5 Summary of the Safety Experience in the Pramipexole Development Program

5.1 General Comments

Overall, the pramipexole development program has included adequate short and long-term pramipexole use to evaluate its safety separately in ET and AT patients. There appears to have been enough experience at 4.5 mg per day, the maximum recommended dose, to evaluate the relative safety of that dose.

Follow-up of patients was good with few patients lost to follow-up. The clinical data provided was sufficient in most cases to describe the general character of most treatment emergent AEs.

On balance, there was little difference between pramipexole and placebo in the ET and AT patient populations. All cause study dropout risk for the ET patients was reported to be 14.4% in the pramipexole treated patients and 16.2% in the placebo, while 15.4% and 20.4%, respectively for the AT pateints. Dropout risk due to AEs for the ET patients was reported to be 11.9% in the pramipexole treated patients and 10.6% in the placebo, while 11.5% and 15.8%, respectively for the AT pateints. Dropout risk due to serious AEs for the ET patients was reported to be 2.1% in the pramipexole treated patients and 1.3% in the placebo, while 3.1% and 2.3%, respectively for the AT pateints. Serious AEs for the ET patients was reported at 5.1% in the pramipexole treated patients and 5.5% in the placebo, while 7.0% and 7.5%, respectively for the AT pateints. Mortality rate for the ET patients was reported at 0.34 in the pramipexole treated patients and 0.34 in the placebo, while 1.1% and 0.4, respectively for the AT pateints.

The events that were reported in more than 5% of pramipexole ET patients that were at least 2 times more frequent than in placebo were hallucinations and somnolence, while hallucinations and dry mouth in AT patients.

As a point of interest the OSH risk in the ET patients was reported at 7.7% in the pramipexole treated patients and 8.9% in the placebo, while 52.7% and 48.1%, respectively for the AT pateints. Risk for syncope in the ET patients was reported at 1.3% in the pramipexole treated patients and 0.9% in the placebo, while 1.5% and 2.7%, respectively for the AT pateints.

5.2 Cardiovascular System

In the preclinical studies, pramipexole lowered blood pressure and heart rate, especially in anesthetized animals. Results of experiments with antagonists indicated that the cardiovascular effects are related to the compound's main mechanism of action, (i.e., agonist at dopamine D2 receptors). This seems to be, however, primarily a first-dose effect. No (in rats) or little (in rhesus monkeys, especially after repeated doses) hypotensive

activity was found after oral administration to conscious animals. No interaction with l-deprenyl or L-dopa plus carbidopa could be observed on cardiovascular parameters.

In clinical pharmacology studies, pramipexole was associated with dose-related symptomatic orthostatic hypotension (OSH) in normal subjects beginning at the 0.2 mg dose and a dose-limiting phenomenon at a 0.4 mg/day dose in some studies. OSH occurred after the first dose in some volunteers and as early as 30 minutes at the highest doses. The duration of OSH varied from 1 hour or less to 8 hours, postural syncope occurred in some subjects. The magnitude of the drug-induced changes in standing blood pressure and pulse rate could not always be assessed because subjects were unable to stand for vital sign measurements. There were no clinically significant changes in ECG measurements during the evaluation periods.

In the phase 2/3 trials, there were exclusion criteria of not enrolling patients with active CV disease. The CV events that were most strongly associated with pramipexole use in the phase 1 trials were not consistent with findings in the phase 2/3 trials. In the ET studies, study dropouts and AE dropouts were similar in the pramipexole and placebo groups. Only one of the serious AE dropouts was CV in nature. There were 20 serious AEs reported in patients exposed to pramipexole and 7 were CV in nature, but none reported syncope or orthostatic hypotension. There were 5 syncopes reported in patients exposed to pramipexole and 2 in patients exposed to placebo.

In the AT studies, pramipexole was not associated with increases in study dropouts either overall or that associated with AEs. There was no clear pattern of AEs associated with dropouts. None of the 18 patients with serious AEs and exposed to pramipexole had syncope or orthostatic hypotension. There were 4 syncopes reported in patients exposed to pramipexole and 7 in patients exposed to placebo.

Overall, irrespective of severity there were 7 reports of dropouts due to the AE orthostatic hypotension in pramipexole treated patients in the combined ET, AT studies (1 and 6, respectively) compared with 3 reports in the placebo group in the combined ET, AT studies (0 and 3, respectively). Overall, there were few reports of symptomatic orthostatic hypotension, but two placebo and one pramipexole treated patients reported syncope as an AE and were discontinued. Of special interest is an ongoing double-blind, placebo-controlled study (protocol 55), where the CV effects of pramipexole in PD is being evaluated by performing the valsalva maneuver and tilt table testing.

ECG recordings in animals revealed bradycardia with a corresponding increase in the R-R interval. Other than bradycardia, there was no evidence in animals or humans that pramipexole affected cardiac conduction or was associated with dysrhythmias.

The 8 deaths that were potentially CV in nature, none could be attributed to any CV effect that pramipexole may have had.

In summary, the CV effects of OSH in healthy normal volunteers appear to result from the dopaminergic activity of pramipexole. Despite the benign clinical picture observed for pramipexole, we must keep in perspective its reported pharmacologic mechanism of action as a D_2 and alpha$_2$ agonist as well as the fact that in the studies, patients with significant underlying CV disease were excluded from participation. The CV effects of pramipexole may be detrimental in patients with advanced Parkinson's disease who may have impaired autonomic nervous system (Shy Drager Syndrome), impaired cardiovascular function, cardiovascular diseases which could be exacerbated by hypotension, in conditions such as hypovolemia and dehydration, and in conditions associated with abnormal early diastolic ventricular filling. Moreover, many elderly patients have resting cerebral blood flow that is close to the threshold for cerebral ischemia and thus, relatively small acute blood pressure reductions may produce cerebral ischemic symptoms such as dizziness, syncope, or falls.

5.3 Central Nervous System

In the animal studies, aside from behavioral changes, there were few significant CNS effects induced by acute treatment with pramipexole. The animal models demonstrated the sedating properties of pramipexole. At various ranges of dosing, ataxia was not reported. Pramipexole did not lower the threshold for seizures. Animal pharmacology studies to determine opiate-like activity for pramipexole were not performed, but there was no evidence of withdrawal.

Adverse events reported from the phase 1 studies were frequently related to the CNS (most frequently dizziness) and did not include any event not seen in phase 2/3 studies.

Reports of CNS AEs were more frequent in the AT group than in the ET group. The following events were considered drug-related in patients with early Parkinson's disease: hallucinations, somnolence, insomnia, and confusion. In the patients with advanced Parkinson's disease the following were considered drug-related: hallucinations, dyskinesia, and confusion. Parenthetically, M.V.A.s occurred in some patients treated with pramipexole and was attributed to somnolence.

There was no evidence of opiate - type withdrawal during the dose-reduction phase in the phase 2/3 studies.

In summary, the CNS adverse effects are known side effects of dopamine agonists. Pramipexole may exacerbate preexisting dyskinesia and potentiate the dopaminergic side effects of such drugs as levodopa.

5.4 Dermatological

There was no increase in the risk for rash. There were no hospitalizations for serious skin reactions in the pramipexole-treated patients.

5.5 Gastrointestinal

Preclinically, like other dopamine agonists, pramipexole induced emesis and the effect was blocked with a dopamine antagonist. Pramipexole inhibited gastrointestinal transit time, which in individuals older than 70 years of age may exacerbate an already existing situation. Nausea and vomiting were frequently reported in the Phase 1 studies. Two patients dropped out because of these events.

In phase 2/3, the AEs nausea and constipation featured prominently in the ET studies, but not in the AT. Other common causes of nausea, M.I.s and hepatitis were not reported in the patients who discontinued pramipexole use.

In summary, nausea as an AE should not be minimized. The potent influence of nausea on vasopressin release and subsequent antidiuretic effect is well established and may have important clinical consequences, particularly in the elderly P.D. patient.

5.6 Genitourinary/Renal

In animal studies, conflicting results were obtained in assessments of the renal effects of pramipexole in rats with respect to effect on urinary volume and electrolyte excretion. Contrasting effects were reported for pramipexole in conscious and anesthetized animals and may have been due to the anesthesia, dose, or strain of rats. The effectiveness of the D_1 antagonist against pramipexole suggest that the renal effects of pramipexole may be mediated by D_1 receptors. Noteworthy is the fact that both D_1 and D_2 receptors are associated with the renal vascular and tubular systems in humans. Moreover, $alpha_1$ receptors are found in the collecting tublules of humans.

In the Phase 1 studies, one pramipexole-treated patient dropped out because of renal colic. There were no reports of hyperuricemia or urinary crystals.

In the Phase 2/3 studies, twice as many AT pramipexole-treated patients reported genitourinary AEs than ET pramipexole-treated patients. There were no differences between the placebo groups. In the AT group, urinary frequency was reported by four times as many pramipexole-treated patients as ET pramipexole-treated patients. The placebo AT and the placebo ET groups were similar. A review of CRFs indicated the presence of calcium oxalate and uric acid crystals in some of the pramipexole treated patients, but these were not analyzed in the data presented by the sponsor and hence difficult to quantitate.

In summary, pramipexole is eliminated through the kidney and patients with renal insufficiency should be cautioned about dosing. Moreover, a normal serum creatinine level may mask renal dysfunction in frail older persons with low muscle mass. Creatinine clearance estimations may be a more useful measure of renal function in this age group of PD patients.

5.7 Hematologic

In animal studies, pramipexole was associated with thrombocytopenia in percent of female rats.

In phase 2/3 studies, there was one case of severe thrombocytopenia which appeared to have been caused by an immune mechanism possibly associated with pramipexole. Of note is the fact that other sulfa-containing drugs also have been implicated in acute thrombocytopenia.

5.8 Metabolic Endocrine

Serum prolactin was decreased in both animals and humans in the preclinical and Phase 1-3 studies during exposure to pramipexole. Dopamine agonists are known to influence the lactotrope and prolactin secretion.

Overall, in the ET and AT studies, dropouts were infrequent. Most of the dropouts were due to elevated CPK levels and occurred more frequently in the pramipexole than the placebo groups.

As discussed previously, more pramipexole-treated patients than placebo-treated patients had reports of CPK levels exceeding predefined limits. The fractionation of CPK was not usually carried out in the studies. Of the 19 reports of elevated CPKs in pramipexole-treated patients, 13 occurred in the ET protocols and 6 in the AT protocols. In the placebo groups, the distribution was 5 and 4, respectively for the above protocols. Dyskinesia did not appear to be a contributing factor to elevated CPKs in all cases.

In summary, CPK increases above baseline occurred in pramipexole and placebo-treated patients. Exposure adjusted rates (per 100 patient-years) were more than twice as high for pramipexole-treated patients compared with placebo. The increases in CPK levels were often preceded by changes in blood pressure and not always preceded by reports of physical over activity and/or excessive muscular exertion. In at least one pramipexole-treated patient, increases in CPK were associated with rhabdomyolysis.

5.9 Musculoskeletal

There was one case of rhabdomyolysis associated with pramipexole. Preclinically, there

were no reports of adverse events associated with this system.

5.10 Respiratory

Preclinically, there were no respiratory effects noted with pramipexole. In Phase 2/3 studies, there was no evidence of pulmonary fibrosis with pramipexole. Pulmonary fibrosis has been reported infrequently with dopamine agonists of different chemical structures. The present database had limited power to have detected any pulmonary fibrosis cases even assuming this condition can be diagnosed accurately.

There was an increase in respiratory AEs in the pramipexole AT patients compared with placebo, whereas the reverse was true in the ET patients. More AT pramipexole- treated patients reported respiratory AEs than ET pramipexole-treated patients. Once again, the reverse was true for the placebo-treated patients. AT pramipexole-treated patients may have been at greater risk for pneumonia. There were no reports of pneumonia in placebo or ET patients. Similarly, there were no reports of pneumonia in the preclinical data base.

5.11 Special Senses

Preclinically, retinal degeneration occurred in albino rats. There were no reports of similar ocular findings in humans. In the phase 2/3 trials a higher incidence of "vision abnormalities" were reported in the pramipexole treated patients. The investigator verbatims of these abnormalities included flashing light in eyes, visual disturbance, seeing spots, visual flickering, floaters, trouble reading small print, white comet shooting forward in front of eye and decreased visual acuity. Some of the reported AEs are possibly related to visual hallucinations. No special eye examinations were conducted on these patients.

6 Conclusion

Since, the overall tolerance and safety profile for pramipexole is good, from the safety point of view pramipexole is approvable. The adverse event profile for pramipexole was similar to that frequently seen with dopamine agonists. In the completed controlled studies in Parkinson's disease, adverse events in the nervous, digestive and cardiovascular systems were most common. Patients with advanced Parkinson's disease who were older and on concomitant levodopa therapy often had higher reporting frequencies of adverse events than the patients with early Parkinson's disease. The adverse events emerged more often during the dose-ascending phase. Overall, there were no distinguishing pattern of adverse events by age except for hallucinations (more frequently in pramipexole patients over 65 years of age). Overall, there were no distinguishing pattern of adverse events to separate males and females except of hallucinations (more frequent in females).

In the cardiovascular system reports of adverse events were times more frequent in the AT placebo and pramipexole-treated patients than in the ET placebo and pramipexole-treated

patients. Orthostatic hypotension was the most frequently reported CV adverse event in both the ET and AT groups and it was reported with several orders of magnitude more frequently in the AT patients than in the ET. It is important to note that, most of the reports of orthostatic hypotension in phase 2/3 were asymptomatic in contradistinction to the phase 1 trials. Pramipexole was not associated with an increased risk of syncope in either the ET or AT patients.

Across the ISS, the overall pramipexole mortality was 5 fold greater in AT compared to ET patients and 3 fold greater in AT compared to ET placebo treated patients. Five of 8 CV deaths occurred in the AT group. CV deaths might be expected from the advanced age of the patient population.

Significant, usually transient, elevations of serum enzymes such as CPK, GGT, AST and ALT occurred in pramipexole-treated patients. The laboratory abnormalities were rarely associated with clinical symptoms; however, rhabdomyolysis was reported in one pramipexole-treated patient who had markedly elevated CPKs. The relationship to pramipexole therapy is uncertain; the patient may have suffered from acute exertional rhabdomyolysis.

In conclusion,when the dose of pramipexole is slowly titrated and individualized to obtain optimum response, pramipexole is a safe treatment for patients with Parkinson's disease.

6.1 Suggested Follow-up Issues

(1) The sponsor should perform in vitro studies to determine the absence of phase I oxidative metabolism. Even in the absence of a P450 pathway, inhibition studies should be performed to evaluate potential drug-drug interactions.

(2) Explore the ET and AT database for the incidence of urinary crystals such as uric acid and calcium oxalate.

7 Labeling Recommendations

Clinical Pharmacology section:

(1) The sponsor should mention that pramipexole possesses alpha-two agonist activity.

(2) The claim that pramipexole reduces dopamine-induced neuronal degeneration is not based on scientific data and should be deleted.

Warnings section:

(1) The sponsor's claim in labeling that tolerance to the AE of orthostatic hypotension develops is not based on scientific evidence and should be deleted.

(2) The sponsor should mention that postural hypotension has been observed after the first dose of pramipexole in a few patients.

(3) The mention of hallucinations is appropriate, but it should be stressed that the elderly and possibly females seem to be at a higher risk.

Adverse Events section:

(1) The 1% table should be redone and two tables reflecting the ET and AT patient populations.

Other Adverse Events section:

(1) The sponsor should note the occurrence of rhabdomyolysis and thrombocytopenia under Rare events.

/S/

John D. Balian, M.D.

11/13/96
Date

APPEARS THIS WAY
ON ORIGINAL

/S/

James F. Knudsen, M.D., PhD

11/13/96
Date

Clinical Reviewers, Safety Group
Div. of Neuropharmacologic Drug Products

APPEARS THIS WAY
ON ORIGINAL

Orig. NDA 20-667
HFD-120 Div. File
HFD-120 GBurkhart\RKatz\KHiggins\JFeeney\JSherry\JKnudsen\JBalian

/S/ 11/6/96

APPEARS THIS WAY
ON ORIGINAL

Pages 59-99 are blank

Appendix 4.1.1 Table of All Pramipexole Studies

TUC Protocol No. Study Phase	Country/ No. Centers (per country)	Dates of Study Period (start - completion)	Study Design/Objectives	Treatment	Total Daily Dosage (mg/day)	Dosing Frequency	Duration of Study Treatment per Patient	Sample Size (N) per Treatment
Phase I - Clinical Pharmacology (Basic Pharmacokinetic Studies, Studies in Factors Affecting Pharmacokinetics, and Safety & Tolerance Studies)								
M/2730/0003 Phase I	United States: 1	8/93-10/93	Dose escalation of pramipexole in healthy volunteers: Evaluation of tolerance development to blood pressure and hormone effects	PPX PBO		q8h	7-15 days	24 PPX 12 PBO
M/2730/0023 Phase I	Switzerland: 1	8/90-8/91	A case control study to investigate the influence of varying single doses of pramipexole (SND 919 CL 2Y) measuring Parkinsonian symptoms with a tracking device in patients with advanced PD	PPX		Single dose	Single dose	3 PPX
M/2730/0025 Phase I	Germany: 1	1/88-3/88	Phase I tolerance and preliminary PK: single-dose, dose-escalating, placebo-controlled, double-blind, healthy volunteers	PPX PBO		Single dose	Single dose 2 doses per volunteer	15 PPX 9 PBO
M/2730/0026 Phase I	Germany: 1	5/88-6/88	Phase I tolerance and preliminary PK: multiple-dose, placebo-controlled, double-blind, healthy volunteers	PPX PBO	0.3	TID (q8h)	7 days	8 PPX 4 PBO

Appendix 4.1.1 Table of All Pramipexole Studies

TUC Protocol No. Study Phase	Country/ No. Centers (per country)	Dates of Study Period (start - completion)	Study Design/Objectives	Treatment	Total Daily Dosage (mg/day)	Dosing Frequency	Duration of Study Treatment per Patient	Sample Size (N) per Treatment
M/2730/0027 Phase I	Germany: 1	8/88-11/88	Phase I tolerance and preliminary PK: single-dose, placebo-controlled, double-blind, pharmacological effects (ie, hormone levels, psychopharmacological evaluations) healthy volunteers	PPX PBO		Single dose	Single dose 2-3 dose/volunteer	15 PPX 9 PBO

Abbreviations: BID=twice a day; BRC=bromocriptine; DOM=domperidone; FLU=fluphenazine; HAL=haloperidol; PER=perazine; IV=intravenous; PBO=Placebo (ie, vehicle); PD=Parkinson's disease; PK=pharmacokinetics; PPX=pramipexole; q6h=every 6 hours; q8h=every 8 hours; TID=three times a day.

Appendix 4.1.1 Table of All Pramipexole Studies

TUC Protocol No. Study Phase	Country/ No. Centers (per country)	Dates of Study Period (start - completion)	Study Design/Objectives	Treatment	Total Daily Dosage (mg/day)	Dosing Frequency	Duration of Study Treatment per Patient	Sample Size (N) per Treatment
M/2730/0028 Phase I	Germany: 1	6/88-7/88	A four-way crossover dose and time pharmacodynamic response study of pramipexole given orally as a single dose to healthy male volunteers	PPX PBO		Single dose	Single dose 4-way crossover	12 total
M/2730/0029 Phase I	Germany: 1	4/89-4/89	Phase I PK and bioavailability study: single-dose, open-label, 3-way crossover, healthy volunteers	PPX PPX PPX	0.1 (IV) 0.3 tablet 0.3 solution	Single dose	Single dose 3-way crossover	12 total
M/2730/0030 Phase I	Germany: 1	10/90-12/90	Phase I PK and metabolism of radiolabeled [^{14}C] PPX, single-dose, open-label, 2-way crossover, healthy volunteers	PPX PPX	0.1 (IV) 0.3 (oral solution)	Single dose	Single dose 2-way crossover	6 total
M/2730/0031 Phase I	Germany: 1	7/90-9/90	Phase I tolerability and PK study of transdermal PPX in healthy volunteers	PPX PBO Patch Study		Continuous transdermal application	14 days	10 PPX 6 PBO
M/2730/0047 Phase I	United States: 1	3/94-4/94	Phase I steady state PK study: multiple-dose, dose-escalating, open-label, healthy volunteers	PPX		Q8h	22 days	16

Abbreviations: BID=twice a day; BRC=bromocriptine; DOM=domperidone; FLU=fluphenazine; HAL=haloperidol; PER=perazine; IV=intravenous; PBO=Placebo (ie, vehicle); PD=Parkinson's disease; PK=pharmacokinetics; PPX=pramipexole; q6h=every 6 hours; q8h=every 8 hours; TID=three times a day.

Appendix 4.1.1 Table of All Pramipexole Studies

TUC Protocol No. Study Phase	Country/ No. Centers (per country)	Dates of Study Period (start - completion)	Study Design/Objectives	Treatment	Total Daily Dosage (mg/day)	Dosing Frequency	Duration of Study Treatment per Patient	Sample Size (N) per Treatment
M/2730/0051 Phase I	England: 1	6/94-11/94	Cardiovascular affects of pramipexole in healthy volunteers and for 0051 their antagonism by domperidone. Randomized, double-blind, four-way crossover, placebo-controlled study	PPX + PBO DOM + PBO PPX + DOM PBO + PBO	0.25 30 0.25 PPX + 30 DOM	Single dose	Single dose 4-way crossover	14 total
M/2730/0060 Phase I	United States: 1	11/94-ongoing	Phase I PK study in volunteers with impaired renal function: single-dose, open-label, parallel	PPX	0.25	Single dose	Single dose	26
M/2730/0061 Phase I	United States: 1	1/95-2/95	Phase I PK study: influence of probenecid and cimetidine on PPX PK, single-dose, 3-way crossover, healthy volunteers	PPX PPX + Probenecid PPX + Cimetidine	0.25 0.25 PPX + 2000 Probenecid 0.25 PPX + 1200 Cimetidine	Single dose PPX 1000 then 500 q6h 300 q6h	Single dose 3-way crossover 4 days 4 days	13 total
M/2730/0062 Phase I	Germany: 1	1/95-4/95	Phase I bioavailability study of clinical and final tablet formulations: 2 x 2 crossover, open-label, multiple-dose, healthy volunteers	PPX	0.375 excalating to 4.5	q8h	30 days	24 total

Appendix 4.1.1 Table of All Pramipexole Studies

TUC Protocol No. Study Phase	Country/ No. Centers (per country)	Dates of Study Period (start - completion)	Study Design/Objectives	Treatment	Total Daily Dosage (mg/day)	Dosing Frequency	Duration of Study Treatment per Patient	Sample Size (N) per Treatment
M/2730/0063 Phase I	United States: 1	2/95-3/95	Phase I PK study of PPX and carbidopa/levodopa: open-label, modified crossover, multiple-dose PPX, single-dose carbidopa/levodopa, healthy volunteers	PPX carbidopa / levodopa	25/250	q8h Single dose	20 days Single dose	10 total

Abbreviations: BID=twice a day; BRC=bromocriptine; DOM=domperidone; FLU=fluphenazine; HAL=haloperidol; PER=perazine; IV=intravenous; PBO=Placebo (ie, vehicle); PD=Parkinson's disease; PK=pharmacokinetics; PPX=pramipexole; q6h=every 6 hours; q8h=every 8 hours; TID=three times a day.

Appendix 4.1.1 Table of All Pramipexole Studies

TUC Protocol No. Study Phase	Country/ No. Centers (per country)	Dates of Study Period (start - completion)	Study Design/Objectives	Treatment	Total Daily Dosage (mg/day)	Dosing Frequency	Duration of Study Treatment per Patient	Sample Size (N) per Treatment
M/2730/0064 Phase I	United States: 1	3/95-3/95	Phase I PK evaluation of co-administration with selegiline: single-dose PPX, multiple-dose selegiline, 2-way crossover, open-label, healthy volunteers	PPX Selegiline	0.25 5	Single dose BID	Single dose 3 days	12 total
M/2730/0065 Phase I	England: 1	6/95-6/95	Phase I PK food interaction study; single-dose, open-label, 2-way crossover, healthy volunteers	PPX	0.25	Single dose	Single dose	12 total
M/2730/0069 Phase I	United States: 1	1/95-1/95	Phase I PK influence of age and gender on PPX PK: single-dose, open-label, healthy volunteers	PPX	0.25	Single dose	Single dose	38
M/2730/0073 Phase I Innovex: F=061 Basotherm GmbH No: IP-Nr 211.1)	Germany: 2	6/93-6/93	Study to investigate the tolerability of SND 919 CL eye drops (0.00625, 0.02, and 0.05%) in ascending order after single instillation into the eye of healthy volunteers	PPX PPX PPX PBO	1.8 µg 6 µg 15 µg	Single dose eye drops	Single dose	3 3 3 3
Parkinson's Disease Studies/Early								

Appendix 4.1.1 Table of All Pramipexole Studies

TUC Protocol No. Study Phase	Country/ No. Centers (per country)	Dates of Study Period (start - completion)	Study Design/Objectives	Treatment	Total Daily Dosage (mg/day)	Dosing Frequency	Duration of Study Treatment per Patient	Sample Size (N) per Treatment
M/2730/0001 Phase III	United States: 26	7/93-1/95	Double-blind, placebo-controlled, parallel-group comparison to assess the safety, tolerance, and efficacy of pramipexole in early Parkinson's disease (Part I) and to assess long term safety with open-label pramipexole (Part II)	PPX PBO		TID	up to 32 weeks	164 PPX 171 PBO
M/2730/0002 Phase III	United States: 26	1/94-ongoing	Multicenter, open-label study in pts with early PD	PPX		TID	up to 27 months	281 PPX

Abbreviations: BID=twice a day; BRC=bromocriptine; DOM=domperidone; FLU=fluphenazine; HAL=haloperidol; PER=perazine; IV=intravenous; PBO=Placebo (ie, vehicle); PD=Parkinson's disease; PK=pharmacokinetics; PPX=pramipexole; q6h=every 6 hours; q8h=every 8 hours; TID=three times a day.

APPEARS THIS WAY
ON ORIGINAL

Appendix 4.1.1 Table of All Pramipexole Studies

TUC Protocol No. Study Phase	Country/ No. Centers (per country)	Dates of Study Period (start - completion)	Study Design/Objectives	Treatment	Total Daily Dosage (mg/day)	Dosing Frequency	Duration of Study Treatment per Patient	Sample Size (N) per Treatment
M/2730/0004 Phase III	Canada: 5 United States: 15	3/94-12/94	Parallel group, placebo controlled, dose-response tolerability, safety and efficacy study of pramipexole in early Parkinson's disease	PPX PBO	1.5, 3, 4.5, 6	TID	11 weeks	213 PPX 51 PBO
M/2730/0005 Phase III	Austria: 2 Belgium: 2 Denmark: 3 Germany: 3 Italy: 9 Spain: 5 Sweden: 3 United Kingdom: 3	9/93-ongoing	A European double-blind, placebo-controlled, parallel-group comparison to assess the safety, tolerance, and efficacy of pramipexole in early Parkinson's disease (Part I) and to assess long term safety with open-label pramipexole (Part II)	PPX PBO		TID	up to 9 months	176 blinded
M/2730/0006 Phase III	Austria: 2 Belgium: 2 Denmark: 3 Germany: 3 Italy: 9 Spain: 5 Sweden: 3 United Kingdom: 3	2/94-ongoing	Open-label study (Follow-up to M/2730/0005)	PPX		TID	up to 29 months	41 PPX
M/2730/0016 Phase III	Canada: 5 United States: 15	6/94 - ongoing	Long term safety study of open-label pramipexole in early Parkinson's disease (extension of M/2730/0004 and M/2730/0017)	PPX		TID	up to 38 months	223 PPX
M/2730/0017 Phase II	United States: 4	3/91-7/92	An ascending dose tolerance and efficacy study of SND 919 in early Parkinson's disease	PPX PBO		TID	up to 11 weeks	28 PPX 27 PBO

Appendix 4.1.1 Table of All Pramipexole Studies

TUC Protocol No. Study Phase	Country/ No. Centers (per country)	Dates of Study Period (start - completion)	Study Design/Objectives	Treatment	Total Daily Dosage (mg/day)	Dosing Frequency	Duration of Study Treatment per Patient	Sample Size (N) per Treatment

Abbreviations: BID=twice a day; BRC=bromocriptine; DOM=domperidone; FLU=fluphenazine; HAL=haloperidol; PER=perazine; IV=intravenous; PBO=Placebo (ie, vehicle); PD=Parkinson's disease; PK=pharmacokinetics; PPX=pramipexole; q6h=every 6 hours; q8h=every 8 hours; TID=three times a day.

Appendix 4.1.1 Table of All Pramipexole Studies

TUC Protocol No. Study Phase	Country/ No. Centers (per country)	Dates of Study Period (start - completion)	Study Design/Objectives	Treatment	Total Daily Dosage (mg/day)	Dosing Frequency	Duration of Study Treatment per Patient	Sample Size (N) per Treatment
M/2730/0021 Phase II	England: 6	1/92-6/93	A study to assess the efficacy and safety of the maximally tolerated oral dose of SND 919 (pramipexole) in patients with early Parkinson's disease	PPX PBO		TID	up to 12 weeks	11 PPX 13 PBO
Parkinson's Disease Studies/Advanced								
M/2730/0010 Phase III	Canada: 4 United States: 22	6/93-1/95	Double-blind, placebo-controlled, parallel-group comparison to assess the safety, tolerance, and efficacy of pramipexole in advanced Parkinson's disease (0679) and to assess long-term safety with open-label pramipexole (0979)	PPX PBO		TID	up to 32 weeks	181 PPX 179 PBO
M/2730/0011 Phase III	Canada: 4 United States: 22	6/93 - ongoing	Long-term safety open-label study (Follow-up to M/2730/0010)	PPX		TID	up to 29 months	305 PPX
M/2730/0012 Phase III	Austria: 4 Denmark: 3 England: 8 France: 14 Germany: 18 Italy: 6 Scotland: 1	9/93 - ongoing	Double-blind, placebo-controlled, parallel-group comparison to assess the safety, tolerance, and efficacy of pramipexole in advanced Parkinson's disease (838.021) and to assess long-term safety with open-label pramipexole (838.022)	PPX PBO		TID	up to 32 weeks	236 blinded

Appendix 4.1.1 Table of All Pramipexole Studies

TUC Protocol No. Study Phase	Country/ No. Centers (per country)	Dates of Study Period (start - completion)	Study Design/Objectives	Treatment	Total Daily Dosage (mg/day)	Dosing Frequency	Duration of Study Treatment per Patient	Sample Size (N) per Treatment
M/2730/0013 Phase III	Austria: 4 Denmark: 3 England: 8 France: 14 Germany: 18 Italy: 6 Scotland: 1	6/94 - ongoing	Long-term safety open-label study (Follow-up to M/2730/0012)	PPX		TID	up to 29 months	88 PPX

Abbreviations: BID=twice a day; BRC=bromocriptine; DOM=domperidone; FLU=fluphenazine; HAL=haloperidol; PER=perazine; IV=intravenous; PBO=Placebo (ie, vehicle); PD=Parkinson's disease; PK=pharmacokinetics; PPX=pramipexole; q6h=every 6 hours; q8h=every 8 hours; TID=three times a day.

Appendix 4.1.1 Table of All Pramipexole Studies

TUC Protocol No. Study Phase	Country/ No. Centers (per country)	Dates of Study Period (start - completion)	Study Design/Objectives	Treatment	Total Daily Dosage (mg/day)	Dosing Frequency	Duration of Study Treatment per Patient	Sample Size (N) per Treatment
M/2730/0022 Phase II	Denmark: 9	9/90-6/92	A double-blind, placebo-controlled, randomized, multi-center study to assess the effects, safety and tolerance of SND 919 in advanced Parkinson's disease	PPX PBO		QID	up to 12 weeks	36 PPX 33 PBO
M/2730/0036 Phase III	Austria: 2 Canada: 12 Germany: 8 Netherlands: 4 Slovakia: 2 United Kingdom: 9	5/94-ongoing	A double-blind, placebo-controlled, randomized, multicenter trial to compare the safety, tolerance and efficacy of oral administration of pramipexole up to 4.5 mg and bromocriptine up to 30 mg in advanced Parkinson's disease	PPX PBO		TID	up to 9 months	124 blinded
M/2730/0055 Phase II	Italy: 1	9//94-12/95	A double-blind, placebo-controlled parallel-group study of the evaluation of some cardiovascular and biochemical effects of pramipexole in L-dopa stable responders in Parkinson's disease patients	PPX/PBO PPX + DOM PBO + DOM	0.25 0.25 + 20 0 + 20	Single dose TID	Single dose then 7-day repeated dose interval	6 blinded
Depression Studies								
M/2730/0037 Phase II	Germany: 2	12/93-ongoing	Tolerability of pramipexole in patients hospitalized for major depressive disorder. An open study to assess the maximum tolerated dose of pramipexole with repeated dosing	PPX		TID	up to 28 days	23 PPX

Appendix 4.1.1 Table of All Pramipexole Studies

TUC Protocol No. Study Phase	Country/ No. Centers (per country)	Dates of Study Period (start - completion)	Study Design/Objectives	Treatment	Total Daily Dosage (mg/day)	Dosing Frequency	Duration of Study Treatment per Patient	Sample Size (N) per Treatment
M/2730/0014 Phase II	Denmark: 8 Germany: 4 New Zealand: 1 Switzerland: 2	11/91-ongoing	An open, uncontrolled, multi-center study to assess the effects, safety and tolerability of SND 919 in advanced Parkinson's disease (1st follow-up study of study no. 838.033 in Switzerland, Austria, Germany; study no. 383.008 in Denmark; study no. 838.005 in New Zealand)	PPX		QID	up to 3 years	89
M/2730/0018 Phase II	United States: 6	5/91-11/92	An ascending dose tolerance and efficacy study of SND 919 in advanced Parkinson's disease	PPX PBO		TID	up to 11 weeks	26 PPX 24 PBO
M/2730/0019 Phase II	Austria: 1 Germany: 7 Switzerland: 2	2/91-8/92	A double-blind, placebo-controlled, randomized, multi-center study to assess the effects, safety and tolerance of SND 919 with concomitant treatment of levodopa (and decarboxylase-inhibitor) in advanced Parkinson's disease	PPX PBO		QID	up to 12 weeks	34 PPX 43 PBO
M/2730/0020 Phase II	New Zealand: 1	8/91-9/92	A double-blind, placebo-controlled, randomized, parallel-group study to assess the efficacy and safety of SND 919 in patients with advanced Parkinson's disease	PPX PBO		TID	up to 16 weeks	9 PPX 10 PBO

Abbreviations: BID=twice a day; BRC=bromocriptine; DOM=domperidone; FLU=fluphenazine; HAL=haloperidol; PER=perazine; IV=intravenous; PBO=Placebo (ie, vehicle); PD=Parkinson's disease; PK=pharmacokinetics; PPX=pramipexole; q6h=every 6 hours; q8h=every 8 hours; TID=three times a day.

Appendix 4.1.1 Table of All Pramipexole Studies

TUC Protocol No. Study Phase	Country/ No. Centers (per country)	Dates of Study Period (start - completion)	Study Design/Objectives	Treatment	Total Daily Dosage (mg/day)	Dosing Frequency	Duration of Study Treatment per Patient	Sample Size (N) per Treatment
M/2730/0022 Phase II	Denmark: 9	9/90-6/92	A double-blind, placebo-controlled, randomized, multi-center study to assess the effects, safety and tolerance of SND 919 in advanced Parkinson's disease	PPX PBO		QID	up to 12 weeks	36 PPX 33 PBO
M/2730/0036 Phase III	Austria: 2 Canada: 12 Germany: 8 Netherlands: 4 Slovakia: 2 United Kingdom: 9	5/94-ongoing	A double-blind, placebo-controlled, randomized, multicenter trial to compare the safety, tolerance and efficacy of oral administration of pramipexole up to 4.5 mg and bromocriptine up to 30 mg in advanced Parkinson's disease	PPX PBO		TID	up to 9 months	124 blinded
M/2730/0055 Phase II	Italy: 1	9//94-12/95	A double-blind, placebo-controlled parallel-group study of the evaluation of some cardiovascular and biochemical effects of pramipexole in L-dopa stable responders in Parkinson's disease patients	PPX/PBO PPX + DOM PBO + DOM	0.25 0.25 + 20 0 + 20	Single dose TID	Single dose then 7-day repeated dose interval	6 blinded
Depression Studies								
M/2730/0037 Phase II	Germany: 2	12/93-ongoing	Tolerability of pramipexole in patients hospitalized for major depressive disorder. An open study to assess the maximum tolerated dose of pramipexole with repeated dosing	PPX		TID	up to 28 days	23 PPX

Appendix 4.1.1 Table of All Pramipexole Studies

TUC Protocol No. Study Phase	Country/ No. Centers (per country)	Dates of Study Period (start - completion)	Study Design/Objectives	Treatment	Total Daily Dosage (mg/day)	Dosing Frequency	Duration of Study Treatment per Patient	Sample Size (N) per Treatment
M/2730/0043 Phase II	United States: 2	11/94-ongoing	Pramipexole in the treatment of outpatients with major depression: a dose response study	PPX PBO		BID	up to 9 weeks	30 blinded

Abbreviations: BID=twice a day; BRC=bromocriptine; DOM=domperidone; FLU=fluphenazine; HAL=haloperidol; PER=perazine; IV=intravenous; PBO=Placebo (ie, vehicle); PD=Parkinson's disease; PK=pharmacokinetics; PPX=pramipexole; q6h=every 6 hours; q8h=every 8 hours; TID=three times a day.

APPEARS THIS WAY
ON ORIGINAL

Appendix 4.1.1 Table of All Pramipexole Studies

TUC Protocol No. Study Phase	Country/ No. Centers (per country)	Dates of Study Period (start - completion)	Study Design/Objectives	Treatment	Total Daily Dosage (mg/day)	Dosing Frequency	Duration of Study Treatment per Patient	Sample Size (N) per Treatment
Schizophrenia Studies, Phase II								
M/2730/0007 Phase II	United States: 3	1/94- ongoing	Pilot trial of pramipexole in the treatment of tardive dyskinesia; single-blind	PPX		BID	up to 12 weeks	5 PPX
M/2730/0015 Phase II	Hungary: 4	1990-1992	Double-blind, randomized, PBO-controlled, preliminary safety and efficacy study in pts with schizophrenia (negative symptoms)	PPX PBO		TID	11 weeks	28 PPX 30 PBO
M/2730/0024 Phase II	France: 17	1991-1992	Double-blind, randomized, multicenter, clinical trial to explore the effects of pramipexole in three doses in patients with acute schizophrenia: a haloperidol-treated group control study	PPX HAL	15	TID	6 weeks	79 PPX 22 HAL
M/2730/0033 Phase II	Germany: 4	1989-1991	Efficacy and safety of pramipexole in patients with acute schizophrenic psychoses in an open, randomized study controlled by the usual antipsychotic treatment of the participating centers	PPX HAL PER FLU	30 600 15	TID	4 weeks	34 PPX 18 HAL 10 PER 1 FLU

Abbreviations: BID=twice a day; BRC=bromocriptine; DOM=domperidone; FLU=fluphenazine; HAL=haloperidol; PER=perazine; IV=intravenous; PBO=Placebo (ie, vehicle); PD=Parkinson's disease; PK=pharmacokinetics; PPX=pramipexole; q6h=every 6 hours; q8h=every 8 hours; TID=three times a day.

Appendix 4.1.1 Table of All Pramipexole Studies

TUC Protocol No. Study Phase	Country/ No. Centers (per country)	Dates of Study Period (start - completion)	Study Design/Objectives	Treatment	Total Daily Dosage (mg/day)	Dosing Frequency	Duration of Study Treatment per Patient	Sample Size (N) per Treatment
M/2730/0034 Phase II	Czechia: 2 Slovakia: 1	9/91-11/92	Double-blind, placebo- and haloperidol-controlled clinical study to determine the tolerability and effectiveness of pramipexole in acute exacerbations of schizophrenia (Protocol 837.009) Czech and Slovak Republics, M/2730/0034, Boehringer Ingelheim, Investigators: Vinar, Svestka, and Konikova)	PPX HAL PBO		TID	4 weeks	22 PPX 22 HAL 22 PBO
M/2730/0048 Phase II	Germany: 1	1990-1992	Double-blind, controlled clinical study to compare the safety and efficacy of pramipexole, haloperidol, and placebo in schizophrenic patients (Protocol 837.001 Germany, M/2730/0048, Boehringer Ingelheim, Investigators: Heinrich and Klieser)	PPX HAL PBO		TID	4 weeks	8 PPX 6 HAL 6 PBO
M/2730/0049 Phase II	Germany: 2	1991-1992	Double-blind, randomized multicenter clinical trial to compare the efficacy and tolerance of pramipexole in patients with schizophrenia characterized by a placebo-treated group	PPX PBO		TID	up to 12 weeks	5 PPX 4 PBO
M/2730/0050 Phase II	United States: 20	11/94-ongoing	Dose-response study in the treatment of negative symptoms of schizophrenia with pramipexole	PPX HAL	10	BID	up to 13 weeks	4 blinded

Appendix 4.1.1 Table of All Pramipexole Studies

TUC Protocol No. Study Phase	Country/ No. Centers (per country)	Dates of Study Period (start - completion)	Study Design/Objectives	Treatment	Total Daily Dosage (mg/day)	Dosing Frequency	Duration of Study Treatment per Patient	Sample Size (N) per Treatment

Abbreviations: BID=twice a day; BRC=bromocriptine; DOM=domperidone; FLU=fluphenazine; HAL=haloperidol; PER=perazine; IV=intravenous; PBO=Placebo (ie, vehicle); PD=Parkinson's disease; PK=pharmacokinetics; PPX=pramipexole; q6h=every 6 hours; q8h=every 8 hours; TID=three times a day.

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

Appendix 4.1.1 Table of All Pramipexole Studies

TUC Protocol No. Study Phase	Country/ No. Centers (per country)	Dates of Study Period (start - completion)	Study Design/Objectives	Treatment	Total Daily Dosage (mg/day)	Dosing Frequency	Duration of Study Treatment per Patient	Sample Size (N) per Treatment
M/2730/0067 Phase II	Austria: 2 Germany: 3	1/94-ongoing	An open-label, dose escalation study in schizophrenia in patients treated orally with pramipexole added to a maintenance therapy with haloperidol	PPX + HAL	PX + 5-20 HAL	BID	up to 28 days	5
M/2730/0079	Austria: 3	10/91-2/92	Double-blind, randomized, parallel-group, multicenter study to assess the efficacy and safety of three fixed doses of pramipexole and one dose of haloperidol in patients with acute exacerbations of schizophrenia.	PPX HAL	15	TID	up to 47 days	2 PPX 1 HAL

Abbreviations: BID=twice a day; BRC=bromocriptine; DOM=domperidone; FLU=fluphenazine; HAL=haloperidol; PER=perazine; IV=intravenous; PBO=Placebo (ie, vehicle); PD=Parkinson's disease; PK=pharmacokinetics; PPX=pramipexole; q6h=every 6 hours; q8h=every 8 hours; TID=three times a day.

Appendix 4.3.1

Demographics ET patiens (Protocols 1 and 4)			
Characteristic		Pramipexole	Placebo
Age (years)	N	377	222
	Mean +/- SD	62.6 +/- 10.49	61.6 +/- 11.61
	Range		
Weight (lbs)	N	364	220
	Mean +/- SD	170.8 +/- 34.17	166.8 +/- 35.18
	Range		
Sex	Male N (%)	243 (64)	130 (59)
	Female N (%)	134 (36)	92 (41)
Race	Caucasian N (%)	363 (96)	210 (95)
	Black N (%)	5 (1)	5 (2)
	Other N (%)	9 (2)	7 (3)

Demographics AT patiens (Protocol 10)			
Characteristic		Pramipexole	Placebo
Age (years)	N	181	178
	Mean +/- SD	63.4 +/- 9.70	63.2 +/- 9.60
	Range		
Weight (lbs)	N	181	178
	Mean +/- SD	162.6 +/- 31.43	160.6 +/- 36.13
	Range		
Sex	Male N (%)	119 (66)	115 (65)
	Female N (%)	62 (34)	63 (35)
Race	Caucasian N (%)	172 (95)	171 (96)
	Black N (%)	3 (2)	4 (2)
	Other N (%)	6 (3)	3 (2)

Demographics All Completed PD Studies (Protocols 1, 4, 10, and 17-22)			
Characteristic		Pramipexole	Placebo
Age (years)	N	701	550
	Mean +/- SD	62.8 +/- 9.99	62.2 +/- 10.25
	Range		
Weight (lbs)	N	687	546
	Mean +/- SD	166.4 +/- 32.78	163.5 +/- 34.9
	Range		
Sex	Male N (%)	452 (64)	348 (63)
	Female N (%)	250 (36)	203 (37)
Race	Caucasian N (%)	672 (96)	531 (96)
	Black N (%)	9 (1)	9 (2)
	Other N (%)	21 (3)	11 (2)

Appendix 4.6.1.1. Number of Patients and Estimated Person-Years in Patients with pramipexole Use up to 2 Years				
	Completed Trials		Completed + Ongoing Trials	
	N	Person-Years	N*	Person-Years
Phase I				
Healthy Volunteers+	250	--	276	--
PD Patients (0023)	3	--	3	--
Phase 2/3 (PD and Schizophrenia)				
All Patients@	879	274.37	1408	815.00**
0-24 Months	879	274.37	1349	662.32
>6-24 Months	286	175.87	543	488.84
>12-24 Months	0	--	178	223.96
All PD Patients#	702	258.78	1231	799.42**
0-24 Months	702	258.78	1172	646.74
>6-24 Months	286	175.87	543	488.84
>12-24 Months	0	--	178	223.96
ET Patients&	416	139.64	675	363.12
0-24 Months	416	139.64	675	363.12
>6-24 Months	137	84.66	312	269.98
>12-24 Months	0	--	91	113.82
AT Patients&&	286	119.14	556	436.30**
0-24 Months	286	119.14	497	283.62
>6-24 Months	149	91.21	231	218.86
>12-24 Months	0	--	87	110.14
Schizophrenia Patients!	177	15.59	177	15.59
0-24 Months	177	15.59	3	15.59
>6-24 Months	0	--	0	--
>12-24 Months	0	--	0	--

* Patients were counted only once

** Includes 59 AT pramipexole patients with continued use beyond 24 months (total of 34.68 additional PY)

+ All completed Studies are 3, 25, 26, 27, 28, 29, 30, 31, 47, 51, 61, 62,63, 64, 65, 69, and 73; one ongoing study (0060)

@ All completed studies are: 1,4, 10, 17, 18, 19, 20, 21, 22, 15, 24, 33, 34, 48, and 49; all open-label ongoing studies are: 2, 6, 11, 13, 14, and 16.

All AT + All ET studies

& All completed ET studies are 1, 4, 17, and 21; all open-label ongoing ET studies are 2, 6, and 16.

&& All completed AT studies are 10, 18, 19, 20, and 22; all open-label ongoing AT studies are 11, 13, and 14.

! All completed schizophrenia studies are 15, 24, 33, 34, 48, and 49.

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

Appendix 4.6.2.1

Duration of Exposure by Mean Dose
ET Patients (Protocols 1 and 4)

Mean Daily Dose (mg)	Number (%) of Patients Duration of Pramipexole Exposure in Weeks												
	0-<1	1-<2	2-<3	3-<4	4-<5	5-<6	6-<8	8-<12	12-<24	24-<36	36-<48	48 & up	Total
>0-1.5	3 (<1)	3 (<1)	6 (2)	5 (1)	5 (1)	1 (<1)	3 (<1)	55 (15)	0	14 (4)	0	0	95 (25)
>1.5-3.0	0	0	0	0	1 (<1)	2 (<1)	6 (2)	95 (25)	2 (<1)	12 (3)	0	0	118 (31)
>3.0-4.5	0	0	0	0	0	0	1 (<1)	41 (11)	8 (2)	107 (28)	6 (2)	0	163 (43)
>4.5-6.0	0	0	0	0	0	0	0	1 (<1)	0	0	0	0	1 (<1)
Total	3 (<1)	3 (<1)	6 (2)	5 (1)	6 (2)	3 (<1)	10 (3)	192 (51)	10 (3)	133 (35)	6 (2)	0	377

Duration of Exposure by Mean Dose
AT patients (Protocol 10)

Mean Daily Dose (mg)	Number (%) of Patients Duration of Pramipexole Exposure in Weeks												
	0-<1	1-<2	2-<3	3-<4	4-<5	5-<6	6-<8	8-<12	12-<24	24-<36	36-<48	48 & up	Total
>0-1.5	1 (<1)	1 (<1)	3 (2)	1 (<1)	2 (1)	1 (<1)	0	1 (<1)	1 (<1)	19 (10)	0	0	30 (17)
>1.5-3.0	0	0	0	0	0	2 (1)	3 (2)	4 (2)	6 (3)	27 (15)	0	0	42 (23)
>3.0-4.5	0	0	0	0	0	0	0	1 (<1)	4 (2)	100 (55)	4 (2)	0	109 (60)
>4.5-6.0	0	0	0	0	0	0	0	0	0	0	0	0	0
Total	1 (<1)	1 (<1)	3 (2)	1 (<1)	2 (1)	3 (2)	3 (2)	6 (3)	11 (6)	146 (81)	4 (2)	0	181

Duration of Exposure by Mean Dose
All Completed PD Studies (Protocols 1, 4, 10, and 17-22)

Mean Daily Dose (mg)	Number (%) of Patients Duration of Pramipexole Exposure in Weeks												
	0-<1	1-<2	2-<3	3-<4	4-<5	5-<6	6-<8	8-<12	12-<24	24-<36	36-<48	48 & up	Total
>0-1.5	6 (<1)	8 (1)	9 (1)	8 (1)	8 (1)	5 (<1)	5 (<1)	66 (9)	1 (<1)	33 (5)	0	0	149 (21)
>1.5-3.0	0	0	0	0	1 (<1)	4 (<1)	15 (2)	117 (17)	27 (4)	39 (6)	0	0	203 (29)
>3.0-4.5	0	0	0	0	0	0	1 (<1)	106 (15)	25 (4)	207 (29)	10 (1)	0	349 (50)
>4.5-6.0	0	0	0	0	0	0	0	1 (<1)	0	0	0	0	1 (<1)
Total	6 (<1)	8 (1)	9 (1)	8 (1)	9 (1)	9 (1)	21 (3)	290 (41)	53 (8)	279 (40)	10 (1)	0	702

Appendix 4.6.2.2

Duration of Exposure by Maximum Dose
ET Patients (Protocols 1 and 4)

Maximum Daily Dose (mg)	Number (%) of Patients — Duration of Pramipexole Exposure in Weeks												
	0-<1	1-<2	2-<3	3-<4	4-<5	5-<6	6-<8	8-<12	12-<24	24-<36	36-<48	48 & up	Total
>0-1.5	3 (<1)	3 (<1)	6 (2)	4 (1)	3 (<1)	0	3 (<1)	50 (13)	0	7 (2)	0	0	79 (21)
>1.5-3.0	0	0	0	1 (<1)	2 (<1)	1 (<1)	2 (<1)	52 (14)	1 (<1)	14 (4)	0	0	73 (19)
>3.0-4.5	0	0	0	0	1 (<1)	1 (<1)	2 (<1)	49 (13)	9 (2)	112 (30)	6 (2)	0	180 (48)
>4.5-6.0	0	0	0	0	0	1 (<1)	3 (<1)	41 (11)	0	0	0	0	45 (12)
Total	3 (<1)	3 (<1)	6 (2)	5 (1)	6 (2)	3 (<1)	10 (3)	192 (51)	10 (3)	133 (35)	6 (2)	0	377

Duration of Exposure by Maximum Dose
AT Patients (Protocol 10)

Maximum Daily Dose (mg)	Number (%) of Patients — Duration of Pramipexole Exposure in Weeks												
	0-<1	1-<2	2-<3	3-<4	4-<5	5-<6	6-<8	8-<12	12-<24	24-<36	36-<48	48 & up	Total
>0-1.5	1 (<1)	1 (<1)	3 (2)	1 (<1)	1 (<1)	0	0	1 (<1)	0	13 (7)	0	0	21 (12)
>1.5-3.0	0	0	0	0	1 (<1)	2 (1)	1 (<1)	2 (1)	3 (2)	20 (11)	0	0	29 (16)
>3.0-4.5	0	0	0	0	0	1 (<1)	2 (1)	3 (2)	8 (4)	113 (62)	4 (2)	0	131 (72)
>4.5-6.0	0	0	0	0	0	0	0	0	0	0	0	0	0
Total	1 (<1)	1 (<1)	3 (2)	1 (<1)	2 (1)	3 (2)	3 (2)	6 (3)	11 (6)	146 (81)	4 (2)	0	181

Duration of Exposure by Maximum Dose
All Completed PD Studies (Protocols 1, 4, 10, and 17-22)

Maximum Daily Dose (mg)	Number (%) of Patients — Duration of Pramipexole Exposure in Weeks												
	0-<1	1-<2	2-<3	3-<4	4-<5	5-<6	6-<8	8-<12	12-<24	24-<36	36-<48	48 & up	Total
>0-1.5	6 (<1)	8 (1)	9 (1)	7 (<1)	5 (<1)	3 (<1)	3 (<1)	57 (8)	0	20 (3)	0	0	118 (17)
>1.5-3.0	0	0	0	1 (<1)	3 (<1)	3 (<1)	10 (1)	63 (9)	8 (1)	34 (5)	0	0	122 (17)
>3.0-4.5	0	0	0	0	1 (<1)	2 (<1)	5 (<1)	98 (14)	31 (4)	225 (32)	10 (1)	0	372 (53)
>4.5-6.0	0	0	0	0	0	1 (<1)	3 (<1)	72 (10)	14 (2)	0	0	0	90 (13)
Total	6 (<1)	8 (1)	9 (1)	8 (1)	9 (1)	9 (1)	21 (3)	290 (41)	53 (8)	279 (40)	10 (1)	0	702

Appendix 4.7.1
Number (%) of Healthy Volunteers with Adverse Events in the Phase I Studies
AEs for Pramipexole (Alone) and Placebo (Alone) Treatments
AEs Occurring ≥ 1%

Body System & Event	Pramipexole[a] (N=240)	Placebo[b] (N=69)
Body as a Whole		
Headache	63(26%)	6(9%)
Asthenia	62(26%)	14(20%)
Pain abdominal	18(8%)	2(3%)
Pain	11(5%)	0(0%)
Chills	7(3%)	2(3%)
Infection	5(2%)	0(0%)
Malaise	5(2%)	0(0%)
Pain back	5(2%)	0(0%)
Abdomen enlarged	4(2%)	0(0%)
Pain chest	3(1%)	0(0%)
Injection site reaction	3(1%)	0(0%)
Cardiovascular		
Pallor	15(6%)	1(1%)
Hypotension postural	8(3%)	2(3%)
Vasodilatation	8(3%)	2(3%)
Palpitations	3(1%)	0(0%)
Syncope	3(1%)	0(0%)
Digestive		
Nausea	63(26%)	5(7%)
Anorexia	20(8%)	1(1%)
Vomiting	15(6%)	0(0%)
Constipation	12(5%)	0(0%)
Dyspepsia	12(5%)	0(0%)
Flatulence	11(5%)	1(1%)
Diarrhea	8(3%)	0(0%)
Dry mouth	4(2%)	1(1%)

[a] Healthy Volunteers included from Protocols M/2730/0003, 0025, 0026, 0027, 0028, 0029, 0030, 0031, 0047, 0051, 0061, 0062, 0064, 0065, 0069, 0073. Protocols 0023 (PD patients), 0060 (ongoing study) and 0063 (concomitant L-dopa) not included. AEs counted once per patient during pramipexole treatment.
[b] Healthy Volunteers included from Protocols M/2730/0003, 0025, 0026, 0027, 0028, 0031, 0051, 0073. AEs counted once per patient during placebo treatment.

Appendix 4.7.1
Number (%) of Healthy Volunteers with Adverse Events in the Phase I Studies
AEs for Pramipexole (Alone) and Placebo (Alone) Treatments
AEs Occurring ≥ 1%

Body System & Event	Pramipexole[a] (N=240)	Placebo[b] (N=69)
Nervous		
Dizziness	50(21%)	3(4%)
Nervousness	11(5%)	0(0%)
Insomnia	10(4%)	3(4%)
Somnolence	7(3%)	1(1%)
Concentration impaired	6(3%)	0(0%)
Agitation	5(2%)	0(0%)
Tremor	4(2%)	0(0%)
Confusion	3(1%)	1(1%)
Respiratory		
Rhinitis	15(6%)	5(7%)
Pharyngitis	6(3%)	2(3%)
Hiccups	3(1%)	0(0%)
Skin		
Sweating	23(10%)	0(0%)
Pruritus	10(4%)	5(7%)
Rash	5(2%)	1(1%)
Special Senses		
Vision abnormal	3(1%)	1(1%)
Urogenital		
Creatinine clearance dec.	10(4%)	0(0%)

[a] Healthy Volunteers included from Protocols M/2730/0003, 0025, 0026, 0027, 0028, 0029, 0030, 0031, 0047, 0051, 0061, 0062, 0064, 0065, 0069, 0073. Protocols 0023 (PD patients), 0060 (ongoing study) and 0063 (concomitant L-dopa) not included. AEs counted once per patient during pramipexole treatment.
[b] Healthy Volunteers included from Protocols M/2730/0003, 0025, 0026, 0027, 0028, 0031, 0051, 0073. AEs counted once per patient during placebo treatment.