Sponsor)

Table 1.2.5.1: 1 Number (%) of patients exposed to pramipexole ER by treatment duration and final dosage level and overall- placebo-controlled Trial 248.524, 33-week analysis / TS

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 (%)	65 (29.1)	66 (29.6)	92 (41.3)	223 (100.0)
Duration of exposure, in days				
Mean (SD)	157.9 (100.2)	208.0 (61.1)	221.5 (38.8)	199.0 (73.0)
Median	229.0	231.0	232.0	231.0
Exposure in weeks N (%)				
N	65 (100.0)	66 (100.0)	92 (100.0)	223 (100.0)
< 1 week	8 (12.3)	0 (0.0)	0 (0.0)	8 (3.6)
1 - < 4 weeks	7 (10.8)	0 (0.0)	0 (0.0)	7 (3.1)
4 - < 8 weeks	4 (6.2)	3 (4.5)	0 (0.0)	7 (3.1)
8 - <13 weeks	1 (1.5)	5 (7.6)	1 (1.1)	7 (3.1)
13 - <18 weeks	2 (3.1)	1 (1.5)	6 (6.5)	9 (4.0)
18 - <23 weeks	3 (4.6)	2 (3.0)	1 (1.1)	6 (2.7)
23 - <28 weeks	0 (0.0)	0 (0.0)	3 (3.3)	3 (1.3)
≥ 28 weeks	40 (61.5)	55 (83.3)	81 (88.0)	176 (78.9)

Source data: [Appendix 7, Table 1.2.4.6](#)

Table 53 Japan Active Control Trial: Dose and exposure (source: Sponsor)

Table 1.2.5.1: 3 Number (%) of patients exposed to pramipexole ER by treatment duration and final dosage level active control 248.610 (DB phase), TS

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 (%)	9 (16.1)	14 (25.0)	33 (58.3)	56 (100.0)
Duration of exposure, in days				
Mean (SD)	62.3 (32.1)	80.1 (15.4)	83.5 (1.1)	79.3 (16.2)
Median	82.0	84.0	84.0	84.0
Exposure in weeks N (%)				
N	9(100.0)	14(100.0)	33 (100.0)	56 (100.0)
1 - < 4 weeks	2 (22.2)	1 (7.1)	0 (0.0)	3 (5.4)
4 - < 8 weeks	1 (11.1)	0 (0.0)	0 (0.0)	1 (5.4)
8 - <13 weeks	6 (66.7)	13 (92.9)	33 (100.0)	62 (92.9)

Source data: [Appendix 7, Table 1.2.4.8](#)

Total cumulative duration of treatment in patient-years was calculated by the Sponsor to be 343 years of exposure for PPX ER in the two placebo controlled confirmatory trials.

Dose and Duration of Exposure in Open Label Trials:

(These numbers reflect the 120 day safety update for Trials 248.633, 248.634 and the open label portion of 248.610. Only open trial exposure/duration data were changed by the 120 day safety update, as the DB trials had all been completed prior to the data cutoff date).

Table 54 Open Label Trials: Dose and duration of exposure (source: Sponsor)

Table 1.2.4: 1 Number (%) of patients exposed to pramipexole ER by treatment duration and final dosage category and overall; OL extension Phase III trials and OL phase of Trial 248.610 combined / TS

	PPX ER 0.375-1.5 mg/day	PPX ER >1.5-3 mg/day	PPX ER >3 mg/day	PPX ER all doses
Number of patients (%)	227 (22.6)	354 (35.2)	425 (42.2)	1006 (100.0)
Duration of exposure, in days				
Mean (SD)	264.2 (91.8)	269.9 (94.9)	262.1 (91.1)	265.3 (92.6)
Median	260.0	273.0	251.0	263.0
Exposure in weeks				
Number of patients (%)	227 (100.0)	354 (100.0)	425 (100.0)	1006 (100.0)
<12 weeks	8 (3.5)	11 (3.1)	12 (2.8)	31 (3.1)
12 - <24 weeks	18 (7.9)	40 (11.3)	36 (8.5)	94 (9.3)
24 - <36 weeks	80 (35.2)	98 (27.7)	165 (38.8)	343 (34.1)
36 - <48 weeks	64 (28.2)	93 (26.3)	103 (24.2)	260 (25.8)
48 - <60 weeks	51 (22.5)	94 (26.6)	93 (21.9)	238 (23.7)
>=60 weeks	6 (2.6)	18 (5.1)	16 (3.8)	40 (4.0)

Source data: Appendix 7, Table 1.2.3

Total cumulative duration of treatment in patient-years was calculated by the Sponsor to be 731 years of exposure for PPX ER in these three open label extension trials.

Demographics of the Target Population

The demographics of the population are tilted toward the younger age groups, likely because of exclusion criteria, especially dementia and significant cardiovascular disease. This may mean that adverse events related to age (especially drug related hallucinations and encephalopathy, orthostasis, syncope and falls) may be less in this trial population than would be found in the typical neurology clinic exposure to PPX ER. The black (i.e.: African American) population is not represented in the trials, and as a result, the therapeutic and adverse effect in a black population is unknown. Gender distribution reflects the slight male preponderance described in most PD epidemiological studies.

Table 55 Advanced PD Trial: Demographic data (source: Sponsor)

Table 1.3.1.1.2: 1 Demographic data, all randomised patients from placebo-controlled Trial 248.525, TS 1 (18 weeks treatment)

248.525 (advanced PD)	Placebo	PPX ER	PPX IR	Total
Number of patients	178	164	175	517
Gender [N (%)]				
Male	94 (52.8)	92 (56.1)	98 (56.0)	284 (54.9)
Female	84 (47.2)	72 (43.9)	77 (44.0)	233 (45.1)
Age [years]				
Mean (SD)	60.9 (9.7)	61.6 (9.7)	62.0 (10.3)	61.5 (9.9)
Age classes [N (%)]				
<65 years	104 (58.4)	94 (57.3)	100 (57.1)	298 (57.6)
>=65 years	74 (41.6)	70 (42.7)	75 (42.9)	219 (42.4)
Race [N (%)]				
White	92 (51.7)	81 (49.4)	87 (49.7)	260 (50.3)
Asian	86 (48.3)	83 (50.6)	88 (50.3)	257 (49.7)
BMI [kg/m ²]				
Mean (SD)	25.0 (4.6)	24.7 (3.9)	24.5 (4.2)	24.7 (4.3)

Source data: [Appendix 7, Table.1.3.1](#) and trial 248.525 final report [U09-1270-01], [Table 11.2.1: 1, Module 5.3.5.1](#)

Table 56 Advanced PD Trial: Baseline disease characteristics (source: Sponsor)

Table 1.3.1.1.2: 2 Selected PD related baseline characteristics, all randomised patients from placebo-controlled Trial 248.525, TS 1 (18 weeks treatment)

248.525 (advanced PD)	Placebo	PPX ER	PPX IR	Total
Number of Patients	178	164	175	517
PD Duration [years]				
mean(SD)	5.9 (3.8)	6.1(4.0)	6.6 (4.4)	6.2 (4.1)
median (IQR)	4.7 (3.0;7.7)	4.9 (3.0;7.4)	5.5 (3.4;8.5)	5.1 (3.1;7.9)
PD known since				
0 - <2 [y]	1 (0.6)	1 (0.6)	3 (1.7)	5 (1.0)
2 - <5 [y]	90 (50.6)	82 (50.0)	76 (43.4)	248 (48.0)
>= 5 [y]	87 (48.9)	81 (49.4)	96 (54.9)	264 (51.1)

Table 57 Early PD Trial: Demographic data (source: Sponsor)

Table 1.3.1.1.1: 1 Demographic data, all randomised patients from placebo-controlled Trial 248.524, TS

248.524 (early PD)		Placebo	PPX ER	PPX IR	Total
Number of Patients		103	223	213	539
Gender					
Male	N (%)	51 (49.5)	127 (57.0)	121 (56.8)	299 (55.5)
Female	N (%)	52 (50.5)	96 (43.0)	92 (43.2)	240 (44.5)
Age [years]					
Age mean(SD)		62.0 (9.6)	61.3 (9.8)	61.7 (9.6)	61.6 (9.7)
Age classes					
Age < 65 years	N (%)	55 (53.4)	131 (58.7)	119 (55.9)	305 (56.6)
Age ≥ 65 years	N (%)	48 (46.6)	92 (41.3)	94 (44.1)	234 (43.4)
Race					
White	N (%)	66 (64.1)	143 (64.1)	133 (62.4)	342 (63.5)
Black	N (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Asian	N (%)	37 (35.9)	80 (35.9)	80 (37.6)	197 (36.5)
Body mass index (kg/m ²)					
BMI mean(SD)		26.9 (4.5)	26.6 (5.0)	26.2 (4.5)	26.5 (4.7)

Source data: [Appendix 7, Table 1.3.2.1.2](#) and [trial 248.524 final report \[U09-1232-01\]](#), [Table 11.2: 1, Module 5.3.5.1](#)

Table 58 Early PD Trial: Baseline disease characteristics (source: Sponsor)

Table 1.3.1.1.1: 2 Selected PD-related baseline characteristics, all randomised patients from placebo-controlled Trial 248.524, TS

248.524 (early PD)		Placebo	PPX ER	PPX IR	Total
Number of patients (%)		103	223	213	539
PD Duration [years]	mean(SD)	0.9 (1.0)	1.0 (1.2)	1.1(1.4)	1.0 (1.2)
	median (IQR)	0.5(0.1;1.4)	0.5 (0.1;1.5)	0.5 (0.1;1.6)	0.5 (0.1;1.6)
PD known since					
0-< 2 [y]	N (%)	88 (85.4)	186 (83.4)	170 (79.8)	444 (82.4)
2-< 5 [y]	N (%)	14 (13.6)	36 (16.1)	41 (19.2)	91 (16.9)
> 5 [y]	N (%)	1 (1.0)	1 (0.4)	2 (0.9)	4 (0.7)
PD pre-treated					
No	N (%)	40 (38.8)	91 (40.8)	77 (36.2)	208 (38.6)
Yes	N (%)	63 (61.2)	132 (59.9)	136 (63.8)	331(61.4)

Table 59 Open Label Trials: Demographic data of subjects (source: Sponsor)

Table 1.3.3: 1 Demographic data, OL extension trials and OL phase of Trial 248.610/ TS

		248.610 APD	248.633 EPD	248.634 APD	Total
Number of Patients (%)		104 (100.0)	487 (100.0)	335 (100.0)	926 (100.0)
Gender					
Male	N (%)	37 (35.6)	272 (55.9)	181 (54.0)	490 (52.9)
Female	N (%)	67 (64.4)	215 (44.1)	154 (46.0)	436 (47.1)
Age [years]					
Age	mean (SD)	67.1 (7.6)	62.9 (9.1)	61.4 (9.9)	62.8 (9.4)
Age classes					
Age <65 years	N (%)	30 (28.8)	261 (53.6)	196 (58.5)	487 (52.6)
Age ≥65 years	N (%)	74 (71.2)	226 (46.4)	139 (41.5)	439 (47.4)
Race					
White	N (%)	0 (0.0)	344 (70.6)	143 (42.7)	487 (52.6)
Black	N (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Asian	N (%)	104 (100.0)	143 (29.4)	192 (57.3)	439 (47.4)
Body mass index [kg/m ²]					
	N	104	480	333	917
BMI	mean (SD)	23.3 (3.3)	26.2 (4.5)	24.7 (4.3)	25.3 (4.4)

Source data: [Appendix 7, Table 1.3.2.3.1](#)

7.2.2 Explorations for Dose Response

The exploration of dose response in these trials is made difficult due to their short duration and the pushed titration to maximum tolerated dose. (The general dose titration strategy in double blind trials was that if there was room for any further clinical improvement to continue to increase to the next higher dose level.) As a result the largest (modal) number of patients occurs in the higher dose levels. It is probable that this does not represent the clinical strategy in the neurological clinic where a conservative dose titration schedule will likely settle at the lowest clinically effective dose for a given patient. Forced titration strategies tend to move past the dose that might accrue the best clinical effect with the least adverse events.

Table 60 Early and Advanced PD and Active Control Trials: Distribution of dose ranges in the trial population

Daily PPX ER Dose				
Double Blind Trials	0.375 -1.5 mg/d	2.25 - 3 mg/d	3.75 - 4.5 mg/d	All
Adv PD 248.525	64	37	63	164
Early PD 248.524	65	66	92	223
Adv Japan 248.610	9	14	33	56
Total (%)	138 (31%)	117 (26%)	118 (42%)	443
Open Label Trials				
248.633, 248.634 and 248.610 OL Extension	227 (23%)	354 (35%)	425 (42%)	1006

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. Of note, the Sponsor omitted laboratory testing of serum creatine (CK).

Along with clinical examination including vital signs, electrocardiography, hematological and serological parameters, a special emphasis was placed upon adverse events known to occur with the class of dopamine agonists. These are listed below by the section in this review in which they are discussed:

- 7.3.5 Submission Specific Safety Concerns
 - Nausea and vomiting
 - Sleep dysfunction
 - Symptomatic orthostatic hypotension
 - Falls

- Dyskinesia
 - Behavioral abnormalities (impulse control disorder, hallucinations)
- 7.4.2 Laboratory Function
 - Hepatic toxicity
 - Renal toxicity
- 7.4.5 Special Safety Studies
 - Retinal pathology
 - Rhabdomyolysis

The Sponsor pre-specified defined criteria for the assessment of abnormal behavior and disturbances of sleep.

Adverse events related to somnolence (excessive daytime sleepiness, and sudden onset of sleep) were collected using open ended questioning. These events were also assessed by using Question 15 of the Parkinson's Disease Sleep Scale (visual analog response for the query: "have you unexpectedly fallen asleep during the day?") and by the Epworth Sleepiness Scale where abnormality was defined by a score > 10, the usually employed cut-off.

In the two placebo-controlled confirmatory trials, the modified Minnesota Impulsive Disorder Interview (mMIDI) was used to assess compulsive behavior and was completed at V2 (baseline), V6 (Week 8), V8 (Week 18), V11 (Week 33) and end of taper phase (Week 34). At other study visits, adverse events related to abnormal behavior, i.e.: Impulse Control Disorder, were solicited by both specific and open ended questioning concerning pathological gambling, compulsive buying, and compulsive sexual behavior among others. In case of a positive response, the relevant portion(s) of the mMIDI interview were then completed.

As noted in the introduction to this section, 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 time frame were assigned to screening or post-treatment assessment periods by the Sponsor.

The major focus of the reviewer's 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 61 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 were obtained at each study visit, performed supine after 5 minutes rest, then after 1 minute standing. Orthostatic hypotension was defined as a decline ≥ 20 mmHg in systolic blood pressure (SBP) and a decline ≥ 10 mmHg in diastolic blood pressure (DBP) at one minute after standing, compared with the previous SBP and DBP obtained after 5 minutes of quiet rest. In addition to the study visit measurements, orthostatic hypotension was also recorded at each study visit using open-ended questions. Only symptomatic orthostasis was recorded as an adverse 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 62 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

Summary of Phase I

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

Phase III events are elaborated upon in the sections below.

Table 63 Phase III trials: distribution of important safety events

Phase III Trials Integrated Safety Events					
(n.b. : a patient may be represented in more than one column)					
Trial / Arm	Death	Non-fatal SAE	AE leading to D/C	Drug related ICD	All treated
248.524 Early PD					539
PCB	0	5	5	1	103
ER	1	13	24	4	223
IR	1	14	22	2	213
248.525 Adv PD					518
PCB	1	15	10	2	178
ER	0	9	14	3	165
IR	3	12	11	5	175
248.610 Active Japan					112
Before drug	1	0	0	0	0
ER	0	14	11	0	56
IR	0	3	3	0	56
248.633 OL for 524 / 636					
ER	3	48	15	3	511
248.634 OL for 525					
ER	2	20	19	2	391

248.636 Overnight Switch					156
ER	0	0	1	1	104
IR	1	1	1	1	52
248.637 Fibromyalgia					61
PCB	0	1	4	1	30
ER	0	6	0	0	31

7.3.1 Deaths

12 deaths are found in this development program up to the cut off date of the safety update. (The Sponsor reported 9, deeming the others to have occurred either before or after receiving drug.) Details of all 12 are summarized below. Upon review, none of these appear to be causally related to PPX.

248.525 Advanced PD

- Patient #6144: PPX IR 4.5 mg/day; cause: cardio-respiratory insufficiency.

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; pentoxifyllin tablets 800 MG p.o. daily; vinpocetine tablets 10 MG p.o. daily; glipizide 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) 2008. He was transferred to Internal Medicine (b) (6) when he died due to cardio-respiratory insufficiency. Autopsy was not performed.

- Patient # 6819: Placebo; cause: neuroleptic malignant syndrome

A 63 year old man with PD since 2002 was begun on placebo February 20, 2008. Medical history included depression and “prostate syndrome”. He had a history of pneumonia. Medications included Sinemet 1250/125 mg daily, Azilect 1 mg /d,

chlomethiazole 768 mg/d, lorazepam 1mg/d for insomnia. On (b) (6) he developed pneumonia, and despite antibiotic treatment proceeded to respiratory insufficiency with intubation. He also developed UTI. The trial was terminated July 24, 2008. He was in intensive care until (b) (6). He was treated with quetiapine 100 mg/d beginning December 1, 2008 and on (b) (6) developed what was termed neuroleptic malignant syndrome. No CK is reported. Despite treatment, the patient died on (b) (6).

- Patient # 8029: PPX IR (post treatment phase); cause: stroke

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) 2008 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 had been discontinued.

248.524 Early PD

- Patient #4220: PPX ER 2.25 mg/d; cause: oral (lip) cancer

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.

- Patient # 2842: PPX IR (post treatment phase); cause: pneumonia

This 81 year old woman with PD entered the trial on February 1, 2008, starting drug on the 27th. Past medical history included depression, hypercholesterolemia, neuropathy, bladder repair and hysterectomy. Concomitant medications included Lipitor, citalopram, Vesicare, and aspirin. On (b) (6), the patient experienced productive coughing, nausea and vomiting and was admitted to the hospital. She went off study drug at this time. A chest X-ray revealed no infiltrates though later it showed progressive infiltrates. On (b) (6) rapid atrial fibrillation was noted. She reverted to normal rhythm with diltiazem but then developed heart block and diltiazem was discontinued. She was placed on antibiotics and mechanical ventilation. She went on to develop ARDS and died (b) (6).

248.636 Overnight Switch

- Patient # 153: PPX IR run-in; cause:

This 59 year old man had been taking commercially available PPX since 2006. In December 2007, he entered the open label run-in phase of this study taking 3.0 mg PPX IR daily. On the 11th day of the run-in phase, he was admitted to the hospital for renal failure related to the initial presentation of rectal carcinoma. He discontinued the run in phase of the trial that day (prior to randomization). He died in (b) (6).

248.633 Open label extension (from early PD)

- Patient # 151: PPX ER 4.5 mg/d; pulmonary embolism.

A 78 year old man with a six year history of PD was enrolled on February 18, 2008. His medical history included stroke treated by aspirin. He was on PPX ER 4.5 mg/d in the double blind portion of the study and then entered the open label trial. He fell, breaking a hip, on (b) (6) and was hospitalized. He died suddenly on (b) (6) of pulmonary embolism.

- Patient # 2082: PPX ER 3.75 mg/day; cause: accidental drowning

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).

- Patient # 2175: PPX ER 4.5 mg; cause: heart failure.

This 66 year old woman was diagnosed with PD in March 2007, began the double blind trial May 31, 2008 and then the open label phase on July 6, 2008. She had a history of diabetes mellitus, stroke and "hypertony". She was taking selegiline 10 mg, Amlozek 5mg/d, aspirin 100mg/d and Meforal for diabetes. On (b) (6) she died suddenly at home one evening due to "left ventricular failure", though this appears likelier to be a ventricular arrhythmia. There was an autopsy but the results are not reported.

248.634 Open label extension (from advanced PD)

- Patient #6342: PPX ER (unknown dose); cause: stroke.

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 1999, and hypercholesterolemia. He was taking Acard 75 mg, Zocor 20 mg, Madopar 250 mg, Madopar HBS 250 mg, and Amantadine 100mg. A "severe"

stroke was reported (b) (6). This resulted in death. Further details are not available.

- Patient #7902: PPX ER 1.5 mg/day; cause: septic shock, pneumonia.

The subject was a 71 year old Asian man who had began the double blind trial, completing it on June 16, 2008 and transferred into the open label extension. Co-morbidities included coronary artery disease, history of two vessel angioplasty, renal disease and hypertension. He had had an episode of pneumonia in April 2008. He was also taking levodopa and entacapone. On (b) (6), 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, committed suicide 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 14th 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 the table 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

Phase I

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.

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**. This was previously reported in the review for NDA 22421 and due to its seriousness, reprised here for completeness.

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.

Phase III Trials

The following adverse events and other happenings led to discontinuation of treatment in the Phase III double blind placebo controlled trials in early and advanced PD:

Table 64 Early and Advanced PD Trials: Distribution of adverse events and discontinuations

Adverse events and discontinuations	Placebo	PPX ER	PPX IR
248.524 Early PD	103	223	213
Any AE (N, %)	80 (78%)	189 (85%)	172 (81%)
AE of severe intensity	4 (4%)	12 (5%)	11 (5%)
SAE, non fatal	5 (5%)	16 (7%)	14 (7%)
Premature Discontinuation due to adverse events	5(5%)	24 (11%)	22 (10%)
Premature Discontinuation, all reasons	12 (12%)	49 (22%)	37 (17%)
248.525 Advanced PD	178	165	175
Any AE	99 (56%)	90 (55%)	112 (64%)
AE of severe intensity	6 (3%)	10 (6%)	11 (6%)
SAE, non-fatal	15 (8%)	9 (5%)	12 (7%)
Premature Discontinuation due to adverse events	10 (6%)	14 (8%)	11 (6%)
Premature Discontinuation, all reasons	31 (17%)	23 (14%)	13 (7%)

Combined Placebo Controlled Trials:	281	388	388
Any AE	179 (64%)	278 (72%)	284 (73%)
AE of severe intensity	10 (4%)	22 (6%)	22 (6%)
SAE, non-fatal	20 (7%)	25 (6%)	26 (7%)
Premature Discontinuation due to adverse events	15 (5%)	40 (10%)	33 (9%)
Premature Discontinuation, all reasons	43 (15%)	72 (19%)	50 (13%)

In the trial in early PD, 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 AE but one that not significant or serious as usually defined.

The percentages of "premature discontinuations, all reasons" in the Early PD study would suggest this, perhaps due to the higher prevalence of nausea and vomiting in drug naïve patients when exposed to any dopaminergic agent (see tables of treatment emergent adverse events , below).

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 known or expected side effects 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 18 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.

In the advanced PD trial, there was considerable dropout in the placebo group, perhaps because it is fairly easy to see an expected clinical effect (or its absence) in the brittle on-off patient. The number of drop-outs in the PPX ER treatment group is higher than the IR group. Six subjects (3%) dropped out due to a psychiatric disorder: hallucinations (2), pathological gambling (2) and a mix of depression, anxiety, sleep attack and suicidal ideation occurred in the remaining two subjects.

Overall, in blinded trials, adverse events leading to trial discontinuation is twice as prevalent in treated as opposed to control groups. Final mean daily dose of PPX in 248.524 and 248.525 by treatment group indicates that exposure among PPX groups was comparable.

Table 65 Combined confirmatory trials: Drug exposure (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

Most of 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.

Open Label Extension Trials:

As expected, the rate of occurrence of adverse events in the open label extensions of the Phase III trials reveals a lesser incidence adverse events leading to discontinuations. Presumably, only those patients who perceive themselves (or are perceived by their physicians) as successfully treated with tolerable side effects will go on to enter these long term extension trials.

Table 66 Open Label Trials: Distribution of important adverse events

Phase III Open Label Extension Trials				
Trial / Arm	Death	Non-fatal SAE	AE leading to discontinuation	N treated
248.633 OL for 524 / 636				
ER	3 (0.6 %)	48 (9 %)	15 (3 %)	511
248.634 OL for 525				
ER	2 (0.5 %)	20 (5 %)	19 (5 %)	391
Total	5 (0.06%)	68 (8 %)	34 (4 %)	902

7.3.5 Submission Specific Primary Safety Concerns

- **Nausea and vomiting**

Clinical experience with immediate release pramipexole 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, CTZ) in the brainstem.

It figures as a prominent adverse event in the early PD patient. In the advanced PD patient it is present but analysis is complicated by the amount of concomitant anti PD drug therapy all the subjects are taking. Chronic exposure may attenuate this specific complaint due to desensitization of receptors in the CTZ. 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 67 Combined confirmatory trials: Nausea and vomiting

(Individuals endorsing complaint)	PLACEBO	PPX ER	PPX IR
248.524 Early PD	(N=103)	(N=223)	(N=213)
Nausea	9 (9%)	48 (22%)	51 (24%)
Vomiting	0 (0%)	10 (4%)	8(4%)

Gastrointestinal disorders (SOC)	21 (20%)	105 (47%)	98 (46%)
	PLACEBO	PPX ER	PPX IR
248.525 Advanced PD	(N=178)	(N=165)	(N=175)
Nausea	19 (11%)	18 (11%)	20 (11%)
Vomiting	5 (3%)	2 (1%)	10 (6%)
Gastrointestinal disorders (SOC)	40 (23%)	39 (24%)	42 (24%)
	PLACEBO	PPX ER	PPX IR
Combined Confirmatory Trials	(N=281)	(N=388)	(N=388)
Nausea	28 (10%)	66 (17%)	71 (18%)
Vomiting	5 (2%)	12 (3%)	18 (5%)
Gastrointestinal disorders (SOC)	61 (22%)	144 (37%)	140 (36%)

This is a very individualized response as demonstrated by a lack of relationship between the dose of PPX and the reporting of GI complaints:

Table 68 Combined confirmatory trials: Dose and gastrointestinal complaints

	Placebo	Pramipexole ER Dose			Pramipexole IR Dose		
(N, %)		Low	Medium	High	Low	Medium	High
Gastrointestinal disorders (SOC)	20 (19%)	66 (30%)	39 (23%)	30 (29%)	60 (28%)	32 (19%)	21 (21%)
Nausea	9 (8.7)	29 (13%)	18 (11%)	11 (11%)	32 (15%)	15 (9%)	9 (9%)

Perspective on the severity of the complaint is confirmed by the reporting of study discontinuations due to GI complaints. In the early PD trial: PCB, 1; PPX ER, 6; PPX IR, 5; in the advanced PD trial: PCB, 1; PPX ER, 2; PPX IR, 1.

Comment is warranted with regard to the lack of concomitant reporting of nausea with vomiting. 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. This has bearing

upon

(b) (4)

which this reviewer would endorse.

- **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. According to Johns (Sleep 1991:14:540-545), mean control score was 5.9+/- SD 2.2 and 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.)

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.

Individuals reporting increased sleepiness.

The table below, derived in JMP from the AE.xpt files for the early and advanced PD trials, lists individuals by Preferred Term who reported AEs related to increased sleepiness. However, on review of the verbatim terms in the AE files it is noted that AE Preferred Terms reflected a wide variety of increased sleepiness coded under different SOC's with prominent splitting as a result. For example, it is not clear how a sleep attack might differ in clinical significance from a sudden onset of sleep, though they represent different Preferred Terms. (Excluded from this analysis were terms related to insomnia or sleep disturbance such as vivid dreams, REM behavior disorder and nightmare.)

Sleep attacks per se represent a small percentage of hypersomnia related events, though they tend to be the more dramatic end of this spectrum. The table reflects that this is a spectrum of dysfunction and that it appears to attenuate with either habituation to dopaminergic drugs, advancement of disease, or even disinclination to recognize it as a true adverse event as the illness progresses. This latter explanation appears very relevant as direct evaluation of hypersomnia in the advanced PD trial using the PDSS Question 15 or ESS reveal that there is no lessening of this phenomenon in advanced disease. The increased incidence in the placebo arms of both trials likely reflects that hypersomnia is an effect of all anti-PD medication, not just dopamine agonists.

Table 69 Combined confirmatory trials: Individuals reporting any sleep related AE by Preferred Term

Individual Subjects reporting any sleep related AE (by Preferred Term)			
(Individuals endorsing complaint)	PLACEBO	PPX ER	PPX IR
248.524 Early PD	(N=103)	(N=223)	(N=213)
Hypersomnia	1	1	2
Advanced sleep phase	0	0	1
Sleep attacks	0	5	3
Sleep disorder	1	5	8
Somnolence	15	81	71
Sudden onset of sleep	1	2	3
Total AEs	18 (17%)	94 (42%)	88 (41%)

	PLACEBO	PPX ER	PPX IR
248.525 Advanced PD	(N=178)	(N=165)	(N=175)
Hypersomnia	5	2	2
Poor quality sleep	0	1	0
Sleep attacks	0	0	1
Sleep disorder	5	7	3
Somnolence	29	24	30
Sudden onset of sleep	1	1	2
Total AEs	40 (22%)	35 (21%)	38 (22%)

	PLACEBO	PPX ER	PPX IR
Combined Confirmatory Trials	(N=281)	(N=388)	(N=388)
All sleep AEs	58 (21%)	129 (33%)	126 (32%)

Table 70 Examples of splitting verbatim sleep related responses

Examples of splitting verbatim sleep related responses found in AE.xpt files		
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

Parkinson's Disease Sleep Scale (PDSS) Question 15

PDSS Q15 "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:

This query was made at Visit 2 (randomization), Visit 4 (week 4 – titration phase), Visit 6 (week 8 - end of the drug titration and beginning of the maintenance period), Visit 8 (week 18) and Visit 11. Visit 11 was used as the termination visit and could occur anywhere from immediately after randomization up to week 33.

There is no clear methodologically correct way to analyze this fragment of the total PDSS scale. The Sponsor used change from baseline score at randomization to week 18 (10th week of maintenance therapy) for the advanced PD trial and change from baseline to week 33 (25th week of maintenance therapy) for the early PD trial. No significant difference was noted in either case.

However, I explored excessive daytime sleepiness during the treatment period by looking at the numbers of patients in each arm with a PDSS Q15 score below 50, the mid point of the scale. The numbers of subjects below this cut-off at baseline (randomization at week 2) is compared to the numbers of subjects who report this degree of increased daytime sleepiness at any time during the treatment period. By this measure, there is increase hypersomnia related to PPX use, regardless of formulation.

Table 71 Combined confirmatory trials: Individual subjects rating PDSS Question 15 at 50 mm or less

Individual Subjects rating PDSS Q15 at 50 mm or less			
(Individuals endorsing hypersomnia)	PLACEBO	PPX ER	PPX IR

248.524 Early PD	(N=103)	(N=223)	(N=213)
At Randomization (Baseline)	11 (11%)	20 (9%)	14 (7%)
At any time during treatment period	19 (18%)	70 (31%)	47 (22%)

	PLACEBO	PPX ER	PPX IR
248.525 Advanced PD	(N=178)	(N=165)	(N=175)
At Randomization (Baseline)	44 (25%)	49 (30%)	46 (26%)
At any time during treatment period	57 (32%)	67 (41%)	78 (45%)

	PLACEBO	PPX ER	PPX IR
Combined Confirmatory Trials	(N=281)	(N=388)	(N=388)
At Randomization (Baseline)	55 (20%)	69 (18%)	60(15%)
At any time during treatment period	76 (27%)	137 (35%)	125 (32%)

Epworth Sleep Scale

As noted above, a score greater than ten indicated excessive daytime sleepiness. This rating was also performed at the same intervals as the PDSS Q15: Visit 2 (randomization), Visit 4 (week 4 – titration phase), Visit 6 (week 8 - end of the drug titration and beginning of the maintenance period), Visit 8 (week 18) and Visit 11 (termination visit).

I used a similar strategy for analyzing the eight item Epworth Sleep Scale. A higher total score reflected an increased tendency for daytime sleepiness (range 0 to 24) with scores greater than 10 considered clinically significant.

Table 72 Combined confirmatory trials: Individual subjects rating the ESS at 10 or less

Individual Subjects With ESS Score > 10			
(Individuals endorsing hypersomnia)	PLACEBO	PPX ER	PPX IR
248.524 Early PD	(N=103)	(N=223)	(N=213)
At Randomization (Baseline)	9 (9%)	20 (9%)	27 (13%)
At any time during treatment period	18 (17%)	67 (30%)	70 (33%)

	PLACEBO	PPX ER	PPX IR
248.525 Advanced PD	(N=178)	(N=165)	(N=175)
At Randomization (Baseline)	34 (19%)	33 (20%)	46 (26%)
At any time during treatment period	58 (33%)	72 (44%)	74 (42%)

	PLACEBO	PPX ER	PPX IR
Combined Confirmatory Trials	(N=281)	(N=388)	(N=388)
At Randomization (Baseline)	43 (15%)	53 (14%)	73(%)
At any time during treatment period	76 (27%)	139 (36%)	144 (37%)

The ESS results similarly suggest that the addition of PPX in either formulation decidedly increases the rate of experiencing hypersomnia and increased daytime sleepiness in both the early and advanced PD population.

This is likely affected by concomitant anti-PD medication, and advancing disease, but the effect on the rate of this phenomenon appears approximately equal in both trials. The placebo group with different baseline rates of hypersomnia in the early and advanced PD trial suggests a greater background rate of increased daytime sleepiness as the disease progresses (and drug therapy increases).

- **Symptomatic orthostatic hypotension**

The Sponsor excluded from both 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.*”

As also specified by the Sponsor, “*only symptomatic orthostatic hypotension was to be recorded as an adverse event*” (reviewer-added emphasis). This is of interest because in the UPDRS Part IV, Complications of Therapy, Question 42 asks “Does the patient have symptomatic orthostasis?” This part of the UPDRS was used in the Advanced PD Trial only:

Table 73 Advanced PD Trial: patients reporting symptomatic orthostasis

Trial 248.525 Advanced PD	PLACEBO	PPX ER	PPX IR
UPDRS Part IV, Question 42: Does the patient have symptomatic orthostasis?	(N=178)	(N=165)	(N=175)
“Yes” - Present at Baseline: N (%)	8 (4%)	12 (7%)	16 (9%)
“Yes” - Occurred during the trial, but <u>not</u> present in subject at baseline: N (%)	11 (6%)	11 (7%)	18 (10%)

It is evident from a tally of the AEs in the reviewer’s tables below, that symptomatic orthostasis was underreported in the trial, and this was not noticed by the Sponsor.

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. 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 the reviewer has combined Preferred Terms which may be reasonably associated with hypotension and which gives a clearer portrait of hypotensive phenomena.

Trial 248.524 Early PD

Table 74 Early PD Trial: reviewer's tally of BP related events from AE.xpt

248.524 Early PD			
Preferred Term	Placebo n=103	PPX ER n=223	PPX IR n=213
Hypotension	1	0	6
Orthostatic hypotension	1	9	1
Dizziness postural	0	1	2
Syncope	0	2	2
Total	2 (2%)	12 (5%)	11 (5%)

Trial 248.525 Advanced PD

Table 75 Advanced PD Trial: reviewer's tally of BP related events from AE.xpt

248.525 Advanced PD			
Preferred Term	Placebo n=178	PPX ER n=165	PPX IR n=175
Hypotension	1	1	1
Orthostatic hypotension	2	3	3
Dizziness postural	2	5	7
Syncope	0	1	2
Total	5 (3%)	10 (6%)	13 (7%)

Subjects often report the inner sensation of orthostatic hypotension as dizziness. Dopamine agonists are not known to have vestibular toxicity which suggests that the common occurrence of “dizziness” (Preferred Term) as an AE in the confirmatory trials may reflect this interpretation.

Table 76 Combined confirmatory trials: Reports of Preferred Term “dizziness” as an AE from AE.xpt

248.524 Early PD Trial	Placebo n=103	PPX ER n=223	PPX IR n=213
Preferred Term: Dizziness	7 (7%)	26 (12%)	25 (12%)
248.525 Advanced PD Trial	Placebo n=178	PPX ER n=165	PPX IR n=175
Preferred Term: Dizziness	9 (5%)	9 (5%)	20 (11%)

Taken as a whole, this suggests that the Sponsor’s claim that the frequency of asymptomatic orthostatic hypotension was no different from that seen in the placebo arm is incorrect.

- **Falls**

The incidence of falls was assessed in the blinded placebo controlled confirmatory trials. In the Early PD trial, falls were experienced by 19 subjects: 9 in each treatment arm and 1 in the placebo group (4% vs. 1%). In the Advanced PD trial, falls were experienced by 23 subjects: 8 each in the Pramipexole ER and placebo treatment arms

and 7 in the Pramipexole IR group (4%, 5%, and 4%, respectively). This observation follows the pattern for dizziness described in the previous section, a phenomenon possibly related to orthostasis in the Early PD subjects. Naturally this raises the speculation that the increased incidence of falls in the Early PD group is a consequence of orthostasis, but there are insufficient data to answer this question.

- **Dyskinesia**

Dyskinesia is a motor complication which results from the interaction of dopaminergic treatment with advancing PD. In 248.524, the early PD trial, no dyskinesia was reported as an adverse event but it should also be noted that Part IV of the UPDRS (*Complications of Therapy in the Past Week*) was not administered in this trial. It is possible that dyskinesia would have been documented if it had. In the multicenter trial of PPX IR in early PD which was the basis of the original approval of pramipexole, 5 of 151 PPX subjects developed dyskinesia before any levodopa use. When levodopa was added to subjects in the PPX treatment arm as a rescue medication, 10 more subjects developed dyskinesia (Parkinson Study Group, JAMA 284 (15) 1931-1938, 2000).

In 248.525, the advanced PD study, dyskinesia is the most commonly reported adverse event.

Table 77 Advanced PD Trial: Dyskinesia reported as an AE from AE.xpt

Dyskinesia reported as AE	PCB	PPX ER	PPX IR
Trial 248.525 Advanced PD	(N=178)	(N=165)	(N=175)
Dyskinesia	17 (10%)	28 (17%)	34 (19%)
Dyskinesia rated as "severe" AE	0 (0%)	2 (1%)	2 (1%)

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 as a dopaminergic medication (PPX) is added to the subject's existing anti-PD drug regimen.

Part IV of the UPDRS evaluates dyskinesia with regard to duration and disability of dyskinesia. The trial protocol makes the statement that "the L-Dopa+ dose may need to be adjusted with the addition of pramipexole (ER or IR)/placebo during the trial." No specific instructions were given. No manipulation of other anti-PD medication was permitted during the trial.

32. Duration: What proportion of the waking day are dyskinesias present?

0 = None

1 = 1-25% of day.

2 = 26-50% of day.

3 = 51-75% of day.

4 = 76-100% of day.

Table 78 Advanced PD Trial: duration of dyskinesia

Duration of dyskinesia	PLACEBO	PPX ER	PPX IR
Trial 248.525 Advanced PD	(N=178)	(N=165)	(N=175)
Baseline Duration			
None	103 (58%)	93 (56%)	104 (59%)
1 - 25% of day	42 (24%)	43 (26%)	49 (28%)
26 - 50% of day	22 (12%)	27 (16%)	17 (10%)
51 - 75% of day	10 (6%)	2 (1%)	3 (2%)
76 - 100% of day	1 (0.6%)	0	2 (1%)
Number of subjects reaching this level of duration of dyskinesia at any point through the treatment period.			
None	77 (43)%	65 (39)%	73 (42)%
1 - 25% of day	47 (26)%	40 (24)%	48 (27)%
26 - 50% of day	31 (17)%	39 (24)%	30 (17)%
51 - 75% of day	16 (9)%	15 (9)%	18 (10)%
76 - 100% of day	7 (4)%	6 (4)%	6 (3)%

33. Disability: How disabling are the dyskinesias?

0 = Not disabling.

1 = Mildly disabling.

2 = Moderately disabling.

3 = Severely disabling.

4 = Completely disabled.

Table 79 Advanced PD Trial: disability due to dyskinesia

Disability due to dyskinesia	PLACEBO	PPX ER	PPX IR
Trial 248.525 Advanced PD	(N=178)	(N=165)	(N=175)

Baseline Disability			
Not disabling	127 (71%)	116 (70%)	128 (73%)
Mildly disabling	33 (19%)	28 (17%)	24 (14%)
Moderately disabling	14 (8%)	17 (10%)	21 (12%)
Severely disabling	4 (2%)	4 (2%)	1 (0.5%)
Completely disabled	0	0	1 (0.5%)
Number of subjects reaching this level of disability due to dyskinesia at any point through the treatment period.			
Not disabling	102 (57)%	94 (57)%	105 (60)%
Mildly disabling	47 (26)%	35 (21)%	36 (21)%
Moderately disabling	21 (12)%	21 (13)%	25 (14)%
Severely disabling	7 (4)%	11 (0.7)%	9 (5)%
Completely disabled	1 (0.5)%	0	0

I inspected the baseline reporting by subjects for duration of dyskinesia and its disability (There was no measure of dyskinesia severity). I then looked at the longest duration and highest level of disability reported by the individual subject at any point during the duration of treatment. There was no difference among the treatment arms and there was considerable variability even within the placebo group. This suggests that this single UPDRS item is neither a sensitive nor specific measure as one might wish for in order to quantify this phenomenon and little more can be said about the nature of dyskinesia in this trial.

- **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 by treatment arm all Preferred Terms from AE.XPT listed as Neurological or Psychiatric SOC that reflect behavior. Behavioral abnormalities for the purpose of this review are construed to be any possible surrogate of cognitive, conative, or behavioral process. While this may superficially appear arbitrary, the remarkable consistency of the results in both the early and advanced PD population supports this method. 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. (Recall that two thirds of the early PD trial population was receiving other anti-PD treatment though not levodopa which was an exclusion criteria.)

Table 80 Early PD Trial: Occurrence of Preferred Terms suggesting cognitive or behavioral adverse events

Trial 248.524 Early PD	PLACEBO	PPX ER	PPX IR
Behavior - related Preferred Terms	(N=103)	(N=223)	(N=213)
Total Events N, (%)	17 (17%)	75 (34%)	73 (34%)
Abnormal behavior	1	0	0
Abnormal dreams	2	4	3
Aggression	1	1	0
Agitation	1	0	0
Anxiety	1	3	9
Apathy	0	0	1
Compulsive sexual behavior	0	0	2
Compulsive shopping	1	1	2
Confusional state	0	3	0
Decreased interest	0	1	0
Depression	0	5	1
Disinhibition	1	0	0
Dyssomnia	0	1	0
Eating disorder	0	0	1
Excessive sexual fantasies	1	1	0
Hallucination	0	7	9
Hallucination, auditory	0	0	2
Hallucination, visual	1	7	5
Hallucinations, mixed	0	0	1
Illusion	0	1	0
Impulsive behavior	0	1	0
Insomnia	3	10	9
Libido decreased	1	2	0

Libido increased	0	0	2
Middle insomnia	0	1	0
Mood swings	0	1	0
Nightmare	0	1	3
Obsessive-compulsive disorder	0	1	0
Panic attack	0	2	0
Panic disorder	0	0	1
Pathological gambling	0	3	0
Rapid eye movements sleep abnormal	0	0	1
Restlessness	0	1	5
Sleep talking	0	1	1
Stress	0	0	1
Suicidal ideation	0	1	0
Violence-related symptom	0	0	1
Ageusia	0	1	0
Amnesia	0	2	1
Aphasia	0	1	1
Cognitive disorder	0	1	0
Dementia	1	1	0
Disturbance in attention	0	2	1
Dysesthesia	1	0	0
Global amnesia	0	1	1
Hyperesthesia	0	0	1
Hypoesthesia	0	2	0
Hypogeusia	0	0	1
Lethargy	0	2	2
Memory impairment	1	1	5
Parosmia	0	1	0

Table 81 Advanced PD Trial: Occurrence of Preferred Terms suggesting cognitive or behavioral adverse events

Trial 248.525 Advanced PD	PLACEBO	PPX ER	PPX IR
Behavior - related Preferred Terms	(N=178)	(N=165)	(N=175)
Total Events N (%)	31 (17%)	53 (32%)	56 (32%)
Abnormal behavior	1	1	1
Abnormal dreams	3	0	1
Aggression	0	0	2

Agitation	0	0	1
Anxiety	3	4	3
Apathy	0	1	0
Cognitive disorder	1	0	0
Compulsive sexual behavior	1	3	0
Compulsive shopping	1	3	2
Confusional state	0	1	0
Delusion	0	1	2
Depressed mood	1	1	1
Depression	3	1	3
Disorientation	0	1	1
Disturbance in attention	0	1	0
Dysgeusia	0	0	2
Early morning awakening	0	1	0
Eating disorder	0	2	0
Formication	0	0	1
Hallucination	2	9	11
Hallucination, auditory	1	1	0
Hallucination, visual	1	4	7
Hypoesthesia	2	1	1
Illusion	0	1	1
Impatience	0	1	0
Insomnia	4	9	8
Jealous delusion	0	0	1
Memory impairment	0	1	0
Mood altered	1	0	1
Nervousness	1	0	0
Paresthesia	2	1	0
Pathological gambling	0	1	3
Poor quality sleep	0	1	0
Psychomotor skills impaired	1	0	0
Psychotic disorder	0	0	2
Restlessness	1	1	0
Sleep talking	1	0	0
Soliloquy	0	1	0
Suicide attempt	0	0	1

Discontinuations due to psychiatric adverse events:

In the tables below are all patients in the two confirmatory placebo controlled trials that discontinued treatment for behavioral reasons, regardless as to whether it was reported as an AE or attributed to treatment. Small numbers prevented analyzing a dose response pattern.

Table 82 Early and Advanced PD Trials: Discontinuations related to behavioral events

248.524 Early PD	PCB	PPX ER	PPX IR
	n=103	n=223	n=213
Discontinue due to Psychiatric SOC AE	1 (1%)	6 (3%)	8 (4%)
AE Preferred Term (subject may have more than one)			
Hallucination	0	2	3
Compulsive shopping	1	0	0
Disinhibition	1	0	0
Pathological gambling	0	2	0
Sleep attacks	0	1	2
Anxiety	0	1	1
Hallucinations, mixed	0	0	1
Panic disorder	0	0	1
Aggression	0	1	0
Confusional state	0	1	0
Insomnia	0	1	0
Suicidal ideation	0	1	0

248.525 Advanced PD	PCB	PPX ER	PPX IR
	n=178	n=164	n=175
Discontinue due to Psychiatric SOC AE	2 (1%)	3 (2%)	8 (5%)
AE Preferred Term (subject may have more than one)			
Hallucination	1	3	6
Abnormal behavior	1	0	0
Agitation	0	0	1
Anxiety	0	1	0
Compulsive sexual behavior	0	1	0
Delusion	0	0	1
Depression	0	0	1

Insomnia	0	0	1
Jealous delusion	0	0	1
Psychotic disorder	0	0	1
Suicide attempt	0	0	1

Screening criteria for the advanced PD trial likely reduced the number of those subjects who might be susceptible to drug related exacerbation of psychiatric behavior.

Impulse Control Disorders:

No instances of impulse control disorder were noted in Phase I studies.

In Phase III placebo controlled blinded trials, instances where the behavior was reported outright as an AE are found in this table (subjects may have had more than one type of compulsion):

Table 83 Early and Advanced PD Trials: ICD related Preferred Terms reported as an AE in AE.xpt

Trial 248.524 Early PD	PLACEBO	PPX ER	PPX IR
ICD related Preferred Terms	(N=103)	(N=223)	(N=213)
Individual subjects (N, %)	2 (2%)	2 (1%)	3 (1%)
Compulsive sexual behavior	0	0	2
Compulsive shopping	1	1	2
Pathological gambling	0	3	0
Impulsive behavior (not specified)	0	1	0
Trial 248.525 Advanced PD	PLACEBO	PPX ER	PPX IR
ICD Preferred Terms	(N=178)	(N=165)	(N=175)
Individual subjects (N, %)	1 (1%)	6 (4%)	4 (2%)
Compulsive sexual behavior	1	3	0
Compulsive shopping	1	3	2
Pathological gambling	0	1	3

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.

Note that a majority of early PD patients were on other anti-PD medication at baseline. The presence of concomitant antiparkinson drug treatment makes specific conclusions difficult for both trials. For both the early and advanced PD studies, there were limited short-term exposures to treatment and small numbers 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.

Table 84 Early and Advanced PD Trials: mMIDI responses confirmed by psychiatric interview

Trial 248.524 Early PD	PLACEBO	PPX ER	PPX IR
Confirmed mMIDI positive responses	(N=103)	(N=223)	(N=213)
Individual subjects (N, %)	2 (2%)	5 (2%)	6 (3%)
Pathological gambling	0	3	0
Compulsive buying	1	1	2
Compulsive sexual behavior	0	0	2
Trial 248.525 Advanced PD	PLACEBO	PPX ER	PPX IR
Confirmed mMIDI positive responses	(N=178)	(N=165)	(N=175)
Individual Subjects N (%)	2 (1%)	9 (6%)	6 (3%)
Pathological gambling	0	0	2
Compulsive buying	1	1	0
Compulsive sexual behavior	0	2	0
Other compulsive behavior	1	6	4

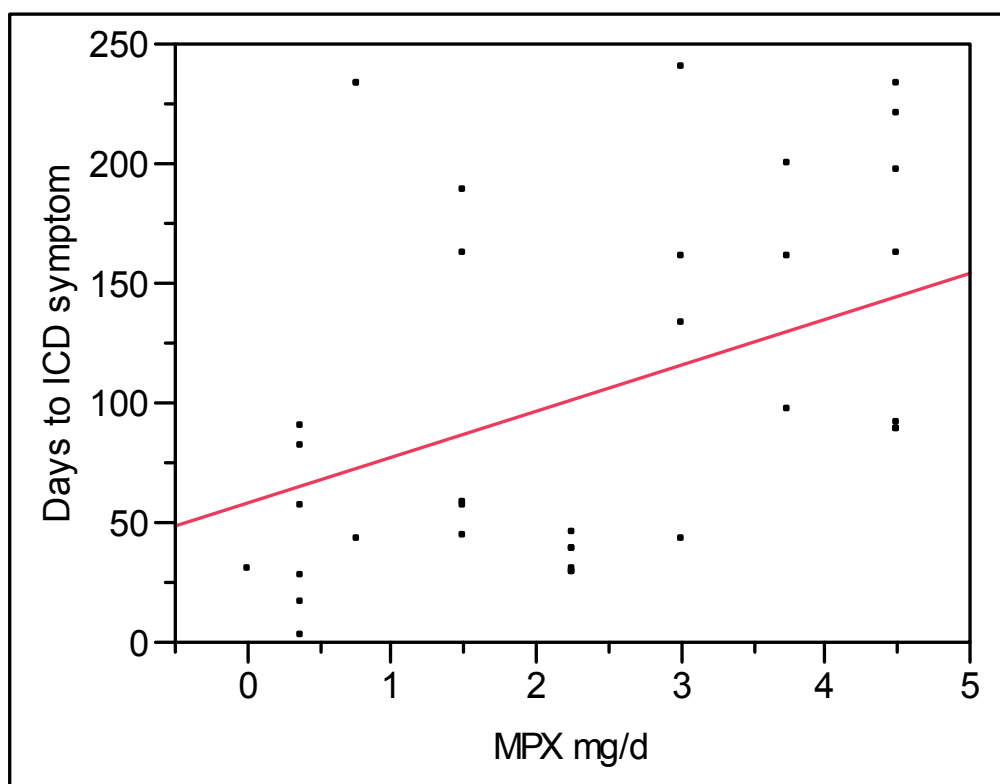
While this confirms that impulse control dysfunction is found in treated PD patients at all stages of disease, it is difficult to say anything more specific. It appears to be more prevalent in advanced disease, but then these subjects also have greater exposure to anti PD drug therapy as a whole. It should also be noted in both trials that directed inquiry elicited significantly greater numbers than usual AE reporting.

An attempt to find a relationship between dose of PPX (whether ER or IR) and time to development of the first ICD symptom in 36 subjects from both trials revealed the following:

PPX dose: Mean: 2.35 mg/d; 95%CI 1.8, 2.9; (range: 0.375-4.5 mg/d)
Days to first ICD symptom: Mean: 103 days; 95% CI 77, 128; (range: 2 - 239 d)

A linear model indicates that longer time to first ICD symptom is associated with higher doses of PPX. This suggests that susceptibility to ICD is a biological disease related phenomenon in certain susceptible individuals rather than a dose related Pramipexole exposure effect. It should be noted that this very simplistic model ignores length and severity of disease, previous mental status and age, all of which likely figure in the risk for ICD.

Figure 19 Combined confirmatory trials: Hypothetical simple linear model of relationship of ICD to dose



Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Ratio
Model	1	31368.24	31368.2	6.4029
Error	34	166567.40	4899.0	Prob > F
C. Total	35	197935.64		0.0162

Parameter Estimates

Term	Estimate	Std Error	t Ratio	Prob> t
Intercept	57.535366	21.35778	2.69	0.0109
PPX	19.229815	7.59951	2.53	0.0162

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. 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:

In general adverse events were collected in a protocol driven consistent manner in the placebo controlled trials. Even there, as witnessed in the orthostatic hypotension data, not all events were likely captured. Active control trials with no placebo group for comparison provide less rigorous data. The nature and quantity of the clinical and laboratory safety data is consistent with dopamine agonist development programs. Creatine was not collected, but no AE profiles suggest that muscle damage is an adverse event of concern. There appear to be no systematic discrepancies with regard to proposed and actual collection of clinical and laboratory safety data.

Using JMP analysis and MAEDService data-mining software using AE.xpt as the numerator and DM.xpt as denominator, these tables indicate the numbers of patients reporting any adverse event:

Table 85 Early and Advanced PD Trials: Subjects reporting at least one adverse event during treatment

248.524 Early PD	PLACEBO	PPX ER	PPX IR
AT LEAST ONE EVENT REPORTED:	(N=103)	(N=223)	(N=213)
PT	70 (68.0%)	183 (82.1%)	161 (75.6%)

248.525 Advanced PD	PLACEBO	PPX ER	PPX IR
AT LEAST ONE EVENT REPORTED:	(N=165)	(N=147)	(N=164)
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 2% of subjects treated with PPX ER or PPX IR and were numerically more frequent than the occurrence in the placebo group are noted. Nothing suggested a low frequency idiosyncratic adverse event. Gastrointestinal and psychiatric events predominated.

Adjustments were made for a few instances of obvious splitting. For example, hallucinations were labeled by four Preferred Terms: hallucinations, auditory, visual or mixed. Sleep attacks and sudden onset of sleep were judged similarly.

Table 86 Early PD Trial: Treatment Emergent Adverse Events (Preferred terms and SOC MedDRA v 11.1)

Body System / Adverse Event	Placebo	MIRAPEX ER	Immediate release MIRAPEX
	(n=103)	(n=223)	(n=213)
	%	%	%
Nervous system disorders			
Somnolence	15	36	33
Dizziness	7	12	12

Tremor	1	3	3
Balance disorder	1	2	0
Memory impairment	1	0	2
Gastrointestinal disorders			
Nausea	9	22	24
Constipation	3	14	12
Dry mouth	1	5	4
Vomiting	0	4	4
Abdominal pain upper	1	3	4
Dyspepsia	2	3	3
Abdominal discomfort	0	2	1
Gastritis	0	2	0
General disorders and administration site conditions			
Fatigue	4	6	6
Edema peripheral	4	5	8
Asthenia	2	3	1
Pyrexia	0	2	1
Discomfort	0	0	2
Musculoskeletal and connective tissue disorders			
Muscle spasms	3	5	3
Psychiatric disorders			
Hallucinations, including visual, auditory and mixed	1	6	8
Insomnia	3	4	4
Sleep attacks and sudden onset of sleep	1	3	6
Sleep disorder	1	2	4
Depression	0	2	0
Anxiety	1	1	4
Restlessness	0	0	2
Injury, poisoning and procedural complications			
Fall	1	4	4
Vascular disorders			
Orthostatic hypotension	1	4	0
Hypotension	1	0	3
Ear and labyrinth disorders			
Vertigo	1	4	2
Metabolism and nutrition disorders			
Increased appetite	1	3	2
Anorexia	2	2	4
Respiratory, thoracic and mediastinal disorders			
Cough	1	3	3
Eye disorders			
Vision blurred	1	2	1
Visual impairment	0	2	0
Investigations			

Weight increased	0	0	3
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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 or PPX IR and were numerically more frequent than the placebo group are noted: Once again, nothing suggested a low frequency idiosyncratic adverse event.

Table 87 Advanced PD Trial: Treatment Emergent Adverse Events (Preferred terms and SOC MedDRA v 11.0)

Body System / Adverse Event	Placebo (n=178) %	MIRAPEX ER (n=165) %	Immediate release MIRAPEX (n=175) %
Nervous system disorders			
Dyskinesia	10	17	19
Somnolence	16	15	17
Headache	3	8	5
Dizziness	5	5	11
Dizziness postural	1	3	4
Dementia	1	0	2
Gastrointestinal disorders			
Nausea	11	11	11
Constipation	5	7	6
Diarrhea	1	3	2
Salivary hypersecretion	0	2	1
Abdominal pain upper	1	2	2
Dyspepsia	1	2	2
Vomiting	3	1	6
Psychiatric disorders			
Hallucinations, including visual, auditory and mixed	2	9	11
Insomnia	2	5	5
Sleep disorder	3	4	2
Compulsive sexual behavior	1	2	0
Compulsive shopping	1	2	1
Pathological gambling	0	1	2
Sleep attacks and sudden onset of sleep	1	1	2
Metabolism and nutrition disorders			
Anorexia	2	6	1
Injury, poisoning and procedural complications			
Fall	4	5	4

General disorders and administration site conditions			
Asthenia	2	4	2
Chest pain	0	2	1
Pain	1	2	1
Fatigue	1	1	2
Musculoskeletal and connective tissue disorders			
Arthralgia	2	2	4
Muscle spasms	1	0	2
Osteoarthritis	0	0	2
Vascular disorders			
Orthostatic hypotension	1	2	2
Hypertension	1	1	2
Respiratory, thoracic and mediastinal disorders			
Cough	1	2	2
Eye disorders			
Cataract	3	2	4
Ear and labyrinth disorders			
Vertigo	1	1	2
Investigations			
Weight decreased	1	0	2

7.4.2 Laboratory Findings

Laboratory data are available for the two placebo controlled confirmatory trials in Early and Advanced PD (248.524 and 248. 525). For the active control Japan trial 248.610, laboratory data were not yet assembled for a study report as of the cut off date. In the open label extensions for these trials, laboratory data was to be collected after 32 weeks, and few patients had reached this milestone by the submission cutoff dates.

Laboratory reference ranges and criteria for clinically significant abnormalities were reviewed (ISS, Tables 3.1.1 and 3.1.2).

The descriptive statistics and measures of central tendency revealed no significance for differences from baseline for any reported value among the 33 week treatment arms for the Early and Advanced PD placebo controlled trials for:

- Hematology (hematocrit, hemoglobin, and absolute red cell, white cell, neutrophil, eosinophil, basophil, monocyte, lymphocyte and platelet counts)
- Electrolytes (sodium, potassium, and chloride)
- Enzymes (AST, ALT, alkaline phosphatase, GGT)
- Metabolic indices: (glucose, cholesterol, urea, creatinine, bilirubin, triglyceride, uric acid, total protein and albumin)

The small numbers of individuals with possibly clinically significant laboratory abnormalities by the Sponsor's criteria are shown in the Sponsor's table below (SCS, Table 3:1.1:5): Frequency of patients (N, %) with any PCS laboratory abnormality, by parameter and treatment group, for the combined 33 week Early and Advanced PD Trials. Indices omitted from the list contained no individuals with PCS increases or decreases in any arm.

Figure 20 Combined confirmatory trials: shift in clinical laboratory findings

Parameter	Treatment group	Number of patients	Decrease N (%)	Increase N (%)
Haematocrit (%)	Placebo	227	2 (0.9)	0
	PPX ER	312	9 (2.9)	0
	PPX IR	329	10 (3.0)	0
Haemoglobin (g/dL)	Placebo	227	5 (2.2)	0
	PPX ER	312	19 (6.1)	0
	PPX IR	329	16 (4.9)	0
Red blood cell ct. ($10^{12}/L$)	Placebo	227	0	0
	PPX ER	312	1 (0.3)	0
	PPX IR	329	3 (0.9)	0
White blood cell ct. ($10^9/L$)	Placebo	227	0	0
	PPX ER	312	1 (0.3)	0
	PPX IR	329	0	0
Neut., poly (segs) (%)	Placebo	227	0	0
	PPX ER	312	2 (0.6)	0
	PPX IR	329	0	0
Eosinophils (%)	Placebo	227	0	3 (1.3)
	PPX ER	312	0	10 (3.2)
	PPX IR	329	0	5 (1.5)
Neut.,poly.(segs), absol. ($10^9/L$)	Placebo	227	0	0
	PPX ER	311	1 (0.3)	0
	PPX IR	329	1 (0.3)	0
Sodium (mmol/L)	Placebo	229	0	0
	PPX ER	314	5 (1.6)	0
	PPX IR	334	7 (2.1)	0
Potassium	Placebo	229	0	0
	PPX ER	313	0	3 (1.0)
	PPX IR	334	0	2 (0.6)
Chloride (mmol/L)	Placebo	229	0	0
	PPX ER	314	2 (0.6)	0
	PPX IR	334	0	0

GGT (U/L)	PPX IR	229	0	1 (0.4)
	Placebo	314	0	5 (1.6)
	PPX ER	334	0	1 (0.3)
Glucose (mg/dL)	Placebo	229	2 (0.9)	2 (0.9)
	PPX ER	314	4 (1.3)	1 (0.3)
	PPX IR	334	1 (0.3)	4 (1.2)
Creatinine (mg/dL)	Placebo	229	0	1 (0.4)
	PPX ER	314	0	1 (0.3)
	PPX IR	334	0	0
Triglyceride (mg/dL)	PPX IR	229	0	11 (4.8)
	Placebo	314	0	11 (3.5)
	PPX ER	334	0	12 (3.6)
Uric acid (mg/dL)	Placebo	229	0	2 (0.9)
	PPX ER	314	0	3 (0.9)
	PPX IR	334	0	1 (0.3)

None of these suggested end organ toxicity of significance or a pattern of system dysfunction. Shift tables were also reviewed for these laboratory parameters and these did not appear to fall into a pattern or represent an idiosyncratic event.

The Sponsor indicates that “compared to the placebo group, small numbers of patients in the active treatment groups had clinically significant decreases in hematocrit and hemoglobin, red blood cell counts, white blood cell counts, neutrophil %, sodium, chloride, and increases in eosinophil %, potassium, alkaline phosphatase, and GGT”. The Sponsor adds that these laboratory changes did not reveal a clinically significant trend, except “possibly a slight tendency for a decrease in hematocrit and hemoglobin (anemia)”. However, when the reviewer looked at consistency among the measures, e.g. hemoglobin, hematocrit and red blood cell count travelling in the same direction, it turned out that few subjects with abnormalities had baseline data (missing: PCB 8/15, PPX ER 10/21, and PPX IR 9/20). Of the remaining, differences were quite small and matched pair analyses indicated that the PPX ER group increased over the trial’s visits, while placebo and PPX IR decreased minimally. No outliers were found.

Hepatic Toxicity:

Phase I:

A single case fulfilling Hy’s Law occurred in Phase I the MIRAPEX ER development program. For the sake of completeness and the reader’s convenience, it is included here again in its entirety.

CRFs and a narrative were reviewed for a 43 year old man (248.530 PPX ER vs. IR: food effect with seven day exposure to drug, subject no. 1033) who 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 below). 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. Of note, alkaline phosphatase remained normal.

Table 88 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	-	-	-	-

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 **Section 8 Postmarket Experience**)

Phase III:

Placebo controlled data (Studies 248.524 and 248.525) for hepatic function was reviewed. No parametric differences were revealed in measures of central tendency. A survey for outliers revealed the following:

After combining the Sponsor's LB.xpt files for the Early and Advanced PD trials (N = 1057), the laboratory results were inspected using JMP for signals related to hepatic dysfunction.

Cases were sought that fulfilled any of the following criteria:

TBILI > 2 x ULN and Alkaline Phosphatase < 2 x ULN: No cases

TBILI > 2 x ULN: No cases

ALT and AST > 3 x ULN: No cases

AST and ALT > 2 x ULN: 3 cases: PCB 1; PPX ER 0; PPX IR 2

AST and ALT > 1.5 x ULN: 7 cases: PCB 1; PPX ER 2; PPX IR 4

Of the evaluable data, the relationship of abnormal TBILI to baseline values was that 1 of 6 Placebo subjects, 4 of 8 Pramipexole ER subjects and 2 of 5 Pramipexole IR subjects rose over the course of the trial (The remainder dropped or remained the same). No TBILI was noted above 2.3 mg/dL over the whole trial.

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 Toxicity:

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. After combining the Sponsor's LB.xpt files for the Early and Advanced PD trials (N = 1057), the laboratory results were inspected using JMP for signals related to renal dysfunction.

Analysis for outliers revealed that 12 subjects had elevations of creatinine over the trial (PCB 4; PPX ER 6; PPX IR 2). None of the elevations were more than trivial. One subject (no. 7557, PPX ER, Advanced PD Trial) did have a single creatinine during the trial of 2.5 but no baseline was provided for that subject. That subject also had elevated urea (10.7 mmol/L). No narrative is provided but the patient did have insomnia and upper respiratory tract infection listed as adverse events.

No safety signal for renal dysfunction was found.

7.4.3 Vital Signs

Blood pressure:

Measures of central tendency of BP were not revealing.

Symptomatic orthostatic hypotension is discussed in **Section 7.3.5** above.

Asymptomatic Orthostatic Hypotension:

The American Autonomic Society (AAS) and the American Academy of Neurology (AAN), using consensus criteria, define orthostatic hypotension as a systolic blood pressure decrease of at least 20 mm Hg or a diastolic blood pressure decrease of at least 10 mm Hg within three minutes of standing up (*Neurology* 1996; 46:1470).

The Sponsor defined orthostatic hypotension as a decline ≥ 20 mmHg in systolic blood pressure (SBP) and a decline ≥ 10 mmHg in diastolic blood pressure (DBP), at one minute after standing, compared with the previous SBP and DBP obtained after 5 minutes of quiet rest. As the table below indicates, this is a much more exclusionary definition. The reviewer analyses all BP measurements throughout both confirmatory trials in their respective VS.XPT files. Patients with orthostatic hypotension by AAS/AAN criteria at screening or randomization (Visits 1 and 2) were set aside from the analysis. Subjects who developed OH by either criterion at any visit during the treatment phase were then identified. The results are indicated in the table below.

Table 89 Early and Advanced PD Trials: asymptomatic orthostasis

Orthostatic Hypotension			
Trial 248.524 Early PD	PLACEBO	PPX ER	PPX IR
	(N=103)	(N=223)	(N=213)
OH at baseline (AAS / AAN Criteria)	4 (4%)	21 (9%)	19 (9%)
No OH at baseline	99	202	194
OH found during trial: AAS / AAN Criteria*	36 (36%)	70 (35%)	59 (30%)
OH found during trial: Sponsor's criteria*	7 (7%)	18 (9%)	9 (5%)
Trial 248.525 Advanced PD	PLACEBO	PPX ER	PPX IR
	(N=178)	(N=165)	(N=175)
OH at baseline (AAS / AAN Criteria)	17 (9%)	17 (10%)	12 (7%)
No OH at baseline	161	148	163
OH found during trial: AAS / AAN Criteria*	52 (32%)	55 (37%)	72 (44%)
OH found during trial: Sponsor's criteria*	9 (6%)	12 (8%)	17 (10%)
AAS / AAN Criteria: either systolic OH OR diastolic OH present.			
Sponsor's criteria: both systolic OH AND diastolic OH present.			
*Percentage calculation uses N in arm without OH at baseline as denominator.			

Using established criteria, the baseline incidence of OH in PD parallels usual descriptions of the disease. It is also a variable phenomenon, as its increased incidence in the placebo arm indicates. It is difficult to know what role concomitant anti-Parkinson treatment may play. The majority of patients in the Early PD trial and all the patients in the Advanced PD trial were receiving other medications for their diseases.

The MIRAPEX 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.”* The data above generally agrees with this assessment.

7.4.4 Electrocardiograms (ECGs) and Heart Rate

Heart Rate:

Measures of central tendency were used to look at heart rate (as measured by radial pulse) in both the Early and Advanced PD placebo controlled trials.

No unusual results were found. Heart rate at baseline occurred within a fairly narrow range for both studies in the supine and standing range and varied very little over the course of the study.

Findings as presented in the Sponsor's tables are as follows:

Table 90 Early PD Trial: Mean pulse rate through treatment period

Table 12.5.1: 2 Mean changes in supine and standing pulse rate from baseline over time, TS

Supine PR [beats/min]	Placebo		Pramipexole ER		Pramipexole IR	
	N	Mean (±SD)	N	Mean (±SD)	N	Mean (±SD)
Baseline	103	71.7 (10.7)	223	72.3 (9.8)	213	73.1 (10.1)
After 8 weeks	97	70.8 (9.2)	198	72.2 (11.0)	196	73.6 (10.0)
After 13 weeks	93	70.9 (9.2)	187	72.5 (10.2)	185	73.0 (9.6)
After 18 weeks	32	72.3 (9.0)	183	71.9 (10.0)	184	73.8 (9.5)
After 33 weeks	100	71.7 (10.5)	218	71.9 (9.8)	208	72.2 (9.1)
Standing PR [beats/min]	Placebo		Pramipexole ER		Pramipexole IR	
	N	Mean (±SD)	N	Mean (±SD)	N	Mean (±SD)
Baseline	102	75.8 (11.7)	222	77.5 (10.7)	213	77.9 (10.2)
After 8 weeks	97	74.5 (9.6)	198	77.4 (11.5)	196	78.9 (10.0)
After 13 weeks	93	75.1 (9.9)	187	77.1 (10.9)	184	78.1 (10.5)
After 18 weeks	92	76.5 (10.6)	183	75.9 (10.6)	184	78.9 (10.3)
After 33 weeks	100	75.3 (11.5)	218	76.6 (10.7)	208	76.9 (9.6)

Source data: [Table 15.3.4: 2](#)

Table 91 Advanced PD Trial: Mean pulse rate though treatment period

Table 12.5: 2 Descriptive statistics for supine and standing pulse rate, 18-week analysis, TS 1

	Placebo	PPX ER	PPX IR
Treated [N (%)]	178 (100.0)	164 (100.0)	175 (100.0)
Supine pulse rate (beat/min)			
Week 8 data N	162	150	167
At baseline (V2) mean (SD)	75.6 (11.5)	74.9 (10.2)	74.8 (10.3)
After 8 weeks (V6) mean (SD)	74.3 (10.6)	74.9 (10.3)	72.8 (10.4)
Change from baseline	-1.3 (9.7)	-0.1 (9.8)	-2.0 (9.6)
Week 18 data N	145	134	152
At baseline (V2) mean (SD)	75.8 (11.4)	75.1 (10.5)	75.2 (10.3)
After 18 weeks (V8) mean (SD)	73.9 (9.9)	73.5 (10.4)	73.8 (10.7)
Change from baseline	-1.9 (10.8)	-1.7 (12.5)	-1.4 (11.5)
Standing pulse rate (beat/min)			
Week 8 data N	161	150	167
At baseline (V2) mean (SD)	78.7 (10.6)	78.7 (10.8)	78.5 (10.6)
After 8 weeks (V6) mean (SD)	78.3 (11.2)	78.4 (10.8)	77.8 (11.7)
Change from baseline	-0.3 (10.0)	-0.3 (10.4)	-0.7 (9.7)
Week 18 data N	145	134	152
At baseline (V2) mean (SD)	78.9 (10.5)	79.0 (11.0)	78.8 (10.6)
After 18 weeks (V8) mean (SD)	78.4 (10.6)	78.2 (10.5)	78.0 (10.4)
Change from baseline	-0.5 (11.2)	-0.8 (11.5)	-0.8 (9.8)

Source data: [Tables 15.3.4.1: 20, 15.3.4.1: 21](#)

All heart rate and electrocardiographic adverse events reported in both confirmatory trials are as follows.

Table 92 Combined confirmatory trials: Heart rate and ECG related adverse events

Combined Trials: Early and Advanced PD			
All heart rate and ECG related AEs			
Preferred Terms:	Placebo	PPX ER	PPX IR
	n = 281	n = 388	n = 388
Atrial fibrillation	1 (0.4%)	0 (0%)	2 (0.5%)
Atrioventricular block first degree	0 (0%)	1 (0.3%)	0 (0%)
Atrioventricular extrasystoles	0 (0%)	1 (0.3%)	0 (0%)
Bradycardia	1 (0.4%)	0 (0%)	0 (0%)
Bundle branch block right	1 (0.4%)	0 (0%)	0 (0%)
Electrocardiogram abnormal	0 (0%)	0 (0%)	1 (0.3%)
Palpitations	5 (1.8%)	2 (0.5%)	5 (1.3%)
Tachycardia	0 (0%)	0 (0%)	1 (0.3%)
Extrasystoles	1 (0.4%)	0 (0%)	0 (0%)

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 IRT-QT 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 20667 PPX 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, were not obtained from the disease population, 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 fundoscopy 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. Analysis of adverse events by MAED Service software yielded no particular pattern of ophthalmological dysfunction.

In looking at the results of fundoscopy or vision examination from screening visit to week 28 in either trial reveals no clear safety signal. What constitutes normal or abnormal for this dichotomized outcome was not clearly specified.

Table 93 Early and Advanced PD Trials: vision and ophthalmologic findings

Vision Examination at Baseline and 28 Weeks.			
	PLACEBO	PPX ER	PPX IR
248.524 Early PD (1:2:2 Randomization)			
Normal Exam at Baseline	54	125	115
Abnormal Exam at Baseline	41	73	85
Normal Baseline Δ Abnormal at 28 Wk	5	10	6
Abnormal Baseline Δ Normal at 28 Wk	6	19	19

	PLACEBO	PPX ER	PPX IR
248.525 Advanced PD (1:1:1 Randomization)			
Normal Exam at Baseline	102	94	96
Abnormal Exam at Baseline	50	43	61
Normal Baseline Δ Abnormal at 28 Wk	5	11	15
Abnormal Baseline Δ Normal at 28 Wk	10	9	9

Fundoscopy Examination at Baseline and 28 Weeks.
--

	PLACEBO	PPX ER	PPX IR
248.524 Early PD (1:2:2 Randomization)			
Normal Exam at Baseline	64	141	139
Abnormal Exam at Baseline	31	57	61
Normal Baseline Δ Abnormal at 28 Wk	5	11	11
Abnormal Baseline Δ Normal at 28 Wk	4	14	13

	PLACEBO	PPX ER	PPX IR
248.525 Advanced PD (1:1:1 Randomization)			
Normal Exam at Baseline	107	101	110
Abnormal Exam at Baseline	44	36	46
Normal Baseline Δ Abnormal at 28 Wk	5	10	5
Abnormal Baseline Δ Normal at 28 Wk	8	3	11

The Sponsor is conducting 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.

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 for NDA 22421 Early PD dealt 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 or severe renal impairment. The IR formulation is available for use in this regard.

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. These were not qualitatively different except for visual hallucinations found more frequently in the older group. This is consistent with the IR label as well. Race and gender had no apparent impact on safety, but it should be noted that the racial populations did not include blacks of either American or African origin.

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.

A few generalities may be advanced: younger patients may be more susceptible to the autonomic effects of pramipexole (blood pressure control and gastrointestinal intolerance). Patients with advanced PD may be more susceptible to behavioral adverse events, and dyskinesia is likely to be increased to some modest degree when pramipexole is added to a stable regimen of antiparkinson medication.

Disturbances of sleep, whether increased daytime sleepiness or sleep phase disorders, are likely to worsen with pramipexole therapy.

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 specific language being suggested in the Clinical Pharmacology review for labeling the reduction in clearance of pramipexole when co-administered with antacids (26%) or H2 blockers (14%).

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 explore 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.

7.7 Additional Submissions

None

8 Postmarket Experience

No post-marketing experience exists with PPX ER which was just approved for use in early PD on February 12, 2010.

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 disproportionally 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 94 Results of Data mining 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	Psych	430	97.227	89.75	105.185

disorder					
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

None

9.1 Literature Review/References

Citations are noted in the text.

9.2 Labeling Recommendations

Background:

Extensive label-related discussion took place during the approval process for MIRAPEX ER in early PD. This has greatly simplified the process for the addition of the indication for advanced PD. The TEAE table is found in Section 7.4.1 Common Adverse Events and little else will be needed in addition.

(b) (4)

Abnormal Behavior:

It is recommended that the side effect profile be adjusted with regard to abnormal behavior related to treatment with PPX ER. Class warnings concerning impulse control disorders and other abnormal behaviors need to be added

(b) (4)

(b) (4)

(b) (4)

(b) (4)

The reviewer agrees with adding compulsive behavior in the PRECAUTIONS and ADVERSE EVENTS sections. While not constituting physical harm, the social consequences of this dopamine related syndrome should not be underestimated. In individual cases it can have disastrous results.

Autonomic Effects:

The physiological effects of PPX upon systolic blood pressure, even in the absence of symptomatic orthostasis should be identified.

Specific recommendations for labeling are also made by the QT-IRT in their review. The QT IRT recommends the following: (Their changes are shown in colored fonts)



The reviewer suggests that the Clinical Pharmacology [redacted] (b) (4) along with most of the Sponsors verbiage related to this section. The HR and BP changes that are described in a volunteer population after rapid titration of medication are of a small magnitude (10 mmHg and 10 bpm) and are not clinically meaningful.

Drug-drug interaction:

Clinical pharmacology review also suggested the addition of labeling to describe drug – drug interaction as indicated in Section 7.5.5.



Other cautions from the IR label apply equally well to this dosage form.

The reviewer feels that there is no indication at this time for risk mitigation, post marketing recommendation or commitment (REMS, PMC or PMR), especially in light of the recommendation for a Complete Response on the basis of risk for medication error

Clinical Review
Kenneth Bergmann, MD, FAAN
NDA 22-514
Mirapex ER / pramipexole dihydrochloride extended-release tablets

due to look-alike pills. Putting this issue aside however, the reviewer sees no other need for post-approval action.

At this time there is no MedGuide but the behavioral abnormalities associated with this class of agent are in Safety Review and result of that inquiry may alter this determination.

9.3 Advisory Committee Meeting

No advisory committee consideration was sought for this application.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22514	ORIG-1	BOEHRINGER INGELHEIM PHARMACEUTICA LS INC	TBD (PRAMIPEXOLE DIHYDROCHLORIDE)ER TABS

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

/s/

KENNETH J BERGMANN
03/17/2010

GERALD D PODSKALNY
03/19/2010

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 22514

**Applicant: Boehringer
Ingelheim Pharma, Inc.**

Stamp Date: May 22, 2009

**Drug Name: Mirapex ER
(pramipexole dihydrochloride
extended release tablets)**

NDA/BLA Type: 505(b)(1)

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			eCTD in EDR and GSR
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (e.g., are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			In SPL; provided original and (b) (4) CBE label.
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (i.e., Module 2 summaries)?	X			Modules 3,4 omitted; cross ref to NDA 22421
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			Module 5.3.5.3.28
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			Module 5.3.5.3.27
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			Module 5.3.5.4.3
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?	X			505(b)(1) with reference to IR and NDA 22421
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (i.e., appropriately designed dose-ranging studies)? Study Number: Study Title: Sample Size: Arms: Location in submission:			X	BA, BE from NDA 22421 and IR product
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application?	X			

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Pivotal Study #1 246.525 Indication: Treatment of Advanced PD N= 517 (164 on ER)				
	Pivotal Study #2 246.524 Indication: Treatment of Early PD (interim analysis previously evaluated for NDA 22421) N= 539 (223 on ER)				
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			
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			
SAFETY					
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			Inadequate QT study per QT-IRT but no evidence of cardiac safety signal in this marketed product
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 ¹) been exposed at the dose (or dose range) believed to be efficacious?	X			926 in 3 OL MPX ER trials: mean 123 days at 2.6 to 3.5 mg mean daily dose.
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 ² used for mapping investigator verbatim terms to preferred terms?	X			MedDRA 11.0
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			Considerable splitting found among the autonomic and behavioral side effects

¹ 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.

² 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			But “withdrawal of consent” narratives not provided and there is possibility that these follow commonly accepted AEs for this class.
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?		X		Data was reviewed from in vitro study; no in vivo ETOH study needed.
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (e.g., label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?		X		Module 1.9.1
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	Nothing to suggest biology of PD is different in different ethnic groups.
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			SDTM but not ADaM compliant
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X	X		Did not carry over from 22421 request for consistent USUBJID in analysis datasets
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			
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
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			But plan to request additional from some “withdrawal of consent cases”
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			Module 1.3.4
GOOD CLINICAL PRACTICE					
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			In final study reports for 246.524 and 246.525

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

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.

[Not applicable.]

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

1. In calculating exposure data for Mirapex ER, we have not always been able to know 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 data cut off date. Please complete this table for the following trials and create an analysis dataset that reflects the information for each unique USUBJID:

"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				
IR				

Study 248.524 Early PD		Open Label Study 248.633		
Placebo				
ER				
IR				

Study 248.525		Open Label Study 248.634		
Placebo				
ER				
IR				

2. For Studies 246.524 and 246.525, in all submitted analysis datasets that do not have one, create a variable USUBJID that corresponds to the PTNO for each subject.
3. For Studies 246.524 and 246.525, send the CRF and a brief narrative providing what information is available for each subject who ended participation in the trial due to withdrawal of consent, i.e. non AE related reasons.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

4. Provide updated datasets for all additional safety information at the time of the 4 Month Safety Update. Data should be pooled and identifiable by trial.
5. For Study 246.525, Site 63204, Quezon, Philippines, Roland Dominic Jamora is listed as PI. However, in the analysis and individual datasets (DM.xpt), the PI is identified as (b) (4). Please provide documentation of qualifications and certification of financial disclosure for this individual.

Kenneth Bergmann, MD	July 8, 2009
Reviewing Medical Officer	Date
Gerald David Podskalny, DO	July 8, 2009
Clinical Team Leader	Date

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this page is the manifestation of the electronic signature.**

/s/

Kenneth Bergmann
7/7/2009 04:00:28 PM
MEDICAL OFFICER

Gerald D Podskalny
7/16/2009 01:31:13 PM
MEDICAL OFFICER