Boehringer Ingelheim

CLINICAL TRIAL PROTOCOL

Document Number:		**c20307124-03**
EudraCTNo.: **EU Trial No:**	Not applicable	
BI Trial No.:	0248-0686	
BI Investigational Product(s):	Pramipexole dihydrochloride monohydrate	
Title:	A two- stage multicenter, open-label, randomized, active controlled parallel group study comparing the efficacy and safety of Pramipexole SR versus Pramipexole IR administered orally over an 18-week treatment on nocturnal symptoms in L-Dopa^{+} treated patients with advanced Parkinson's disease (PD)	
Lay Title:	The **SUSTAIN** study compares the effects of **S**ustained and immediate-release pramipexole on the noct**U**rnal **S**ymptoms of pa**T**ients with **A**dvanced Park**I**nso**N**'s diease who also take L-Dopa	
Clinical Phase:	IV	
Clinical Trial Leader:	Phone: Fax: Email:	
Coordinating Investigator:	Fax: Email: Phone: Fax: Email:	
Status:	Final Protocol (Revised Procotol based on global amendment 2)	
Version and Date:	**Version:**	**Date:**
	3.0	18 Dec 2018

CLINICAL TRIAL PROTOCOL SYNOPSIS

Company name	Boehringer Ingelheim
Finished product name	Pramipexole sustained release (SR)
Active ingredient name:	Pramipexole dihydrochloride monohydrate
Protocol date	30 Nov 2017
Revision date	18 Dec 2018
Trial number	0248-0686
Title of trial:	A two- stage multicenter, open-label, randomized, active controlled parallel group study comparing the efficacy and safety of Pramipexole SR versus Pramipexole IR administered orally over an 18-week treatment on nocturnal symptoms in L-Dopa^{+} treated patients with advanced Parkinson's disease (PD)
Coordinating Investigator:	Phone: Fax: Email: Phone: Fax: Email:
Trial site(s):	National multi-centre trial
Clinical phase:	IV
Objective(s):	Stage I: To explore the efficacy of Pramipexole SR versus Pramipexole IR (as measured by the change from baseline to week 18 in Parkinson's disease Sleep Scale 2nd version (PDSS-2) total score) in treating nocturnal symptoms in patients on L-Dopa^{+} with advanced PD. Stage II: To further evaluate or confirm the efficacy between Pramipexole SR versus Pramipexole IR (as measured by the change from baseline to week 18 in PDSS-2 total score) in treating nocturnal symptoms in patients on L-Dopa^{+} with advanced PD based on the results from Stage I.
Methodology:	A two-stage multicenter, open-label, randomized, active controlled parallel group study design with comparison of two groups over 18 weeks
Number of patients	Stage I: 86 randomized

entered:	Stage II: To be calculated based on the results from Stage I
Number of patients on each treatment:	Stage I: Pramipexole SR: 43; Pramipexole IR: 43 Stage II: To be calculated based on the results from Stage I Patients will be randomized into Pramipexole SR and Pramipexole IR treatments at a randomization ratio of 1:1.
Diagnosis :	Patients with idiopathic PD diagnosed
Main in- and exclusion criteria	• Patients diagnosed as idiopathic PD with at least 2 years' PD history, 30 years of age or older at time of diagnosis, with a modified Hoehn and Yahr stage of 2 to 4 at on-time. • They must have clinically relevant sleep disturbances (i.e. PDSS-2 total score $\geqslant$18 at baseline). • They must feel uncomfortable at night because they were unable to turn around in bed or move due to immobility (i.e. the scoring of question 9 in PDSS-2 $\geq$ 2 that means frequency is at least 2 to 3 days during the past week). • They must have early morning off (i.e. the frequency of "feeling like bodily movements are poor when you wake up?" is at least 2 to 3 days during the past week). • They must have motor fluctuations (at least 2 cumulative hours of off-time every day during waking hours, documented on a patient diary completed for 2 consecutive days before randomization visit). • Patients must be treated with L-Dopa^{+} (i.e. standard and/or sustained release Levodopa/DDC inhibitor), or with a combination of L-Dopa^{+} and entacapone, at an optimized dose according to investigator's judgement, this dose being stable for at least 4 weeks prior to randomization visit. • Patients must not have been treated with sustained release dopaminergic drug (i.e. sustained release Levodopa/DDC inhibitor) after supper, or any anti-PD medication after 9 pm within 4 weeks prior to randomization visit. • Patients must not have been treated with dopamine agonists within 4 weeks prior to randomization visit. 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 randomization visit and the investigator does not intend to change this treatment during the treatment phase): - anti-parkinsonian anticholinergics; - selegiline, rasagiline, or other MAO-B-Inhibitor; - amantadine; - entacapone (or other COMT-Inhibitor).
Test product(s):	Pramipexole SR (tablets of 0.375 mg, and 0.75 mg)
dose:	SR Dose: 0.375 mg, 0.75mg, 1.5mg, 2.25mg, 3.0mg, 3.75mg, or 4.5mg, once daily, at 7-9 pm before bedtime. The dose of Pramipexole SR should be titrated to an optimized level, to achieve a maximum therapeutic effect without intolerable side effects.
mode of administration:	oral (p.o.)
Comparator products:	Pramipexole IR (tablets of 0.25 mg, and 1.0 mg)
dose:	Tablets administered in equally divided doses three times per day to achieve a total daily dose of 0.375mg, 0.75mg, 1.5mg, 2.25mg, 3.0mg, 3.75mg, or 4.5mg, the third dose at 7-9 pm before bedtime.

	The dose of Pramipexole IR should be titrated to an optimized level, to achieve a maximum therapeutic effect without intolerable side effects.
mode of administration:	oral (p.o.)
Duration of treatment:	Seven-week flexible up-titration, followed by eleven-week maintenance phase and one-week down-titration (if applicable).
Endpoints	Primary efficacy endpoint(to be assessed at week 18): • PDSS-2 total score (change from baseline). Secondary efficacy endpoints (to be assessed at week 18): • Nocturnal Hypokinesia Questionnaire (NHQ) score (change from baseline) • SCOPA-Sleep score (change from baseline) • Early morning off (EMO) score (change from baseline) • Responder rate for PDSS-2 total score <18 • Responder rate for EMO score • The Parkinson's disease Questionnaire (PDQ)-8 score (change from baseline) • Responder rate for Clinical Global Impression of Improvement (CGI-I) • Responder rate for Patient Global Impression of Improvement (PGI-I) • Epworth Sleepiness Scale (ESS) score (change from baseline)
Safety criteria:	Physical examination, weight, vital signs, 12-Lead ECG, laboratory tests, adverse events, serious adverse events, and Modified Minnesota Impulsive Disorders Interview (MMIDI)
Statistical methods:	Stage I: Primary analysis: Restricted maximum likelihood (REML) - based repeated measures approach. Analyses will include the fixed, categorical effects of treatment, visit in the maintenance period, and treatment-by-visit interaction, as well as the continuous, fixed covariates of baseline and baseline-by-visit interaction. Secondary analysis: For continuous endpoints, the same method as the primary analysis will be used. For responder rates, logistic regression analyses will be performed with treatment and baseline (if baseline was measured) as the independent variables. Stage II: If the decision is continuing, the sample size for Stage II will be calculated based on the results of Stage I.

FLOW CHART[13]

Trial Period	**S[1]**	**R[1]**	**Flexible up-titration phase**							**Maintenance phase**			**Follow up visit after <down titration phase/EOT>**
Visit	V1	V2	TC1	V3	TC2	V4	TC3[11]	TC4[11]	TC5[11]	V5	V6	V7[2]	V8[2]
Week(s)	-2 to -1	0	1	2	3	4	5	6	7	8	12	18	Not applicable
Day(s)	-14 to -3	0	7	14	21	28	35	42	49	56	84	126	Last study dose +2
Time window for visits Day(s)	0	0	±2	±2	±2	±2	±2	±2	±2	±3	±3	±3	+3
Written Informed consent[3]	×												
Assign patient number	×												
Supply Trial identification card	×												
Demographics	×												
Medical history	×												
Review of In-/exclusion criteria	×	×											
Physical examination	×											×	
BP, Pulse, Weight, Height[4]	×	×		×		×				×	×	×	×
Check for abnormal behavior[7]				×		×					×		
MMIDI		×								×		×	×
MMSE	×												
Modified Hoehn and Yahr stage at on-time	×												
Randomization		×											
Instruct and supply patient diary	×												
Review patient diary		×											
EMO		×		×		×				×	×	×	

Trial Period	**S[1]**	**R[1]**	**Flexible up-titration phase**							**Maintenance phase**			**Follow up visit after <down titration phase/EOT>**
Visit	V1	V2	TC1	V3	TC2	V4	TC3[11]	TC4[11]	TC5[11]	V5	V6	V7[2]	V8[2]
Weeks	-2 to -1	0	1	2	3	4	5	6	7	8	12	18	Not applicable
Days	-14 to -3	0	7	14	21	28	35	42	49	56	84	126	Last study dose +2
Time window for visits Day(s)	0	0	±2	±2	±2	±2	±2	±2	±2	±3	±3	±3	+3
CGI-I						×				×		×	
PGI-I			×	×	×	×	×	×	×	×	×	×	
ESS		×		×		×				×	×	×	
PDSS-2		×		×		×				×	×	×	
NHQ		×		×		×				×	×	×	
SCOPA-Sleep		×		×		×				×	×	×	
PDQ-8		×								×		×	
Safety lab tests	×											×	×[8]
Urine Pregnancy test[9] (if applicable)	×											×	
12-lead ECG	×											×	×[8]
Dispense trial drugs		×		×		×				×	×	×	
Compliance check			×	×	×	×	×	×	×	×	×	×	×[6]
Concomitant therapy	×	×	×	×	×	×	×	×	×	×	×	×	×
Adverse events	×	×	×	×	×	×	×	×	×	×	×	×	×
Instruct and supply health economics questionnaire	×	×		×		×				×	×		
Review health economics questionnaire[10]		×		×		×				×	×	×	

1. Abbreviations are for “Screening” and “Randomization”.
2. All assessments planned at visit 7 and visit 8 have to be done even if a patient is prematurely withdrawn from the treatment phase. For visit 8, follow up visit after down-titration phase or follow up visit after EOT (end of treatment) should be conducted after the end of residual effect period (i.e., 2 days after the last study dose)
3. Re-consenting may become necessary when new relevant information becomes available and should be conducted according to the sponsor’s instructions.
4. Height will only be measured at Screening (visit 1).
5. At visit 7, for patients who want to enter a down-titration phase, study medication will be dispensed; for other patients who want to maintain their dosages, commercial Pramipexole IR/SR will be provided by themselves under the judgement of investigators.
6. At visit 8, check medication compliance during the down-titration phase if applicable.
7. In case the patient experiences any abnormal behavior, then the Modified MIDI sub-scale has to be completed.
8. To be done at visit 8 only if abnormal at visit 7.
9. Urine pregnancy test required for all women of child bearing potential. Pregnancy testing is one indicator of pregnancy. Changes in a subject’s menstrual cycle that may indicate pregnancy must also be considered and a further pregnancy test can be taken if the investigator feels it to be appropriate.
10. The health economics questionnaire should be completed when any health care resources utilized and any cost for PD from 4 weeks prior to randomization visit to week 18. The questionnaire should be reviewed by site staff at each on-site visit. (All protocol-driven visits shall not be included unless the additional medical resources and costs are consumed, such as registration, disease-related lab test/examination and prescriptions)
11. From TC3 to TC5, if pramipexole dose should be adjusted due to unsatisfactory efficacy or adverse event, on-site visit should be added to adjust dose.

13. The flow chart applies only to Patients enrolled in Stage I.

TABLE OF CONTENTS

ABBREVIATIONS

AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BI	Boehringer Ingelheim
CGI-I	Clinical Global Impression of Improvement
CI	Confidence Interval
CTL	Clinical Trial Leader
CTM	Clinical Trial Manager
CNS	Central Nervous System
COMT	Catechol-O-Methyltransferase
CRA	Clinical Research Associate
CRF	Case Report Form, paper or electronic (sometimes referred to as “eCRF”)
CRO	Contract Research Organisation
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
DB	Double-blind
DBL	Database Lock
DDC	Dopa-Decarboxylase
DS	Daytime sleepiness scale
EDC	Electronic Data Capture
ECDEU	Early Clinical Drug Evaluation Unit
ePRO	Electronic Patient Reported Outcome
EOT	End of Treatment
ESS	Epworth Sleepiness Scale
EMO	Early Morning Off
EU	European Union
EudraCT	European Clinical Trials Database
FAS	Full Analysis Set
FC	Flow Chart
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	Gamma Glutamyl transferase
IEC	Independent Ethics Committee
IR	Immediate Release
IRB	Institutional Review Board
ISF	Investigator Site File
LPDD	Last Patient Drug Discontinuation
L-Dopa	Levodopa
L-Dopa^{+}	Levodopa combined with a Dopa-Decarboxylase-inhibitor
MAO	Monoamine Oxydase
MCID	Minimal Clinically Important Difference

MedDRA	Medical Dictionary for Drug Regulatory Activities
MMSE	Mini-Mental State Examination
MMIDI	Modified Minnesota Impulsive Disorders Interview
NHQ	Nocturnal Hypokinesia Questionnaire
NIMP	Non-Investigational Medicinal Product
NS	Nighttime Scale
OL	Open Label
OPU	Operative Unit
PD	Parkinson's disease
PDQ	The Parkinson's disease Questionnaire
PDSS-2	Parkinson's disease Sleep Scale 2nd version
PGI-I	Patient Global Impression of Improvement
PK	Pharmacokinetics
p.o.	per os (oral)
PPX	Pramipexole
PPS	Per protocol set
q.d.	quaque die (once a day)
REP	Residual Effect Period
REML	Restricted maximum likelihood
ROP	Randomisation operator
SAE	Serious Adverse Event
SmPC	Summary of Product Characteristics
SR	Sustained Release
SUSAR	Suspected Unexpected Serious Adverse Reactions
TC	Telephone Call
t.i.d.	ter in die (3 times a day)
TS	Treated set
TSAP	Trial Statistical Analysis Plan
UPDRS	Unified Parkinson's disease Rating Scale
WHO	World Health Organization
WOCBP	Woman of childbearing potential

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

Parkinson's disease (PD) is a chronic degenerative disorder of the central nervous system, with slowly progressive degeneration of the nigrostriatal dopaminergic systems [R96-2351].

Classically, the symptoms are tremor, muscular rigidity and bradykinesia. The underlying Pathophysiology is a deficiency of dopamine in the basal ganglia [R96-2350].

The estimated incidence of Parkinson's disease is 4.5 to 16/ 100.000 persons/year and PD is associated with severe disability or death, which may be expected in 25% of patients within 5 years, in 65% of them within 10 years and in 80% of them within 15 years of onset [R02-2068].

The management of Parkinson's disease is specific for different stages: in early stages, the main objective is to reduce and/or delay the disease progression, while in advanced stages (after 5 to 7 years), the goal is to reduce and/or control functional disability, and improve quality of life.

In PD patients, sleep disturbances are very common, especially in patients with fluctuation undergoing long-term therapy. Sleep disturbances adversely affect quality of life, leading to considerable problems for patients as well as difficulties for caregivers [R17-4023].

Levodopa (combined with DDC (Dopa-Decarboxylase) inhibitor) is an effective symptomatic therapy of PD. However, motor complications are frequent and disabling after several years of treatment with Levodopa (L-Dopa) [P02-02651]. Motor complications involve fluctuations, erratic or unstable responses to medications (e.g. wearing-off phenomena) and dyskinesias or involuntary movements.

Dopamine agonists are used either in monotherapy for the treatment of PD in the early stage of the disease (as part of L-Dopa sparing strategy to delay as much as possible the occurrence of L-Dopa-related motor fluctuations) or in the later phase of the disease to lessen motor complications caused by L-Dopa. The beneficial effects of dopamine agonists used as adjuvant therapy in patients experiencing response fluctuations or diminished response to L-Dopa are well documented.

1.2 DRUG PROFILE

Pramipexole is a non-ergot dopamine agonist with high in vitro specificity at the D2 subfamily of dopamine receptors. Pramipexole is a full agonist and exhibits higher affinity to the D3 receptor subtypes than to D2 or D4 receptor subtypes.

Pramipexole immediate release (IR) tablets, administered three times per day (t.i.d.), are indicated for the treatment of signs and symptoms of either early or advanced Parkinson's

disease (PD), alone (without levodopa) or in combination with levodopa. They are marketed under the trade-name MIRAPEX®/MIRAPEXIN®/SIFROL®/ PEXOLA®. Pramipexole IR tablets were first authorised in the USA in 1997, followed by marketing authorisations in the European Union (EU), Iceland, Norway, Switzerland, Australia, New Zealand, Canada, Japan, Eastern European countries, South Africa, countries of the Near and Far East and South America.
In addition, Pramipexole IR tablets have been approved in April 2006 by the European Medicines Agency (EMA) and in November 2006 by the Food and Drug Administration (FDA) and in other countries (see above) for the treatment of moderate to severe primary Restless Legs Syndrome (RLS).

Boehringer Ingelheim has developed a sustained-release (SR) formulation of Pramipexole, that can be administered once daily (q.d.) for the treatment of signs and symptoms of idiopathic PD. This formulation showing a slower release of the active ingredient than that of the IR formulation will be beneficial to patients as it will allow patients to treat their symptoms with a single daily dose, instead of three doses per day, thereby increasing patient convenience and compliance.

Applications for Pramipexole SR for the treatment of PD have been submitted to the FDA and EMA in October 2008, followed by submission of applications in further countries since then. Pramipexole SR was approved in the EU for the treatment of early and advanced PD on 8 October 2009. Further marketing authorisations were obtained in Iceland, Norway, Switzerland, Australia, Canada, Eastern European countries, countries of the Near and Far East and South America.

Pramipexole SR was approved in the US for the treatment of early PD on 19 February 2010 and for the treatment of advanced PD on 19 March 2010.
The clinical trial data presented in the following is as of January 2010. In the meantime the two open label trials 248.633 & 248.634 and the open label part trial 248.610 have been finalized [U10-1624-01]. The overall patient number as well as the safety and efficacy evaluation of Pramipexole SR did not change.

In addition, one Phase I trial in Japanese healthy volunteers has been reported in September 2010 (248.677) [U10-2447-01]. Dose strength bioequivalence between the Pramipexole SR 1.5 mg x 1 tablet q.d. and Pramipexole SR 0.375 mg x 4 tablets q.d. in both fasted and fed conditions was proven. In addition, no food effect on the bioavailability of Pramipexole after administration of Pramipexole SR 1.5 mg tablet was observed in this trial. No specific concern was noted for safety profile of Pramipexole SR.

In China two registration trials started in 2010. The Phase I trial 248.665 had been initiated in December 2010, the Phase III trial 248.671 in August 2010. Both of the studies have been finished. Pramipexole SR was approved in China for the treatment of PD in August 2014.

Pharmacokinetic:

The pharmacokinetic properties of Pramipexole IR formulation are well established.

Additional pharmacokinetic (PK) properties for the SR formulation have been evaluated in four Phase I PK and bioavailability (BA) trials. In addition, the steady-state pharmacokinetics of Pramipexole SR tablets were evaluated in patients in the early PD trial 248.524 [U08-1904-01].

The absolute bioavailability of Pramipexole is greater than 90%, indicating that it is well absorbed and undergoes little presystemic metabolism [U92-0018, U91-0026]. In humans the protein binding of Pramipexole is very low (<20%) and the volume of distribution is large (400L). Pramipexole is metabolised in man only to a small extent [U92-0018].

Renal excretion of unchanged Pramipexole is the major route of elimination. Approximately 90% of a 14C labelled dose is excreted through the kidneys while less than 2% is found in the faeces. The total clearance of Pramipexole is approx. 500mL/min and the renal clearance is approx. 400mL/min. Its terminal half-life (t1/2) is about 8 hours in the young and about 12 hours in the elderly [U92-0018]. The terminal half-life does not change for the SR formulation.

In Phase I trials, Pramipexole SR tablets administered q.d. resulted in equivalent 24-hour exposure as Pramipexole IR tablet administered t.i.d., with about the same inter-individual variability. Dose proportionality was demonstrated for the final formulation of Pramipexole SR tablets over the entire dose range from 0.375 to 4.5 mg, [U07-1551]. The Pramipexole SR matrix tablet formulation given q.d. did, thus, fulfil all PK requirements to allow a replacement of the current IR tablet given t.i.d. Concomitant food intake did not affect the PK of Pramipexole SR in a clinically relevant way and did not result in any irregular release and absorption ("dose dumping") of Pramipexole [U06-1598-01] and [U07-1551]. Accordingly, in the Phase III studies, the drug could be taken with or without food. Food was not identified as a significant covariate in the early PD trial 248.524. There is no clinically relevant influence of age, gender, race, or concomitant medications (e.g. drugs affecting gastrointestinal motility or gastric pH, or antiacids) on the PK properties of Pramipexole SR [U08-1904-01].

Toxicology:

For the development of Pramipexole IR tablets for PD, a non-clinical safety program has been completed. Repeat-dose toxicity studies with Pramipexole did not show significant findings which would raise serious safety concerns for further clinical trials. The major findings in rodent and non-rodent species (mainly involving the Central Nervous System and, in the rat, the female reproductive system) were probably due to an exaggerated pharmacodynamic effect of Pramipexole in animals. No additional toxicological studies had been performed with the Pramipexole SR formulation.

Safety and tolerability:

The following adverse reactions are expected under the use of Pramipexole: abnormal behaviours (reflecting symptoms of impulse control disorders and compulsions) such as binge eating, compulsive shopping, hypersexuality and pathological gambling; abnormal dreams, amnesia, cardiac failure, confusion, constipation, delusion, dizziness, dyskinesia,

dyspnoea, fatigue, hallucinations, headache, hiccups, hyperkinesia, hyperphagia, hypotension, inappropriate antidiuretic hormone secretion, insomnia, libido disorders, nausea, paranoia, peripheral oedema, pneumonia, pruritus, rash and other hypersensitivity; restlessness, somnolence, sudden onset of sleep, syncope, visual impairment including diplopia, vision blurred and visual acuity reduced, vomiting, weight decrease including decreased appetite, weight increase, delirium, mania, antecollis, spasms.

Based on the analysis of pooled placebo-controlled trials, comprising a total of 1,778 Parkinson's disease patients on pramipexole and 1,297 patients on placebo, adverse drug reactions were frequently reported for both groups. 67% of patients on pramipexole and 54% of patients on placebo reported at least one adverse drug reaction.

The majority of adverse drug reactions usually start early in therapy and most tend to disappear even as therapy is continued.

Pramipexole IR

Early Parkinson's disease
In the three double-blind, placebo-controlled trials of patients with early Parkinson's disease, the most common adverse reactions (>5%) that were numerically more frequent in the group treated with pramipexole tablets were nausea, dizziness, somnolence, insomnia, constipation, asthenia, and hallucinations.

Approximately 12% of 388 patients with early Parkinson's disease and treated with pramipexole IR tablets who participated in the double-blind, placebo-controlled trials discontinued treatment due to adverse reactions compared with 11% of 235 patients who received placebo. The adverse reactions most commonly causing discontinuation of treatment were related to the nervous system (hallucinations [3.1% on pramipexole IR tablets vs 0.4% on placebo]; dizziness [2.1% on pramipexole IR tablets vs 1% on placebo]; somnolence [1.6% on pramipexole IR tablets vs 0% on placebo]; headache and confusion [1.3% and 1.0%, respectively, on pramipexole IR tablets vs 0% on placebo]) and gastrointestinal system (nausea [2.1% on pramipexole IR tablets vs 0.4% on placebo]).

In a fixed-dose study in early Parkinson's disease, occurrence of the following reactions increased in frequency as the dose increased over the range from 1.5 mg/day to 6 mg/day: postural hypotension, nausea, constipation, somnolence, and amnesia. The frequency of these reactions was generally 2-fold greater than placebo for pramipexole doses greater than 3 mg/day. The incidence of somnolence with pramipexole at a dose of 1.5 mg/day was comparable to that reported for placebo.

Advanced Parkinson's disease
In the four double-blind, placebo-controlled trials of patients with advanced Parkinson's disease, the most common adverse reactions (>5%) that were numerically more frequent in the group treated with pramipexole IR tablets and concomitant levodopa were postural (orthostatic) hypotension, dyskinesia, extrapyramidal syndrome, insomnia, dizziness, hallucinations, accidental injury, dream abnormalities, confusion, constipation, asthenia,

somnolence, dystonia, gait abnormality, hypertonia, dry mouth, amnesia, and urinary frequency.

Approximately 12% of 260 patients with advanced Parkinson's disease who received pramipexole IR tablets and concomitant levodopa in the double-blind, placebo-controlled trials discontinued treatment due to adverse reactions compared with 16% of 264 patients who received placebo and concomitant levodopa. The reactions most commonly causing discontinuation of treatment were related to the nervous system (hallucinations [2.7% on pramipexole IR tablets vs 0.4% on placebo]; dyskinesia [1.9% on pramipexole IR tablets vs 0.8% on placebo]) and cardiovascular system (postural [orthostatic] hypotension [2.3% on pramipexole IR tablets vs 1.1% on placebo]).

Pramipexole SR

Early Parkinson's disease
The most common adverse reactions (≥5% and more frequent than placebo) after 33 weeks of treatment with pramipexole SR tablets in the trial of early Parkinson’s disease patients were somnolence, nausea, constipation, dizziness, fatigue, hallucinations, dry mouth, spasms, and peripheral edema.
Twenty four of 223 (11%) patients treated with pramipexole SR tablets for 33 weeks discontinued treatment due to adverse reactions compared to 4 of 103 (4%) patients who received placebo and approximately 20 of 213 (9%) patients who received pramipexole IR tablets. The adverse reaction most commonly causing discontinuation of treatment with pramipexole SR tablets was nausea (2%).

A double-blind, randomized, parallel group trial evaluated the tolerability of an overnight switch from pramipexole IR tablets to pramipexole SR tablets at the same daily dose in 156 early Parkinson’s disease patients with or without levodopa. One of 104 patients switched from pramipexole IR tablets to pramipexole SR tablets discontinued due to adverse reactions (vertigo and nausea).

Advanced Parkinson's disease
The most common adverse reactions (≥5% and greater frequency than in placebo) during 18 weeks of treatment with pramipexole SR tablets in the trial of advanced Parkinson’s disease patients with concomitant levodopa were dyskinesia, nausea, constipation, hallucinations, headache, and anorexia.

Eight of 164 (5%) patients treated with pramipexole SR tablets for 18 weeks discontinued treatment due to adverse reactions compared to 7 of 178 (4%) patients who received placebo and 8 of 175 (5%) patients who received pramipexole IR tablets. The most common adverse reactions leading to discontinuation of treatment with pramipexole SR tablets were nausea (1%) and hallucination (1%).

Adverse reactions can initially occur in either the titration or maintenance phase. Some adverse reactions developed in pramipexole SR-treated patients during the titration phase and persisted (≥7 days) into the maintenance phase (i.e., pramipexole SR % - placebo % =

treatment difference ≥2%); persistent adverse reactions were dyskinesia and insomnia.

Efficacy:

In a placebo-controlled DB trial in early PD patients, superiority of Pramipexole SR over placebo was demonstrated at Week 18 on both the primary Unified Parkinson's disease Rating Scale ((UPDRS) II+III and the key secondary Clinical Global Impression of Improvement (CGI-I) and Patient Global Impression of Improvement (PGI-I) responder rates efficacy endpoints. Non-inferiority was demonstrated at Week 33 between Pramipexole SR and IR [U09-1232-03].

In a placebo-controlled DB trial in advanced PD patients, superiority of Pramipexole SR over placebo was demonstrated at Week 18 on both the primary and the key secondary (percentage off-time during waking hours) efficacy endpoints [U09-1270-04].

In both the above trials, maintenance of efficacy was shown in patients treated for 33 weeks. The efficacy of an overnight switch from Pramipexole IR to SR at the same daily dose was evaluated in a "switch" trial conducted in early PD patients. Of 103 patients randomised to Pramipexole SR, 87 (84.5%) were successfully switched (i.e. no worsening of the UPDRS Parts II+III score by more than 15% from baseline and no drug-related AEs leading to withdrawal) after a possible dose adaptation; 72 of 87 did not change the dose. An overnight switch from Pramipexole IR to SR at the same total daily dose can be recommended [U08-1964-01].

Lastly, long term maintenance of efficacy of Pramipexole SR in early and advanced PD patients was demonstrated after 32 weeks of treatment in the OL long-term extension trials 248.633 and 248.634. In addition, patients with advanced PD can be safely switched overnight from Pramipexole (PPX) IR to PPX SR at the same total daily dose, while maintaining efficacy [U10-1341-01] and [U10-1369-01].

1.3 RATIONALE FOR PERFORMING THE TRIAL

This is a two-stage, multicentre, open-label, randomized, active controlled parallel group study comparing the efficacy and safety of Pramipexole SR versus Pramipexole IR administered orally over an 18-week treatment on nocturnal symptoms in L-Dopa^{+} treated patients with advanced Parkinson's disease (PD).

As reported with other chronic disease, non-adherence of drug use (either mistimed doses or missed doses) is common in parkinsonian patients and may be responsible for failure to relieve symptoms or emergence of drug-related side effects [P04-06261]. Poorer compliance is associated significantly with taking more anti-parkinsonian tablets per day [P05-13388].

Sustained release formulations of several products for the treatment of Parkinson's disease have been approved for registration. Sustained release formulation of Pramipexole turned out to be beneficial to parkinsonian patients, by improving patients' convenience and compliance to the treatment.

Concentration of SR is higher than IR in the latter night (11 pm - 4 am on second day) if taking Pramipexole SR once daily after dinner and IR 3 times daily which may result in potential benefit on nocturnal symptoms.

The general aim of study stage I is to explore the efficacy of Pramipexole SR versus Pramipexole IR (as measured by the change from baseline to week 18 in Parkinson's disease Sleep Scale-2 (PDSS-2) total score) in treating nocturnal symptoms in patients on L-Dopa^{+} with advanced PD. The general aim of study stage II is to further evaluate or confirm the efficacy between Pramipexole SR versus Pramipexole IR (as measured by the change from baseline to week 18 in PDSS-2 total score) in treating nocturnal symptoms in patients on L-Dopa^{+} with advanced PD based on the results from Stage I.

Patients must be treated with L-Dopa^{+} (i.e. standard and/or sustained release Levodopa/DDC inhibitor), or with a combination of L-Dopa^{+} and entacapone, at an optimized dose according to investigator's judgment, this dose being stable for at least 4 weeks prior to randomization visit. Sustained release Levodopa/DDC inhibitor must not been used after supper within 4 weeks prior to randomization visit.

Pramipexole IR will be administered in equally divided doses 3 times per day and Pramipexole SR will be administered once daily at 7-9pm before bedtime. After a 1- to 2-week screening phase, patients will be randomized to one of the two treatment groups, with a balanced ratio of 1:1 (Pramipexole SR: Pramipexole IR). During the 7-week up-titration phase, the dose of study medication will be up-titrated until the optimal daily dose is reached. The degree of improvement will be based upon the clinical judgement of the investigator. At the end of this up-titration phase, patients will enter the 11-week maintenance phase. The maintenance dose of study medication will be the optimal daily dose reached at the end of the up-titration phase. Following the maintenance-phase, patients will enter a short dose reduction phase which can last for up to 7 days (depending on the daily dose administered during the maintenance-phase) or continue Pramipexole IR/SR treatment judged by investigators and patients with commercial supply at visit 7.The purposes of the dose-reduction phase are to gradually reduce the dose of Pramipexole, to prevent possible Adverse Events associated with rapid dose-reduction.

The primary efficacy endpoint used to evaluate the patient's treatment response will be PDSS-2 total score (change from baseline to the end of the maintenance period). Secondary efficacy endpoints and safety endpoints are described in Section 2.1 and 2.2.

1.4 BENEFIT - RISK ASSESSMENT

The efficacy and tolerability of both Pramipexole IR and SR have been demonstrated in both early [U95-0560; U95-0588; U00-0074; U09-1232-03] and advanced [U95-3150; U96-0232; U09-1270-04] PD trials. In addition, non-inferiority between Pramipexole SR and Pramipexole IR was demonstrated after 33 weeks of treatment in an international Phase III trial in patients with early PD, at similar mean total daily dose of Pramipexole and similar dose distribution in the two groups [U09-1232-03].

This study is designed to explore firstly, then further evaluate or confirm the efficacy between Pramipexole SR versus Pramipexole IR (as measure by PDSS-2 score) in Chinese PD patients.

A flexible up-titration design will be used in the trial, to allow each patient to be up-titrated until an optimal therapeutic response is achieved. The dose range for Pramipexole SR (from 0.375 mg to 4.5 mg per day) is identical to daily doses approved for Pramipexole IR [U04-1242-06] and to the dosing scheme used in previous international and local Phase III trials for the clinical development of Pramipexole SR [U09-1232-03] and [U09-1270-04].

Exclusion criteria have been defined in the trial according to the Pramipexole Summary of Products Characteristics (SmPC). At each study visit, adverse events will be elicited by asking the patients how they have felt since the last visit. The study duration and procedures do not expose the patients to any specific risk, as a treatment (Pramipexole SR or IR) will be given to all patients, and this treatment may be taken concomitantly to any other antiparkinsonian treatments (anti-parkinsonian anticholinergics, MAO-B-inhibitors, amantadine, entacapone, L-Dopa^{+}). In addition, patients and investigators may decide to discontinue the study at any time.

2. TRIAL OBJECTIVES AND ENDPOINTS

2.1 MAIN OBJECTIVES, PRIMARY AND SECONDARY ENDPOINTS

2.1.1 Main objectives

The main objective of the study is to explore firstly, then further evaluate or confirm the efficacy between Pramipexole SR versus Pramipexole IR on nocturnal symptoms (as measured by the change from baseline to the end of the maintenance period in PDSS-2 score) in L-dopa^{+} treated patients with advanced PD.

2.1.2 Primary endpoint(s)

The primary endpoint is the change from baseline to week 18 in PDSS-2 total score.

2.1.3 Secondary endpoint(s)

Secondary efficacy endpoints are (to be assessed at week 18):
- Nocturnal Hypokinesia Questionnaire (NHQ) score (change from baseline);
- SCOPA-Sleep score (change from baseline);
- Early Morning Off (EMO) score (change from baseline);
- Responder rate for PDSS-2 total score<18;
- Responder rate for EMO score;
- The Parkinson's disease Questionnaire (PDQ)-8 score (change from baseline);
- Responder rate for Clinical Global Impression of Improvement (CGI-I);
- Responder rate for Patient Global Impression of Improvement (PGI-I);
- Epworth Sleepiness Scale (ESS) score (change from baseline).

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

This is a two-stage, multicentre, open-label, randomized, active controlled parallel group to compare the efficacy and safety of Pramipexole SR versus Pramipexole IR administered orally for 18 weeks in Chinese patients with advanced Parkinson's disease (PD) treated with L-Dopa^{+}(i.e. standard and/or sustained release L-Dopa /DDC inhibitor). After a 2-week screening phase and a 7-week flexible up-titration phase, there will be an 11-week maintenance phase, followed by a 1-week down titration phase. Therefore, the trial can last for up to 21 weeks totally. Investigators in this study will be neurologists. More details about the administrative structure of the trial are given in the Investigator Site File (ISF). During the trial, there will be 8 visits and 5 telephone calls (see Flow Chart).

The stage I part of this trial will be conducted as a pilot study to explore the difference of change from baseline to week 18 in PDSS-2 total score between Pramipexole SR and IR. Stage II will be planned as a confirmatory or exploratory design. Stage I and II are totally separated, and the patients in Stage I will not be used in Stage II.

3.2 DISCUSSION OF TRIAL DESIGN, INCLUDING THE CHOICE OF CONTROL GROUP(S)

The trial will be conducted using a two-stage, open-label, randomized, active controlled parallel-group design.
The phase IV study was designed as two-stage due to the limited prior clinical evidences and the unclear deviations in the target population. Therefore, the Stage I was designed as a pilot to detect the signal. Based on the favorable results from Stage I, the Stage II will be continued for further confirmation or further evaluation.
There will be two treatment arms in this trial: Pramipexole SR as investigational medication, Pramipexole IR as an active control. Placebo won't be used in this study.
A double-blinded trial requires either over-encapsulation and subsequent equivalency testing be completed for two distinct packaging schema of the comparator (i.e. one Aluminium-aluminium blister in Pramipexole SR and three Aluminium-aluminium blisters-packaging in Pramipexole IR and unbalanced nature of different dose for each tablet between Pramipexole IR and Pramipexole SR). Therefore, this study will be conducted in an open-label fashion. But this study will use randomization to minimize the potential bias incorporated.

3.3 TRANSITION FROM STAGE I TO STAGE II

The guidance described in the Table 3.3:1 serves as decision making rules for transition to Stage II.

Table 3.3:1 Guidance for decision making for transition to Stage II

Scenarios	Result of primary endpoint in Stage I			Decision making for Stage II
	Clinical value		Statistics	
A	Achieve the minimal clinically important difference (MCID): The adjusted mean difference <= -3.44	AND	P<0.05	Stop
B	Achieve MCID The adjusted mean difference <= -3.44	AND	P>=0.05	Continue
C	Not achieve MCID The adjusted mean difference > -3.44	AND	Any P	Stop

NOTE: The adjusted mean difference is the primary analyse result of the primary endpoint.

In summary, there are 3 scenarios for decision making for transition to Stage II based on Stage I results as below,

- Scenario A - Stop upon achieving MCID[R17-4026] (i.e., the adjusted mean difference <= -3.44 at Stage I) and statistical significance (P<0.05);
- Scenario B - Continue upon achieving MCID (i.e., the adjusted mean difference <= -3.44 at Stage I) and no statistical significance (P>=0.05);
- Scenario C - Stop upon not achieving MCID (i.e., the adjusted mean difference > -3.44 at Stage I).

For Scenario B and C, the analysis results of Stage I in conjunction with other factors will be used to allow BI to make a joint decision on whether the benefit and risk support the continuation of the trial into Stage II. For example, in Scenario C, if there is another endpoint showing great benefit of SR, the trial may continue into Stage II with this endpoint as the primary endpoint.

3.4 SELECTION OF TRIAL POPULATION

A total of 86 eligible, male and female patients with advanced PD, Modified Hoehn and Yahr stages 2 to 4 at on-time with motor fluctuations and nocturnal symptoms (determined by PDSS-2 total score ≥18) will be randomized in stage I.
It is anticipated that approximately 102 patients will be screened and 86 eligible patients will be obtained for randomization in stage I (assuming a 15%-screening failure rate).
The sample size of stage II will be calculated based on the results from stage I.
Approximately 10 to 15 centers will be selected for the trial. Investigators who fail to enter at least one patient in the first three months after trial initiation at each center may be excluded from the further participation. If recruitment is delayed, additional centers can be recruited.

Screening of patients for this trial is competitive, i.e. screening for the trial will be stopped at all sites at the same time once a sufficient number of patients has been screened. Investigators will be notified about the screening completion and will then not be allowed to screen additional patients for this trial.
This clinical study can fulfill its objectives only if appropriate patients are enrolled. The following eligibility criteria are designed to select patients for whom Pramipexole treatment is considered appropriate. All relevant medical and non-medical conditions should be taken into consideration when deciding whether this protocol is suitable for a particular patient.
A log of all patients enrolled into the trial (i.e. who have signed the informed consent) will be maintained in the ISF at the investigational site irrespective of whether they have been treated with investigational product or not.

3.4.1 Main diagnosis for trial entry

Please refer to section 8.3.1 (Source Documents) for the documentation requirements pertaining to the in- and exclusion criteria.

3.4.2 Inclusion criteria

1. Male or female patient with advanced idiopathic PD confirmed by at least bradykinesia and one of the following signs: resting tremor, rigidity.
2. Diagnosed as Parkinson's disease, with at least 2 years' PD history.
3. Of age ≥ 30 years at time of diagnosis.
4. Modified Hoehn and Yahr stage of 2 to 4 at on-time.
5. They must have clinically relevant sleep disturbances (i.e. PDSS-2 total score ≥ 18 at baseline).
6. They must feel uncomfortable at night because they were unable to turn around in bed or move due to immobility (i.e. the scoring of question 9 in PDSS-2 ≥ 2, which means frequency is at least 2 to 3 days during the past week).
7. They must have early morning off (i.e. the frequency of "feeling like bodily movements are poor when you wake up?" is at least 2 to 3 days during the past week).
8. Patients must have motor fluctuations (at least 2 cumulative hours of off-time every day during waking hours, documented on a patient diary completed for 2 consecutive days before randomization visit).
9. Patients must be treated with L-Dopa^{+} (i.e. standard and/or sustained release Levodopa/DDC inhibitor), or with a combination of L-Dopa^{+} and entacapone, at an optimized dose according to investigator's judgment, this dose being stable for at least 4 weeks prior to randomization visit.
10. Patients must not have been treated with sustained release dopaminergic drug (i.e. sustained release Levodopa/DDC inhibitor) after supper, or any anti-PD medication after 9pm within 4 weeks prior to randomization visit.

11. Patients must not have been treated with dopamine agonists within 4 weeks prior to randomization visit. 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 randomization visit and the investigator does not intend to change this treatment during the treatment phase):

    - Anti-parkinsonian anticholinergics;
    - Selegiline, rasagiline, or other MAO-B-Inhibitor;
    - Amantadine;
    - Entacapone (or other COMT-Inhibitor).

12. Male or female patients. Women of childbearing potential (WOCBP)[1] and men able to father a child must be ready and able to use highly effective methods of birth control per ICH M3 (R2) that result in a low failure rate of less than 1% per year when used consistently and correctly. A list of contraception methods meeting these criteria is provided in the patient information.

13. Signed and dated written informed consent in accordance with ICH-GCP and local legislation prior to admission to the trial.

3.4.3 Exclusion criteria

1. Secondary parkinsonian syndromes due to drugs (e.g., metoclopramide, flunarizine), metabolic disorders (e.g., Wilson's disease), encephalitis or degenerative diseases (e.g., progressive supranuclear palsy).
2. Dementia, as defined by a Mini-Mental State Exam score < 24 at screening visit [R96-2656].
3. Any psychiatric disorder according to DSM-V Diagnostic and Statistical Manual of Mental Disorders, 5th edition criteria that could prevent compliance or completion of the study and/or put the patient at risk if he/she takes part in the study.
4. History of psychosis, except history of drug induced hallucinations (provided the investigator considers that participation to the trial would not represent a significant risk for the patient).
5. History of deep brain stimulation.
6. History of nucleus lesioning.
7. Clinically significant electrocardiogram (ECG) abnormalities at screening visit, according to investigator's judgement.
8. Clinically significant hypotension (i.e. supine systolic blood pressure < 90 mmHg) and/or symptomatic orthostatic hypotension (i.e. clinical symptoms of orthostatic hypotension

[1] A woman is considered of childbearing potential (WOCBP), i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile.
Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy.
Tubal ligation is NOT a method of permanent sterilisation.
A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

associated with a decline ≥ 20 mmHg in systolic blood pressure and a decline ≥ 10 mmHg in diastolic blood pressure, at 1 minute after standing compared with the previous supine systolic and diastolic blood pressure obtained after 5 minutes of quiet rest) at screening or randomization visit.

9. Major surgery (major according to the investigator's assessment) performed within 12 weeks prior to randomization or planned within 12 months after screening, e.g. hip replacement.
10. Any other clinically significant disease, whether treated or not, that could put the patient at risk or could prevent compliance or completion of the study.
11. Serious Sleep Apnea Hypopnea Syndrome (i.e. the scoring of question 15 in PDSS-2 ≥ 3, that means frequency is at least 4 to 5 days during the past week)
12. Any documented active or suspected malignancy or history of malignancy within 5 years prior to screening, except appropriately treated basal cell carcinoma of the skin or in situ carcinoma of uterine cervix.
13. Serum levels of AST (SGOT), ALT (SGPT), alkaline phosphatases or total bilirubin >2 ULN (on screening lab test).
14. Patients with a creatinine clearance < 50 mL/min (estimated by the local lab / the investigator using the Modification of Diet in Renal Disease (MDRD, please refer to Appendix 10.1), and calculated on screening lab test).
15. Any hypnotic medication within 4 weeks prior to the randomization visit (i.e. diazepam, clonazepam, estazolam, alprazolam, zolpidem, etc.).
16. Any medication (including intra-muscular formulations) with central dopaminergic antagonist activity within 4 weeks prior to the randomization visit (i.e. typical neuroleptics, atypical antipsychotics, reserpine, methyldopa, centrally-active antiemetics, etc.).
17. Any of the following drugs within 4 weeks prior to randomization visit: methylphenidate, cinnarizine, amphetamines.
18. Flunarizine within 3 months prior to randomization visit.
19. Known hypersensitivity to Pramipexole or its excipients.
20. Patients who must or wish to continue the intake of restricted medications (see section 4.2.2.1) or any drug considered likely to interfere with the safe conduct of the trial.
21. Previous enrolment in this trial.
22. Currently enrolled in another investigational device or drug trial, or less than 30 days since ending another investigational device or drug trial(s), or receiving other investigational treatment(s).
23. Chronic alcohol or drug abuse or any condition that, in the investigator's opinion, makes them an unreliable trial patient or unlikely to complete the trial.
24. Women who are pregnant, nursing, or who plan to become pregnant in the trial.

3.4.4 Withdrawal of patients from therapy or assessments

Patients may potentially be withdrawn from trial treatment or from the trial as a whole ("withdrawal of consent") with very different implications, please see sections 3.4.4.1 and 3.4.4.2 below.
Every effort should be made to keep the randomised patients in the trial: if possible on treatment, or at least to collect important trial data.
Measures to control the withdrawal rate include careful patient selection, appropriate explanation of the trial requirements and procedures prior to randomization, as well as the explanation of the consequences of withdrawal.
The decision to withdraw from trial treatment or from the whole trial as well as the reason must be documented in the patient files and Case Report Form (CRF).

3.4.4.1 Withdrawal from trial treatment

An individual patient is to be withdrawn from trial treatment if:

- The patient wants to withdraw from trial treatment, without the need to justify the decision.
- The patient needs to take concomitant drugs that interfere with the investigational product or other trial medication.
- The patient can no longer be treated with trial medication for other medical reasons (such as surgery, adverse events, other diseases, or pregnancy).
- The patient has repeatedly shown to be non-compliant with important trial procedures and, in the opinion of both, the investigator and sponsor representative, is not willing or able to stick to the trial requirements in the future.

Given the patient's agreement, the patient will undergo the procedures for early treatment discontinuation and follow up as outlined in the Flow Chart (FC) and section 6.2.2 and section 6.2.3. For all patients the reason for withdrawal from trial treatment (e.g. adverse events) must be recorded in the CRF. These data will be included in the trial database and reported.

3.4.4.2 Withdrawal of consent for trial participation

Patients may withdraw their consent for trial participation at any time without the need to justify the decision.
This will however mean that no further information may be collected for the purpose of the trial and negative implications for the scientific value may be the consequence. Furthermore it may mean that further patient follow up on safety cannot occur.
If a patient wants to withdraw consent, the investigator should explain the difference between treatment withdrawal and withdrawal of consent for trial participation and explain the options for continued follow up after withdrawal from trial treatment, please see section 3.4.4.1 above.

3.4.4.3 Discontinuation of the trial by the sponsor

Boehringer Ingelheim reserves the right to discontinue the trial overall or at a particular trial site at any time for the following reasons:

1. Failure to meet expected enrollment goals overall or at a particular trial site
2. Emergence of any efficacy/safety information invalidating the earlier positive benefit-risk-assessment that could significantly affect the continuation of the trial
3. Violation of GCP, the trial protocol, or the contract impairing the appropriate conduct of the trial

The investigator / the trial site will be reimbursed for reasonable expenses incurred in case of trial termination (except in case of the third reason).

4. TREATMENTS

4.1 INVESTIGATIONAL TREATMENTS

Pramipexole SR 0.375 mg and 0.75 mg tablets, Pramipexole IR 0.25 mg and 1.0 mg tablets will be supplied by Boehringer Ingelheim.

4.1.1 Identity of the Investigational Medicinal Products

Table 4.1.1: 1 Test product 1: Pramipexole SR

Substance:	Pramipexole dihydrochloride monohydrate
Pharmaceutical formulation:	Tablets
Source:	Boehringer Ingelheim Pharma GmbH & Co KG, Germany
Unit strength:	0.375 mg and 0.75mg
Posology	0.375 mg, 0.75mg, 1.5mg, 2.25mg, 3.0mg, 3.75mg, or 4.5mg, once daily, at 7-9 pm before bedtime
Route of administration:	Oral (p.o.)

Table 4.1.1: 2 Test product 2: Pramipexole IR

Substance:	Pramipexole dihydrochloride monohydrate
Pharmaceutical formulation:	Tablets
Source:	Boehringer Ingelheim Pharma GmbH & Co KG, Germany
Unit strength:	0.25 mg and 1.0 mg
Posology	0.375 mg, 0.75mg, 1.5mg, 2.25mg, 3.0mg, 3.75mg, or 4.5mg, 3 times daily, the third dose at 7-9pm before bedtime
Route of administration:	Oral (p.o.).

4.1.2 Selection of doses in the trial

The dosing schedule for this study follows the standard doses for Pramipexole.
Doses for this study used during the up-titration and the maintenance phase consist of the following seven dose levels:

Pramipexole SR 0.375 mg, 0.75 mg, 1.5 mg(0.75 mg*2), 2.25 mg (0.75 mg*3), 3.0 mg (0.75 mg *4), 3.75 mg (0.75 mg*5) or 4.5 mg (0.75 mg*6) at 7-9 pm before bedtime.

Pramipexole IR 0.375 mg (0.25mg*1/2 t.i.d.), 0.75 mg (0.25 mg t.i.d.), 1.5 mg (1.0mg*1/2 t.i.d.), 2.25 mg (1.0 mg *1/2 t.i.d. +1.0 mg *1/4mg t.i.d.), 3.0 mg (1.0 mg t.i.d.), 3.75 mg (1.0 mg t.i.d. + 1.0 mg *1/4mg t.i.d.), or 4.5 mg (1.0 mg t.i.d. + 1.0mg*1/2 t.i.d.)

During the 7-week up-titration phase, the need for up-titration will be assessed by the investigator at on-site visits and telephone contacts, based on efficacy (PGI-I) and tolerability. Between on-site visits, the investigator will contact the patient by phone call to check efficacy (PGI-I) and tolerability of the study treatment and, if necessary, decide if the dose level has to be up-titrated or down-titrated. The dose of study medication should be up titrated in all patients who are not at least “a little better” on the PGI-I. If the dose is not increased, the reason should be given by the investigator and recorded in the eCRF (e.g. dose not increased due to an Adverse Event). In case of dopaminergic side effects (dyskinesia, psychosis, etc.) during the up-titration phase, the investigator can reduce the level of the study medication to the previous dose level.

4.1.3 Method of assigning patients to treatment groups

After confirming that the patient meets all the eligibility criteria at Visit 2, the patient will be randomly assigned to SR or IR arm (with a randomization ratio of 1:1).
The randomization list will be carried out centrally using BI randomisation operator (ROP). Based on the randomization list, the external vendors will implement the assignment. The BI standard validated random number generating system will be used to generate the randomization list, which will be verified by an independent statistician who is not involved in the trial. The access to the randomization code will be supervised by the Clinical Trial Support Group. Any personnel directly involved in the conduct and analysis of the trial will have no access to the randomization schedule prior to the database lock.
The investigators will receive a manual describing how to communicate and implement the assignment with the support of the external vendor.

4.1.4 Drug assignment and administration of doses for each patient

The study consists of an 18-week, active treatment phase (up to a 7-week titration phase until optimal response, followed by an 11-week maintenance phase). At the end of the maintenance phase, patients who want to enter a down-titration phase, with a final visit to monitor tapering of the study medication. For other patients who want to maintain their

dosages, commercial Pramipexole IR/SR will be provided by themselves under the judgement of investigators.

Study site authorized personnel (registered in the investigator site file) will dispense the study medication during the on-site visits.
Pramipexole IR doses will be taken orally, in equally divided doses, three times per day with the third dose at 7-9 pm before bedtime, with a glass of water (approximately 150 mL) with or without food.
Pramipexole SR doses will be taken orally q.d. at 7-9 pm before bedtime. Each dose will be taken with a glass of water (approximately 150 mL) with or without food
Missed doses of IR will be skipped at any time.

Missed dose of SR should be taken within 12 hours after the regularly scheduled time. After 12 hours, the missed dose should be left out and the next dose should be taken on the following day at the next regularly scheduled time.

The dose level determined at the end of the titration phase will be maintained throughout the Maintenance Phase. Patients will use their last maintenance dose on the day of visit 7.

Patients who won't continue Pramipexole IR/SR treatment after trial completion will enter a down-titration phase on the day following Visit 7. Patients will take the taper medication during the week between visit 7 and follow-up visit 8. The medication dose will be reduced daily by one dose level. This tapering will take a maximum of six days (for patients treated with the highest dose level of 4.5 mg per day during the maintenance phase). Patients will return for a follow-up visit (visit 8) at last study dose + 2 days after visit 7 (at least 48 hours after the last study drug intake in the down titration phase).

Commercial Pramipexole IR/SR is allowed to be prescribed to patients at visit 7 in the judgement by investigators and patients. In this case, taper process is not applicable to those patients. However, all other procedures at visit 7 and visit 8 will be performed as no major changes, except for compliance check of taper medication.

4.1.5 Blinding and procedures for unblinding

4.1.5.1 Blinding

There will be no blinding as discussed in Section 3.2.

4.1.5.2 Unblinding and breaking the code

Not applicable.

4.1.6 Packaging, labelling, and re-supply

The investigational products will be provided by BI. For details of packaging and the description of the label, refer to the ISF.

IMPs will be packaged and labelled in accordance with the principles of Good Manufacturing Practice (GMP).Trial drug packages will have unique medication numbers which will be used for tracking purposes only. The medication numbers will not be linked to randomisation numbers.
Pramipexole SR will be supplied as film-coated tablets. Available dosage strength will be 0.375 mg and 0.75 mg. Tablets will be supplied in Aluminium-aluminium blister sealed with Aluminium plastic plate containing 10 tablets.
Pramipexole IR will be supplied as film-coated tablets. Available dosage strength will be 0.25 mg and 1.00 mg. Tablets will be supplied in Aluminium-aluminium blister sealed with Aluminium plastic plate containing 30 tablets.
Re-supply to the sites will be managed as manually. Study site authorized personnel and Clinical Research Associate (CRA) will monitor the IMP number in site and inform Clinical Trial Manager (CTM) for re-supply if the IMPs are inadequate.

4.1.7 Storage conditions

Trial medication, which will be provided by the sponsor, must be kept in a secure, limited access storage area under the storage conditions defined below until supplied/administered to patient. Temperature logs must be maintained to make certain that the drug supplies are stored at the correct temperature. In case temperature would be out of range, this has to be managed based on STORM document in ISF
Only authorized personnel as documented in the <Trial Staff List> form in the ISF may dispense medication to trial subjects. Receipt, usage and return of the trial medication must be documented on the respective forms in the ISF.

4.1.7.1 Storage conditions for IR

Store sealed below 30°C (86°F), away from light. Keep out of the reach of children.

4.1.7.2 Storage conditions for SR

Pramipexole SR must be store sealed in the room temperature. Keep out of the reach of children.

4.1.8 Drug accountability

The investigator and/or pharmacist and/or investigational drug storage manager will receive the investigational drugs delivered by the sponsor when the following requirements are fulfilled:

- Approval of the clinical trial protocol by the Institutional Review Board (IRB) / ethics committee,
- Availability of a signed and dated clinical trial contract between the sponsor and the investigational site,
- Approval/notification of the regulatory authority, e.g. competent authority,

- Availability of the curriculum vitae of the Principal Investigator,
- Availability of a signed and dated clinical trial protocol,

Investigational drugs are not allowed to be used outside the context of this protocol. They must not be forwarded to other investigators or clinics. The patients will be instructed to return to the study site all dispensed blister packs at each on-site visit, including unused and partially used study medication. The unused and partially used study medication will be returned to patients for treatment after drug accountability until the end of treatment.
The investigator and/or pharmacist and/or investigational drug storage manager must maintain records of the product's delivery to the trial site, the inventory at the site, the use by each patient, and the return to the sponsor or warehouse / drug distribution centre or alternative disposal of unused products. If applicable, the sponsor or warehouse / drug distribution centre will maintain records of the disposal.

These records will include dates, quantities, batch / serial numbers, expiry ('use- by') dates. The investigator / pharmacist / investigational drug storage manager will maintain records that document adequately that the patients were provided the doses specified by the Clinical Trial Protocol (CTP) and reconcile all investigational products received from the sponsor. At the time of return to the sponsor and/or appointed Contract Research Organisation (CRO), the investigator / pharmacist / investigational drug storage manager must verify that all unused or partially used drug supplies have been returned by the clinical trial patient and that no remaining supplies are in the investigator's possession.

4.2 OTHER TREATMENTS, EMERGENCY PROCEDURES, RESTRICTIONS

4.2.1 Other treatments and emergency procedures

- **L-Dopa$^+$ treatment:**

At study entry, patients must be treated with L-Dopa$^+$ (i.e. standard and/or sustained release Levodopa/DDC inhibitor), or with a combination of L-Dopa$^+$ and entacapone, at an optimized dose according to investigator's judgment, this dose being stable for at least 4 weeks prior to visit 2. While patients have to be on a stable dose of L-Dopa$^+$ prior visit 2 for at least 4 weeks, it is possible that the L-Dopa$^+$ dose may need to be adjusted with the addition of Pramipexole (SR or IR) during the trial.

- **Other Parkinson's disease treatments:**

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 randomization visit and the investigator does not intend to change this treatment during the treatment phase):
- Anti-parkinsonian anticholinergics;
- And/or selegiline, rasagiline, or other MAO-B-Inhibitor;
- And/or amantadine;
- And/or entacapone (or other COMT-Inhibitor).

The above list may not be exhaustive. In case another treatment is taken by the patient for his PD, a previous agreement should be given by the CTM before the patient can be enrolled in the trial.
Patients must not have been treated with sustained release dopaminergic drug (i.e. sustained release Levodopa/DDC inhibitor) after supper, or any anti-PD medication after 9 pm within 4 weeks prior to randomization visit.

The timing of administration as well as the doses of these treatments will have to remain stable during the treatment phase.

- **Other concomitant treatments:**

Other concomitant therapies that are not listed as restrictions will be allowed at the discretion of the investigator or sub-investigator. They should be limited to therapies essential for the care of the patient. The reason for use will be documented in the e-CRF.

- **Rescue medication**

There is no established antidote for overdose of a dopamine agonist. If signs of central nervous system stimulation are present, a neuroleptic agent may be indicated. Management of the overdose may require general supportive measures along with gastric lavage, intravenous fluids, and electrocardiogram monitoring. Haemodialysis has not been shown to be helpful.

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

The administration of any other dopamine agonists with the study medication will necessitate termination of the patient's participation in this study.

The following therapies must not be taken for the specified times prior to visit 2 and during the treatment phase:
- Dopamine agonist (including Pramipexole): at least 4 weeks,
- Any hypnotic medication (i.e. diazepam, clonazepam, estazolam, alprazolam, zolpidem, etc.): at least 4 weeks,
- Any medication with central dopaminergic antagonist activity (i.e. typical neuroleptics, atypical antipsychotics, reserpine, methyldopa, centrally-active antiemetics, etc.): at least 4 weeks,
- Flunarizine: at least 3 months,
- Methylphenidate: at least 4 weeks,
- Cinnarizine: at least 4 weeks,
- Amphetamines: at least 4 weeks,
- Any other investigational drugs: at least one month or five-times the half-life of the investigational drug (whichever is longer).

A previous treatment with Pramipexole IR/SR is allowed 4 weeks before visit 2, provided the treatment was not discontinued due to a serious/clinically significant drug related Adverse Event, according to investigator's judgement.

The above list is not exhaustive. If the investigator has used or if he/she intends to use similar drugs not specified above, he/she should contact the sponsor to confirm patient's participation to the trial / continuation in the trial.

4.2.2.2 Restrictions on diet and life style

Since somnolence is a frequent adverse event with potentially serious consequences, patients should neither drive a car nor engage in other potentially dangerous activities until they have gained sufficient experience with SIFROL® sustained release tablets and SIFROL® immediate release tablets to gauge whether or not it affects their mental and/or motor performance adversely.

4.2.2.3 Restrictions regarding women of childbearing potential

Women of childbearing potential must use the contraception methods described in the patient information.

4.3 TREATMENT COMPLIANCE

Patients are requested to bring all remaining trial medication including the empty package material with them at each visit. The investigator will be responsible for the assessment of patient compliance with study medication at each visit, by physical count of returned study medication. This information will be recorded and retained in the patient's record. Percent compliance will be calculated based on dose in mg.

Medication compliance should be between 80-120% inclusive, at every visit. Isolated episodes of compliance should be evaluated on a case-by-case basis, before arbitrary discontinuation of a patient for non-compliance. The investigator will be encouraged to counsel patients on the importance of taking study medication as directed at each visit. For trial evaluation, handling of non-compliant patients will be described in the Trial Statistical Analysis Plan (TSAP). Decisions regarding patient eligibility due to poor compliance will finally be determined at Blinded Report Planning Meetings (BRPM), which will occur prior to locking of the database.

5. ASSESSMENTS

5.1 ASSESSMENT OF EFFICACY

Refer to flow-chart and to Section 6 for a detailed time schedule for measurements.

Data analysis specifications for the observations mentioned below will be described in the statistical section (Section 7) or the TSAP.

Parkinson's disease Sleep Scale 2nd version (PDSS-2) [R04-0948]
The PDSS-2 consists of 15 questions about various sleep and nocturnal disturbances which are to be rated by the patients using one of five categories, from 0 (never) to 4 (very often). Patients will be asked to rate the severity of each question based on their experience during the past week (7 days) from 0 (Never) to 4 (Very often, that means 6 to 7 days a week). PDSS-2 total score ranges from 0 (no disturbance) to 60 (maximum nocturnal disturbance). There are three sub-scales from the three-factor solution, one comprising nocturnal movement-related problems (factor 1: "motor problems at night"), a second describing the disease specific symptoms (factor 2: "PD symptoms at night") and the third representing sleep specific disturbances (factor 3: "disturbed sleep"). A total score of ≥ 18 defines clinically relevant PD-specific sleep disturbances. According to previous study, any improvements in PDSS-2 less than −3.44 points can represent clinically important changes for the patients. That is to say, a minimal clinically important difference (MCID) of PDSS-2 [R17-4026] is -3.44 points.

Nocturnal Hypokinesia Questionnaire (NHQ)
The Nocturnal Hypokinesia Questionnaire is designed to assess hypokinesia symptoms in night in PD patients, composed of two sections. Section 1 is assessed by PD patients. There are four domains in section 1 to assess "turning over in bed", "getting out of bed", "parkinsonian motor symptoms" and "others" separately. The domains in section 2 are the same with it in section 1. Section 2 is assessed by spouses or caregivers who are with the patients during the night.

SCOPA-Sleep [R08-5312]
The SCOPA-Sleep is a short, self-rating scale designed to evaluate nocturnal sleep quality and daytime sleepiness in patients with PD. It is composed of three parts: a nighttime scale (NS), a single-item about perceived quality of nocturnal sleep, and a daytime sleepiness scale (DS) that includes an item about unexpected onset of sleep.
The NS is a five-item scale with four response options (0-not at all to 3-very much) that addresses nighttime disturbances that "occurred in the previous month". The five items include sleep initiation, sleep fragmentation, sleep efficiency, sleep duration, and early wakening. Total NS score runs from 0 to 15, with higher scores reflecting more severe problems. The additional "quality of sleep" question assesses the overall nighttime sleep quality on a seven-point scale (ranging from slept very well to slept very badly). This item is not included in the total NS score. The DS subscale evaluates daytime sleepiness, also in the past month, and includes six items with four response options, from 0 (never) to 3 (often), and a maximum total score of 18. These DS items are addressed to how often the patient fell

asleep unexpectedly, but in particular situations (while sitting quietly, watching TV or reading, talking to someone), had difficulty to remain awake, and self-perception of daytime sleepiness as a problem.

Early Morning Off (EMO) [P17-11335]
The EMO is measured by the question of "do you feel like your bodily movements are poor when you wake up?" Patients will answer this question according to frequency during the past one week by scoring from 0 ("never") to 4 ("very often" or "6 to 7 days a week"). EMO score should be rated before the first anti-PD drug taking in early morning, and within half an hour after waking up. The responder of EMO is the patient improved at least 1 comparing to his/her baseline condition.

Parkinson's disease Questionnaire (PDQ) -8 [R04-4222]
The PDQ-39 is a self-administered, disease specific measure of health status which covers eight dimensions of ill-health, and contains 39 questions. The 8 domains include:
- Mobility (e.g. fear of falling when walking): 10 items,
- Activities of daily living (e.g. difficulty cutting food): 6 items,
- Emotional well-being (e.g. feelings of isolation): 6 items,
- Stigma (e.g. social embarrassment): 4 items,
- Social support: 3 items,
- Cognition: 4 items,
- Communication: 3 items,
- Bodily discomfort: 3 items.

The PDQ-8, an 8 item self-report questionnaire derived from PDQ-39. Each item selected is the one most highly correlated with the overall domain score to which it contributes. The items were summed together and transformed onto a score from 0 to 100. The PDQ-8 has been shown to exhibit appropriate levels of reliability, validity and responsiveness.

Clinical Global Impression of Improvement (CGI-I) [R96-0188];
The CGI was developed by the Early Clinical Drug Evaluation Unit (ECDEU) of the National Institute of Mental Health as an independent, simple way for clinicians to make overall evaluations of a patient's central nervous system (CNS) disease status. The ratings were used initially in outpatients with various psychiatric disorders. The CGI-I will be rated (from 1: very much improved, to 7: very much worse) by the same evaluator to assess the overall status of Parkinson's disease, after interviewing the patient about the various aspects of the PD and after evaluating AE and concomitant treatments. The evaluator will complete the scale by comparing the patients' status during the past week to their baseline condition. The responder of CGI-I is the patient rated of any improvement (1 = Very much better, 2 = Much better, or 3 = A little better).

Patient Global Impression of Improvement (PGI-I) [R96-0188];
The PGI-I scale is a patient-rated instrument which will be used to measure the improvement (from 1: very much better, to 7: very much worse) of the patient's Parkinson disease symptoms throughout the study. Patients will complete the scale by comparing their status during the past week to their baseline condition. The responder of PGI-I is the patient rated of any improvement (1 = Very much better, 2 = Much better, or 3 = A little better).

Epworth Sleepiness Scale (ESS) [R97-0791];
The ESS is a patient-rated scale about how likely one is to fall asleep during situations as passive and inconsequential as "watching TV" to as active as "sitting and talking to someone" and as consequential as "in a car, while stopped for a few minutes in traffic." "Chance of dozing" is rated as an integer from 0 (no chance) to 3 (high).

5.2 ASSESSMENT OF SAFETY

5.2.1 Physical examination

A complete physical examination will be performed at the time points specified in the flowchart. It includes at a minimum general appearance, neck, lungs, cardiovascular system, abdomen, extremities, and skin.
Measurement of height and body weight will be performed at the time points specified in the flowchart.
The results must be included in the source documents available at the site.

5.2.2 Vital signs

Vital signs will be evaluated at the time points specified in the flowchart, prior to blood sampling.
Vital signs (supine and standing systolic and diastolic blood pressure and pulse rate) and weight will be measured throughout the study. The blood pressure and pulse rate will be determined after 5 minutes of quiet rest in supine position and after 1 minute in the standing position. The incidence of symptomatic and asymptomatic orthostatic hypotension will also be tabulated for each visit. Symptomatic orthostatic hypotension should be recorded as an Adverse Event (AE).

5.2.3 Safety laboratory parameters

Safety laboratory parameters to be assessed are listed in Table 5.2.3:1. For the sampling time points please see the flow chart.

All analyses will be performed by the local laboratory of each site, and the respective reference ranges will be collected and filed in the ISF.
Patients have to be fasted for the blood sampling for the safety laboratory.

It is the responsibility of the investigator to evaluate the laboratory reports. The significant abnormality as judged by the investigator will be reported as adverse events (please refer to Section 5.2.6).

Table 5.2.3:1 Safety laboratory tests

Category Test name	Category Test name
Haematology	Haematocrit, haemoglobin, 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.

5.2.4 Electrocardiogram

The 12-lead ECGs will be recorded as scheduled in the flowchart. The investigator or a designee will evaluate whether the ECG is normal or abnormal and whether it is clinically relevant, if abnormal. ECGs may be repeated for quality reasons and the repeated recording used for study.
Additional ECGs may be recorded for safety reasons. Dated and signed printouts of ECG with findings should be documented in patient's medical record.
Clinically relevant abnormal findings will be reported either as baseline condition (if identified at the screening visit) or otherwise as adverse events and will be followed up and/or treated as medically appropriate.

5.2.5 Other safety parameters

Modified Minnesota Impulsive Disorders Interview (MMIDI) [R06-1142].

The MMIDI is a semi-structured clinical interview designed to assess a number of impulse control disorders. This scale will be completed to evaluate impulse control disorders which

may potentially occur in patients treated with Pramipexole. The instrument has been modified by Boehringer-Ingelheim to focus on compulsive behaviours which may occur in this patient population (pathological gambling, compulsive buying and compulsive sexual behaviour). The other behaviours included in the MMIDI will not be assessed.
The MMIDI asks a series of questions to the patient and tabulates the total score as a measure of the probability for impulsivity. Each item is scored either "No" or "Yes".
The MMIDI will be completed at visit 2 (week 0), visit 5 (week 8), visit 7 (week 18) and visit 8 (follow-up). In case the patient experiences any abnormal behavior at visit 3 (week 2), visit 4 (week 4) and visit 6 (week 12), then the Modified MIDI sub-scale has to be completed. In addition, at each other on-site visit, the investigator will ask the patient the following question: "Since the last visit, did you experience any of the following abnormal behaviours: Pathological gambling? Compulsive buying? Compulsive sexual behavior?" In case any of these questions is answered "Yes", then MMIDI interview for relevant sub-scale(s) will be performed.

5.2.6 Assessment of adverse events

5.2.6.1 Definitions of AEs

Adverse event
An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Serious adverse event
A serious adverse event (SAE) is defined as any AE which fulfils at least one of the following criteria:

- results in death,
- is life-threatening, which refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if more severe.
- requires inpatient hospitalisation or
- requires prolongation of existing hospitalisation,
- results in persistent or significant disability or incapacity, or
- is a congenital anomaly / birth defect,
  or
- is deemed serious for any other reason if it is an important medical event when based on appropriate medical judgement which may jeopardise the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation or development of dependency or abuse.

AEs considered "Always Serious"
Cancers of new histology and exacerbations of existing cancer must be classified as a serious event regardless of the duration between discontinuation of the drug and must be reported as described in 5.2.6.2, subsections "AE Collection" and AE reporting to sponsor and timelines"
In accordance with the European Medicines Agency initiative on Important Medical Events, Boehringer Ingelheim has set up a list of further AEs, which by their nature, can always be considered to be "serious" even though they may not have met the criteria of an SAE as defined above.
The latest list of "Always Serious AEs" can be found in the Electronic Data Capture (EDC) system. These events should always be reported as SAEs as described above.

Adverse events of special interest (AESIs)
The term AESI relates to any specific AE that has been identified at the project level as being of particular concern for prospective safety monitoring and safety assessment within this trial, e.g. the potential for AEs based on knowledge from other compounds in the same class.
AESIs need to be reported to the sponsor's Pharmacovigilance Department within the same timeframe that applies to SAEs, please see above.

No AESIs have been defined for this trial.

Intensity (severity) of AEs
The intensity (severity) of the AE should be judged based on the following:

Mild:	Awareness of sign(s) or symptom(s) that is/are easily tolerated
Moderate:	Sufficient discomfort to cause interference with usual activity
Severe:	Incapacitating or causing inability to work or to perform usual activities

Causal relationship of AEs
Medical judgement should be used to determine the relationship, considering all relevant factors, including pattern of reaction, temporal relationship, de-challenge or re-challenge, confounding factors such as concomitant medication, concomitant diseases and relevant history.

Arguments that may suggest that there is a reasonable possibility of a causal relationship could be:

- The event is consistent with the known pharmacology of the drug.
- The event is known to be caused by or attributed to the drug class.
- A plausible time to onset of the event relative to the time of drug exposure.
- Evidence that the event is reproducible when the drug is re-introduced
- No medically sound alternative aetiologies that could explain the event (e.g. pre-existing or concomitant diseases, or co-medications).
- The event is typically drug-related and infrequent in the general population not exposed to drugs (e.g. Stevens-Johnson syndrome).
- An indication of dose-response (i.e. greater effect size if the dose is increased, smaller effect size if dose is diminished).

Arguments that may suggest that there is no reasonable possibility of a causal relationship could be:

- No plausible time to onset of the event relative to the time of drug exposure is evident (e.g. pre-treatment cases, diagnosis of cancer or chronic disease within days / weeks of drug administration; an allergic reaction weeks after discontinuation of the drug concerned)
- Continuation of the event despite the withdrawal of the medication, taking into account the pharmacological properties of the compound (e.g. after 5 half-lives). Of note, this criterion may not be applicable to events whose time course is prolonged despite removing the original trigger.
- Additional arguments amongst those stated before, like alternative explanation (e.g. situations where other drugs or underlying diseases appear to provide a more likely explanation for the observed event than the drug concerned).
- Disappearance of the event even though the trial drug treatment continues or remains unchanged.

5.2.6.2 Adverse event collection and reporting

AE Collection

The investigator shall maintain and keep detailed records of all AEs in the patient files.

The following must be collected and documented on the appropriate CRF(s) by the investigator:

- From signing the informed consent onwards until the individual patient's end of trial:
  -all AEs (serious and non-serious).
- After the individual patient's end of trial:
  the investigator does not need to actively monitor the patient for AEs but should only report related SAEs of which the investigator may become aware of by any means of communication, e.g. phone call. Those AEs should however, not be reported in the CRF.

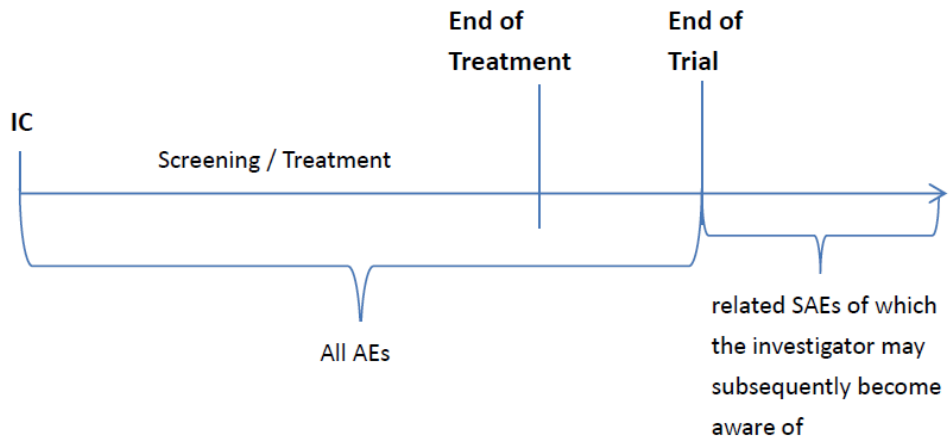

Figure 5.2.6.2: 1 adverse event collection and reporting

AE reporting to sponsor and timelines
The investigator must report SAEs and non-serious AEs which are relevant for the reported SAE, on the BI SAE form via fax immediately (within 24 hours) to the sponsor's unique entry point and local PV China (country specific contact details will be provided in the ISF). The same timeline applies if follow-up information becomes available. In specific occasions the investigator could inform the sponsor upfront via telephone. This does not replace the requirement to complete and fax the BI SAE form.
With receipt of any further information to these events, a follow-up SAE form has to be provided. For follow-up information the same rules and timeline apply as for initial information.

Information required
For each AE, the investigator should provide the information requested on the appropriate eCRF pages and the BI SAE form, if applicable. The investigator should determine the causal relationship to the trial medication and any possible interaction between the trial medication and a Non-Investigational Medicinal Product (NIMP).

The following should also be recorded as an (S) AE in the CRF and BI SAE form (if applicable):

- Worsening of the underlying disease or of other pre-existing conditions
- Changes in vital signs, ECG, physical examination and laboratory test results, if they are judged clinically relevant by the investigator.

If such abnormalities already pre-exist prior to trial inclusion they will be considered as baseline conditions and should be collected in the eCRF only. All (S)AEs, including those persisting after individual patient's end of trial must be followed up until they have resolved, have been assessed as "chronic" or "stable" , or no further information can be obtained.

Pregnancy
In rare cases, pregnancy might occur in a clinical trial. Once a patient has been enrolled in the clinical trial and has taken trial medication, the investigator must report any drug exposure during pregnancy in a trial participant immediately (within 24 hours) by means of Part A of the Pregnancy Monitoring Form to the sponsor's unique entry point.

Similarly, potential drug exposure during pregnancy must be reported if a partner of a male trial participant becomes pregnant. This requires a written consent of the pregnant partner.

The outcome of the pregnancy associated with the drug exposure during pregnancy must be followed up and reported to the sponsor's unique entry point on the Pregnancy Monitoring Form for Clinical Trials (Part B).
The ISF will contain the Pregnancy Monitoring Form for Clinical Trials (Part A and B).

As pregnancy itself is not to be reported as an AE, in the absence of an accompanying SAE, only the Pregnancy Monitoring Form for Clinical Trials and not the SAE form is to be completed. If there is an SAE associated with the pregnancy an SAE form must be completed in addition.

5.3 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

5.3.1 Assessment of pharmacokinetics

Not applicable.

5.3.2 Methods of sample collection

Not applicable.

5.3.3 Analytical determinations

Not applicable.

5.3.4 Pharmacokinetic – pharmacodynamic relationship

Not applicable since no pharmacodynamics data will be collected or analysed in this trial.

5.4 ASSESSMENT OF BIOMARKER(S)

Not applicable since no biomarker data will be collected and analysed in this trial.

5.4.1 Biobanking

Not applicable since no sample will be collected and analysed for biobanking in this trial.

5.5 OTHER ASSESSMENTS

Demographics, Height and Baseline Conditions: Demographics details, height and baseline conditions will be documented.

Medical History: Medical history will be collected to assess the qualification of subjects (including PD and concomitant diseases, if applicable).

Modified Hoehn and Yahr scale [R02-0836]: Modified Hoehn and Yahr scale will be completed at on-time. Stages of the Parkinson's disease will be assessed on 8 degrees between stage 0 (no sign of disease) to stage 5 (wheelchair bound or bedridden unless aided) in steps of 0, 1, 1.5, 2, 2.5, 3, 4 and 5.

Patient Diary: The cumulative hours of off-time every day during waking hours will be documented on a patient diary completed for 2 consecutive days before randomization visit.

Mini-Mental State Examination (MMSE) [R96-2656]: The MMSE is a patient reported instrument which evaluates orientation, memory, attention, concentration, naming, repetition, comprehension, ability to create a sentence, and ability to copy two intersecting polygons. A lower score indicates more cognitive impairment.

Urine Pregnancy Test: In women of childbearing potential, urine will be taken for pregnancy tests.

Concomitant Therapy (start date, end dates and changes): Concomitant therapy related to PD will be collected at least 3 months prior to randomization visit which should be recorded in the eCRF. All the concomitant therapy should be recorded in the eCRF starting from the date of signing study informed consent, and ending at the follow up visit. After the follow up visit, only concomitant therapy indicated for treatment of an AE has to be reported.

Compliance: The investigator will be responsible for the assessment of patient compliance to study drug (see also section 4.3).

5.6 APPROPRIATENESS OF MEASUREMENTS

NHQ will be used to evaluate the severity of nocturnal hypokinesia which was not covered by SCOPA scale. It is considered as a “non standard” criterion.

The EMO will be used to evaluate the bodily movements when patient wakes up in the morning. It is considered as a “non standard” criterion.

The rest of efficacy and safety criteria evaluated in this study are conventionally used in PD clinical trials. None of them could be considered as a "non standard" criterion.

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

The time window of all visits has been outlined in the Flow Chart.

If a patient does not appear to a visit, all efforts should be made to contact the patient. If a visit is conducted outside of the planned time interval, further process should be discussed with the sponsor.

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

6.2.1 Screening period

Screening Period – visit 1

- Obtain written informed consent
- Assign patient number
- Obtain comprehensive medical history and demographics to determine eligibility according to inclusion/exclusion criteria
- Perform comprehensive physical examination (including heart, lungs, abdomen, extremities, height and weight, etc.) including also a skin examination
- Obtain vital signs (blood pressure, pulse rate measurements),weight and height
- Perform MMSE
- Perform a Modified Hoehn & Yahr Scale staging at on-time
- Review inclusion/exclusion criteria
- Instruct the patient how to complete the diary and supply the patient with one. The diary will be collected and reviewed at visit 2
- Collect fasted blood sample for safety laboratory evaluation
- Perform spot urine pregnancy test (for females with childbearing potential)
- Perform a 12-lead ECG
- Record concomitant therapies including PD therapies
- Record any AE which might have occurred during the screening visit, after the informed consent was signed (e.g. if a patient gets a bleeding at the puncture site when the blood is drawn for the screening lab test)
- Instruct and supply health economics questionnaire
- Supply trial identification card

6.2.2 Treatment period(s)

6.2.2.1 Randomization visit (visit 2) at day 0

If the patient still qualifies for the study the following assessments are provided by the investigator:

Visit 2 (Randomisation visit) at day 0:

- Obtain vital signs (blood pressure, pulse) and weight
- Collect and review the completed patient diary. Check that the patient diary has been accurately completed, i.e. that there are no more than 4 double or missing entries on either day.
  If there are more than 4 double or missing entries on one day, no other activities or ratings should be done, i.e. the patient is not eligible for baseline evaluation. Another attempt to obtain a valid baseline diary can be undertaken and the randomization visit rescheduled.
  If the diary has been accurately completed (i.e. no more than 4 double or missing entries on either day), documented on a patient diary completed for 2 consecutive days before randomization visit, the patient can be randomized.
- Ask patient to complete the PDSS-2
- Review use of concomitant therapies including PD therapies
- Review inclusion/exclusion criteria to ensure patient still qualifies
- Randomize patient
- Perform MMIDI

- Ask patient to score the severity of EMO
- Ask patient to complete the ESS
- Ask patient to complete the NHQ Section 1. NHQ Section 2 should be completed by spouses or caregivers who are with the patients during the night at the same day. If no spouses or caregivers during the night, document it in the medical note and no need to complete NHQ Section 2.
- Ask patient to complete the SCOPA-Sleep
- Ask patient to complete the quality of life assessment (PDQ-8 and EQ-5D-5L)

- Dispense study medication to the patient to ensure the sufficient study medication until the next on-site visit with verbal instructions on how to take the medication. Remind the patient to take the study medication Pramipexole IR regularly three times per day with the third dose at 7-9 pm before bedtime or take study medication Pramipexole SR once daily at 7- 9 pm before bedtime. Additionally, remind the patient to bring the medication boxes (including all blank blister(s), unused and partially used study medication) back at the next scheduled on-site visit. The unused and partially used study medication will be returned to patients for treatment after drug accountability until the end of treatment. Study medication must be administered at the next day after randomization.
- Record AEs or follow-up on AEs continuing from the prior visit

- Schedule patient’s next contact (telephone call, TC1) to study site one week later

6.2.2.2 Up-titration phase

Patients will have weekly contact to the study site during the up-titration phase either as office visits or telephone calls. The complete seven weeks of up-titration are used to safely increase the study medications to the highest tolerated optimal dose for effective response. The investigator should use his/her clinical judgment in adjusting the dose to a dose where clinical improvement is reached. Furthermore, if a patient is unable to tolerate an increased dose level, the medication can be lowered one level.

It is possible that the L-Dopa^{+} dose may need to be adjusted with the addition of Pramipexole (SR or IR) during the up-titration Phase.

Visit 3 (i.e., week 2) at day 14 ± 2:
- Obtain vital signs (blood pressure, pulse) and weight
- Check for abnormal behavior. The MMIDI sub-scale has to be completed if the patient experiences any abnormal behavior
- Ask patient to score the severity of EMO
- Ask patient to complete the ESS
- Ask patient to complete the PDSS-2
- Ask patient to complete the NHQ Section 1. NHQ Section 2 should be completed by spouses or caregivers who are with the patients during the night at the same day. If no spouses or caregivers during the night, document it in the medical note and no need to complete NHQ Section 2.
- Ask patient to complete the SCOPA-Sleep
- Ask patient to complete the PGI-I questionnaire
- Perform medication compliance check
- Review concomitant therapies including PD therapies
- Record AEs or follow-up on AEs continuing from a prior visit
- Dispense study medication to the patient to ensure the sufficient study medication until the next on-site visit with verbal instructions on how to take the medication. Remind the patient to take the study medication Pramipexole IR regularly three times per day with the third dose at 7-9 pm before bedtime or take study medication Pramipexole SR once daily at 7- 9 pm before bedtime. Additionally, remind the patient to bring the medication boxes (including all blank blister(s), unused and partially used study medication) back at the next scheduled on-site visit. The unused and partially used study medication will be returned to patients for treatment after drug accountability until the end of treatment.

- Schedule patient's next contact (telephone call, TC2) to study site one week later

Visit 4 (i.e., week 4) at day 28 ± 2:
- Obtain vital signs (blood pressure, pulse) and weight

- Check for abnormal behavior. The MMIDI sub-scale has to be completed if the patient experiences any abnormal behavior.
- Perform MDS-UPDRS part IV
- Perform CGI-I questionnaire
- Ask patient to score MDS-UPDRS part II
- Ask patient to score the severity of EMO
- Ask patient to complete the PGI-I questionnaire
- Ask patient to complete the ESS
- Ask patient to complete the PDSS-2
- Ask patient to complete the NHQ Section 1. NHQ Section 2 should be completed by spouses or caregivers who are with the patients during the night at the same day. If no spouses or caregivers during the night, document it in the medical note and no need to complete NHQ Section 2.
- Ask patient to complete the SCOPA-Sleep
- Perform medication compliance check
- Review concomitant therapies including PD therapies
- Record AEs or follow-up on AEs continuing from a prior visit
- Dispense study medication to ensure the sufficient study medication until the next on-site visit the patient with verbal instructions on how to take the medication. Remind the patient to take the study medication Pramipexole IR regularly three times per day with the third dose at 7-9 pm before bedtime or take study medication Pramipexole SR once daily at 7- 9 pm before bedtime.. Additionally, remind the patient to bring the medication boxes (including all blank blister(s), unused and partially used study medication) back at the next scheduled on-site visit. The unused and partially used study medication will be returned to patients for treatment after drug accountability until the end of treatment.
- Review the health economics questionnaire. Instruct and supply one with patient to bring home.
- Ask a patient's caregiver to complete CBI at on-site visit. If the caregiver absent on-site visit, patients should bring this questionnaire to her/his caregiver to complete it at the same day. If no caregiver, document it in the medical note and no need to complete CBI.
- Schedule patient's next contact (telephone call, TC3) to study site one week later
- Schedule patient's under next contact (telephone call, TC4) to study site two weeks later
- Schedule patient's fifth contact (telephone call, TC5) to study site three weeks later

Interim Telephone Calls (TC1 to TC5):
Interim telephone calls will be performed in order to avoid weekly on-site visits for the patients. If for some instance a patient will not have telephone access at home, the patient could perform a clinic visit. These unscheduled visits need to be reported then formally as TC's with a remark in the comments section of the corresponding eCRF page.
In the telephone calls the following information needs to be obtained:

- Check medication compliance
- Ask patient to complete the PGI-I questionnaire (the value will be recorded in the eCRF)
- Review concomitant therapies including PD therapies
- Record AEs or follow-up on AEs continuing from a prior visit. Evaluate patient's response to current dose level. If warranted, increase to next dose level. If patient is

already at optimal dose level, instruct patient to continue with the same dose level. If patient experienced side effects, the dose level can be adjusted to the next lower dose level.
- Schedule patient's next on-site visit.

TC5 will be the last time when the investigator can decide to down-titrate or to up-titrate the study medication. From TC3 to TC5, if pramipexole dose should be adjusted due to unsatisfactory efficacy or adverse event, on-site visit should be added to adjust dose.

6.2.2.3 Maintenance phase

In this phase three on-site visits will be performed (V5 to V7). During the maintenance phase, no dose adjustments will be allowed for the study medication. A patient's dose will be adjusted for medical reasons if considered in the best interest of the patient upon agreement between investigators and Sponsor.

Visit 5 - week 8, day 56 ± 3:
- Obtain vital signs (blood pressure, pulse) and weight

- Perform CGI-I questionnaire

- Ask patient to score the severity of EMO
- Ask patient to complete the PGI-I questionnaire
- Ask patient to complete the ESS
- Ask patient to complete the PDSS-2
- Ask patient to complete the NHQ Section 1. NHQ Section 2 should be completed by spouses or caregivers who are with the patients during the night at the same day. If no spouses or caregivers during the night, document it in the medical note and no need to complete NHQ Section 2.
- Ask patient to complete the SCOPA-Sleep
- Ask patient to complete the quality of life assessment (PDQ-8and EQ-5D-5L)

- Perform medication compliance check
- Review concomitant therapies including PD therapies
- Record AEs or follow-up on AEs continuing from a prior visit
- Dispense study medication to the patient to ensure the sufficient study medication until the next on-site visit with verbal instructions on how to take the medication. Remind the patient to take the study medication Pramipexole IR regularly three times per day with the third dose at 7-9 pm before bedtime or take study medication Pramipexole SR once daily at 7- 9 pm before bedtime. Additionally, remind the patient to bring the medication boxes (including all blank blister(s), unused and partially used study medication) back at the next scheduled on-site visit. The unused and partially used study medication will be returned to patients for treatment after drug accountability until the end of treatment.

- Schedule patient's next visit (Visit 6) four weeks later

Visit 6 - week 12, day 84 ± 3:
- Obtain vital signs (blood pressure, pulse) and weight
- Check for abnormal behavior. The MMIDI sub-scale has to be completed if the patient experiences any abnormal behavior.
- Ask patient to score the severity of EMO
- Ask the patient to complete the PGI-I questionnaire
- Ask patient to complete the ESS questionnaire
- Ask patient to complete the PDSS-2
- Ask patient to complete the NHQ Section 1. NHQ Section 2 should be completed by spouses or caregivers who are with the patients during the night at the same day. If no spouses or caregivers during the night, document it in the medical note and no need to complete NHQ Section 2.
- Ask patient to complete the SCOPA-Sleep
- Perform medication compliance check
- Review concomitant therapies including PD therapies
- Record AEs or follow-up on AEs continuing from a prior visit
- Dispense study medication to the patient to ensure the sufficient study medication until the next on-site visit with verbal instructions on how to take the medication. Remind the patient to take the study medication Pramipexole IR regularly three times per day with the third dose at 7-9 pm before bedtime or take study medication Pramipexole SR once daily at 7- 9 pm before bedtime. Additionally, remind the patient to bring the medication boxes (including all blank blister(s), unused and partially used study medication) back at the next scheduled on-site visit. The unused and partially used study medication will be returned to patients for treatment after drug accountability until the end of treatment.

- Schedule patient's next visit (Visit 7) six weeks later

Visit 7 - week 18, day 126 ± 3 or premature discontinuation:
All patients should complete these assessments, even those who terminate early.
- Obtain vital signs (blood pressure, pulse) and weight
- Perform comprehensive physical examination (including heart, lungs, abdomen, extremities, height and weight, etc.) including also a skin examination

- Perform CGI-I questionnaire
- Perform MMIDI

- Ask patient to score the severity of EMO
- Ask the patient to complete the PGI-I questionnaire
- Ask patient to complete the ESS questionnaire
- Ask patient to complete the PDSS-2
- Ask patient to complete the NHQ Section 1. NHQ Section 2 should be completed by spouses or caregivers who are with the patients during the night at the same day. If no spouses or caregivers during the night, document it in the medical note and no need to complete NHQ Section 2.
- Ask patient to complete the SCOPA-Sleep
- Ask patient to complete the quality of life assessment (PDQ-8 and EQ-5D-5L)

- Collect fasted blood sample for safety laboratory evaluation
- Perform spot urine pregnancy test (for females with childbearing potential)
- Perform medication compliance check
- Review concomitant therapies including PD therapies
- Record AEs or follow-up on AEs continuing from a prior visit
- Perform a 12-lead ECG
- Dispense study medication to ensure the sufficient study medication for the down-titration phase if patient won't continue Pramipexole IR/SR treatment after trial completion. Remind those patients to take the study medication Pramipexole IR regularly three times per day with the third dose at 7-9 pm before bedtime or take study medication Pramipexole SR once daily at 7- 9 pm before bedtime. Additionally, remind the patient to bring the medication boxes (including all blank blister(s), unused and partially used study medication) back at the next scheduled on-site visit.
  Return the study medication boxes (including all blank blister(s), unused and partially used study medication) to study site if patient will continue Pramipexole IR/SR treatment after trial completion at this visit.

- Schedule patient's next visit (Visit 8) one week later.

6.2.3 Follow up period and trial completion

Visit 8 - 2 days after the last study dose +3 days:
All assessments planned at this visit must be performed by all subjects after 48 hours of the last intake of study medication (+3 days), including those who have been prematurely withdrawn from the trial. Study medication should be completely tapered according to clinical practice at this visit except the patient who will continue the Pramipexole IR/SR treatment. Assessments performed during visit 8 include the following:

- Obtain vital signs (blood pressure, pulse) and weight
- Perform MMIDI interview
- Collect fasted blood sample for safety laboratory evaluation if abnormal at visit 7
- Perform 12-lead ECG if abnormal at visit 7

- Perform compliance check of taper medication
- Review concomitant therapies including PD therapies
- Record AEs or follow-up on AEs continuing from a prior visit

End of the trial is defined as the last visit (**follow up visit**) completed by each patient.

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

Details of all analyses will be provided in the TSAP.

7.1 STATISTICAL DESIGN - MODEL

This is a two-stage multicentre, open-label, randomized, active controlled paralled group phase IV study. This two-stage study includes stage I and stage II. The stage I part of this trial will be conducted as a pilot study to explore the difference of change from baseline to week 18 in PDSS-2 total score between Pramipexole SR and IR. Stage II will be planned as a confirmatory or exploratory design. and II are totally separated, and the patients in Stage I will not be used in Stage II.

7.2 NULL AND ALTERNATIVE HYPOTHESES

For pilot stage I, there is no (confirmatory) hypothesis testing foreseen in a strict statistical sense. Analyses are descriptive in nature including two-sided p-values and confidence intervals throughout from statistical models used for explorative purposes.

For stage II, the assumption of the hypothesis testing will be based on the results of pilot stage I, which will be added once the topline results of stage I are worked out.

7.3 PLANNED ANALYSES

The analysis on the efficacy and safety endpoints will be based on the following populations:
· Treated set (TS) is defined as all patients who were dispensed study medication and were documented to have at least one dose of investigational treatment.
· Full analysis set (FAS) is defined as all patients who were randomized to treatment and received at least one dose of study drug and providing a baseline and at least one PDSS-2 total score measurement in maintenance period.
· Per protocol set (PPS) is defined as a subset of FAS, including only patients without important protocol violations for efficacy. Details will be provided in the TSAP.

The primary efficacy endpoint will be analyzed on the FAS (as the primary analysis) as well as on the PPS (as the sensitivity analysis). The secondary and further efficacy endpoints will be analyzed on the FAS.

Safety endpoints will be analyzed on the TS.

Demographic and baseline characteristics will be analyzed on the TS using descriptive statistics.

7.3.1 Primary endpoint analyses

Mean changes from baseline will be analyzed using a restricted maximum likelihood (REML) - based repeated measures approach. Analyses will include the fixed, categorical effects of treatment, visit in the maintenance period, and treatment-by-visit interaction, as well as the continuous, fixed covariates of baseline and baseline-by-visit interaction. An unstructured covariance structure will be used to model the within-patient measurements.
If this analysis fails to converge, the following covariance structures will be tested in order: (UN → ANTE (1) → SP (1)). The first model to converge will be used as the primary analysis. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom. Descriptive p-values will be based on least-squares means using a two-sided $\alpha = 0.05$ (two-sided 95% confidence intervals). In case the model failed to converge under PROC MIXED, the "singular" option could be considered. The primary treatment comparisons will be the contrast between treatments at the endpoint visit.

7.3.2 Secondary endpoint analyses

For continuous endpoints, the same method as the primary analysis will be used. For responder rates, logistic regression analyses will be performed with treatment and baseline (if baseline was measured) as the independent variables.

7.3.4 Safety analyses

Adverse events will be coded using the Medical Dictionary for Drug Regulatory Activities (MedDRA). Standard BI summary tables and listings will be produced. All adverse events with an onset between start of treatment and end of the residual effect period (REP), a period of 2 days (inclusive) after the last dose of trial medication, will be assigned to the on-treatment period for evaluation.

All treated patients will be included in the safety analysis. In general, safety analyses will be descriptive in nature and will be based on BI standards. No hypothesis testing is planned.

Statistical analysis and reporting of adverse events will concentrate on treatment-emergent adverse events, i.e. all adverse events occurring between start of treatment and end of the

residual effect period. Adverse events that start before first drug intake and deteriorate under treatment will also be considered as 'treatment-emergent'.
Frequency, severity, and causal relationship of adverse events will be tabulated by system organ class and preferred term after coding according to the current version of the MedDRA at the database lock.

Laboratory data, vital signs, physical examinations, or other safety-relevant data will be analysed quantitatively or qualitatively. MMIDI will be analysed descriptively. Details will be provided in the TSAP.

7.3.5 Pharmacokinetic and pharmacodynamic analyses

Not applicable.

7.4 INTERIM ANALYSES

No interim analysis is planned.

7.5 HANDLING OF MISSING DATA

Each patient will be included in the evaluation as far as his/her data are available. If a patient misses a visit, the missing data will not be imputed. The mixed effect model will handle missing data based on a likelihood method under the "missing at random" assumption. The individual data from patients who fail to complete the study (premature dropouts or withdrawals) will also be reported as far as the data are available. Details will be provided in the TSAP.

7.6 RANDOMISATION

After screening, eligible patients will be randomized to receive either active treatment Pramipexole SR or IR in a ratio of 1:1.
BI will provide the randomisation list, and the labelling of trial medication will be done by the external vendor. The randomisation list will be generated using a validated system, which involves a pseudo-random number generator so that the resulting treatment will be both reproducible and non-predictable. The block size will be documented in the Clinical Trial Report. Access to the codes will be controlled and documented.

7.7 DETERMINATION OF SAMPLE SIZE

Stage I
The stage I part is pilot. The intent is to provide the evidence that will allow informed decision making in terms of the next stage's development. Therefore, the total sample size of

80 was mainly determined by the trial feasibility instead of the given power. Considering the drop-out rate as 5%, the total randomized sample size should be 86.
Assume the common standard deviation is 8 [R17-4025]. Table 7.7: 1 summarizes the probabilities for the observed difference less than or equal to certain values (-3.00, -3.44) with various true mean difference for change from baseline in PDSS-2 at Week 18 between Pramipexole SR and IR. All calculations were performed using R software (version 3.2.2). For example, assuming the true mean difference between SR and IR is -4.00, the probability of observed difference less than or equal to the MCID [R17-4026] (i.e., -3.44) will be 62.3% with the sized 80. If the true mean difference between SR and IR is -5.00, the probability will be 80.8%.

Table 7.7: 1 The probability (%) of the observed difference <= -3.00 and -3.44 with various assumptions of the true mean difference and sample size

N	**Cut-off values of observed difference**	**True mean difference**				
		-2.00	-3.00	-3.44	**-4.00**	-5.00
70	-3.00	30.1	50.0	59.1	69.9	85.2
	-3.44	22.6	40.9	50.0	61.5	79.3
80	-3.00	28.8	50.0	59.7	71.2	86.8
	-3.44	21.0	40.3	50.0	**62.3**	**80.8**
90	-3.00	27.7	50.0	60.3	72.3	88.2
	-3.44	19.7	39.7	50.0	63.0	82.3

Stage II
The sample size will be updated once the Stage II is decided to continue.

8. INFORMED CONSENT, TRIAL RECORDS, DATA PROTECTION, PUBLICATION POLICY, AND ADMINISTRATIVE STRUCTURE

The trial will be carried out in compliance with the protocol, the ethical principles laid down in the Declaration of Helsinki, in accordance with the ICH Harmonized Tripartite Guideline for Good Clinical Practice (GCP), relevant BI Standard Operating Procedures (SOPs) and other relevant regulations.

Standard medical care (prophylactic, diagnostic and therapeutic procedures) remains the responsibility of the treating physician of the patient.

The investigator will inform the sponsor immediately of any urgent safety measures taken to protect the trial patients against any immediate hazard, as well as of any serious breaches of the protocol or of ICH GCP.

The Boehringer Ingelheim transparency and publication policy can be found on the following web page: trials.boehringer-ingelheim.com. The rights of the investigator and of the sponsor with regard to publication of the results of this trial are described in the investigator contract. As a rule, no trial results should be published prior to finalization of the Clinical Trial Report.

The certificate of insurance cover is made available to the investigator and the patients, and is stored in the ISF.

8.1 TRIAL APPROVAL, PATIENT INFORMATION, INFORMED CONSENT

This trial will be initiated only after all required legal documentation has been reviewed and approved by the respective Institutional Review Board (IRB) / Independent Ethics Committee (IEC) and competent authority (CA) according to national and international regulations. The same applies for the implementation of changes introduced by amendments.

Prior to patient participation in the trial, written informed consent must be obtained from each patient (or the patient's legally accepted representative) according to ICH / GCP and to the regulatory and legal requirements of the participating country. Each signature must be personally dated by each signatory and the informed consent and any additional patient-information form retained by the investigator as part of the trial records. A signed copy of the informed consent and any additional patient information must be given to each patient or the patient's legally accepted representative."

Re-consenting may become necessary when new relevant information becomes available and should be conducted according to the sponsor's instructions.

The consent and re-consenting process should be properly documented in the source documentation.

8.2 DATA QUALITY ASSURANCE

A quality assurance audit/inspection of this trial may be conducted by the sponsor, sponsor's designees, or by IRB / IEC or by regulatory authorities. The quality assurance auditor will have access to all medical records, the investigator's trial-related files and correspondence, and the informed consent documentation of this clinical trial.

8.3 RECORDS

CRFs for individual patients will be provided by the sponsor. For drug accountability, refer to Section 4.1.8.

8.3.1 Source documents

In accordance with regulatory requirements the investigator should prepare and maintain adequate and accurate source documents and trial records that include all observations and other data pertinent to the investigation on each trial patient. Source data as well as reported data should follow good documentation practices and be attributable, legible, contemporaneous, original and accurate. Changes to the data should be traceable (audit trail). Data reported on the CRF must be consistent with the source data or the discrepancies must be explained.

The current medical history of the patient may not be sufficient to confirm eligibility for the trial and the investigator may need to request previous medical histories and evidence of any diagnostic tests. In this case the investigator must make three documented attempts to retrieve previous medical records. If this fails a verbal history from the patient, documented in their medical records, would be acceptable.

During the site visit the sponsor's CRA or auditor must be granted access to the original patient file (please see section 8.3.2). The investigator must ensure that all patient identifiers (e.g. patient's name, initials, address, phone number, social security number) have properly been removed or redacted from any copy of the patients' source documents before sending them to the sponsor.

If the patient is not compliant with the protocol, any corrective action e.g. re-training must be documented in the patient file.
For the CRF, data must be derived from source documents, for example:

- Patient identification: gender, year of birth (in accordance with local laws and regulations)
- Patient participation in the trial (substance, trial number, patient number, date patient was informed)
- Dates of patient's visits, including dispensing of trial medication
- Medical history (including trial indication and concomitant diseases, if applicable)
- Medication history
- Adverse events and outcome events (onset date (mandatory), and end date (if available))

- Serious adverse events (onset date (mandatory), and end date (if available))
- Concomitant therapy (start date, end dates, changes)
- Originals or copies of laboratory results and other imaging or testing results, with proper documented medical evaluation (in validated electronic format, if available)
- Completion of patient's participation in the trial" (end date; in case of premature discontinuation document the reason for it).
- Prior to allocation of a patient to a treatment into a clinical trial, there must be documented evidence in the source data (e.g. medical records) that the trial participant meets all inclusion criteria and does not meet any exclusion criteria. The absence of records (either medical records, verbal documented feedback of the patient or testing conducted specific for a protocol) to support inclusion/exclusion criteria does not make the patient eligible for the clinical trial.

8.3.2 Direct access to source data and documents

The sponsor will monitor the conduct of the trial by regular on-site monitoring visits and in-house data quality review. The frequency of site monitoring will be determined by assessing all characteristics of the trial, including its nature, objective, methodology and the degree of any deviations of the intervention from normal clinical practice.
The investigator /institution will allow site trial-related monitoring, audits, IRB / IEC review and regulatory inspections. Direct access must be provided to the CRF and all source documents/data, including progress notes, copies of laboratory and medical test results, which must be available at all times for review by the CRA, auditor and regulatory inspector (e.g. FDA). They may review all CRFs and informed consents. The accuracy of the data will be verified by direct comparison with the source documents described in section 8.3.1. The sponsor will also monitor compliance with the protocol and GCP.

8.3.3 Storage period of records

Trial site(s):
The trial site(s) must retain the source and essential documents (including ISF) according to contract or the local requirements valid at the time of the end of the trial (whatever is longer).
Sponsor:
The sponsor must retain the essential documents according to the sponsor's SOPs.

8.4 EXPEDITED REPORTING OF ADVERSE EVENTS

BI is responsible to fulfil their legal and regulatory reporting obligation in accordance with regulatory requirements.

8.5 STATEMENT OF CONFIDENTIALITY AND PATIENT PRIVACY

Individual patient data obtained as a result of this trial is considered confidential and disclosure to third parties is prohibited with the exceptions noted below. Patient privacy will

be ensured by using patient identification code numbers.
Data protection and data security measures are implemented for the collection, storage and processing of patient data in accordance with the principles 6 and 12 of the World Health Organization (WHO) GCP handbook.
Treatment data may be given to the patient's personal physician or to other appropriate medical personnel responsible for the patient's welfare. Data generated as a result of the trial need to be available for inspection on request by the participating physicians, the sponsor's representatives, by the IRB / IEC and the regulatory authorities.

8.5.1 Collection, storage and future use of biological samples and corresponding data

Measures are in place to comply with the applicable rules for the collection, storage and future use of biological samples from clinical trial participants and the corresponding data, in particular

- A Quality Management System has been implemented to ensure the adherence with the Principles of Good Clinical Practice as outlined in 'Note For Guidance On Good Clinical Practice' (CPMP/ICH/13 5/95)
- The BI-internal facilities storing and analysing biological samples and data from clinical trial participants as well as the laboratories' activities for clinical trials sponsored by Boehringer Ingelheim are regularly audited. The analytical groups and the banking facility are therefore assessed to be qualified for the storage and use of biological samples and data collected in clinical trials.
- Samples and data are used only if an appropriate informed consent is available.

8.6 TRIAL MILESTONES

The **start of the trial** is defined as the date when the first patient in the whole trial signs informed consent.
The end of the trial is defined as the date of the last visit of the last patient in the whole trial ("Last Patient Out"). The "**Last Patient Drug Discontinuation"** (LPDD) date is defined as the date on which the last patient at an individual trial site ends trial medication (as scheduled per protocol or prematurely). Individual investigators will be notified of Suspected Unexpected Serious Adverse Reactions (SUSARs) occurring with the trial medication until 30 days after LPDD at their site. **Early termination of the trial** is defined as the premature termination of the trial due to any reason before the end of the trial as specified in this protocol.
Temporary halt of the trial is defined as any unplanned interruption of the trial by the sponsor with the intention to resume it.
Suspension of the trial is defined as an interruption of the trial based on a Health Authority request.

8.7 ADMINISTRATIVE STRUCTURE OF THE TRIAL

The trial is sponsored by Boehringer Ingelheim (BI).
Two coordinating Investigators are responsible to coordinate investigators at the different sites participating in this trial. Tasks and responsibilities are defined in a contract.
Relevant documentation on the participating (Principal) Investigators (e.g. their curricula vitae) will be filed in the (Investigator Site File) ISF. The investigators will have access to the BI clinical trial portal (Clinergize) to facilitate document exchange and maintain electronic ISF.

BI has appointed a Clinical Trial Leader (CTL), responsible for coordinating all required activities, in order to

- manage the trial in accordance with applicable regulations and internal SOPs,
- direct the clinical trial team in the preparation, conduct, and reporting of the trial,
- ensure appropriate training and information of CTM, Clinical Research Associates (CRAs), and investigators of participating countries.

The organisation of the trial in the participating countries will be performed by the respective local or regional BI-organisation (Operating Unit, OPU) in accordance with applicable regulations and BI SOPs, or by a Contract Research Organisation (CRO) with which the responsibilities and tasks will have been agreed and a written contract filed before initiation of the clinical trial. Data Management will be done by a CRO with which the responsibilities and tasks will have been agreed and a written contract filed before initiation of the clinical trial. Statistical Evaluation will be done by BI according to BI SOPs. IRT will not be used for this study. The local laboratory service at each site will be used for this study.
Tasks and functions assigned in order to organise, manage, and evaluate the trial are defined according to BI SOPs. A list of responsible persons and relevant local information can be found in the ISF.

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9.2 UNPUBLISHED REFERENCES

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[U04-1242-06] Investigator's brochure: Pramipexole Extended-release (ER) tablets Parkinson's disease. 24 Feb 2009.

[U06-1598-01] A single dose five-way cross-over study to establish an in vitro/ in vivo correlation (IVIVC) for oral slow release (SR) tablets with 0.375 mg Pramipexole in healthy male volunteers. BI trial No. 248.560. 11 July 2006. Revision No. 1 dated 25 April 2007

[U07-1551]
A multiple dose study with increasing Pramipexole doses (0.375 mg to 4.5 mg q.d.) of oral sustained release (SR) tablets with a three-way cross comparison of 4.5 mg Pramipexole SR q.d. fasted versus 4.5 mg Pramipexole SR q.d. fed versus 1.5 mg Pramipexole immediate release tablets t.i.d. fasted in healthy male volunteers. 10 Jul 2007.

[U08-1904-01] Population Pharmacokinetic analysis of 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 patients with early Parkinson's disease (PD). 26 Sep 2008

[U08-1964-01] , A double-blind, double-dummy, randomized, parallel groups study to assess the Efficacy, Safety and Tolerability of switching patients with early Parkinson's disease (PD) from Pramipexole IR to Pramipexole ER or Pramipexole IR.

[U09-1232-03] . A doubleblind 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 patients with early Parkinson's disease (PD). 10 Jul 2009.

[U09-1270-04] A double-blind, double-dummy, placebocontrolled, 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 LDopa+ treated patients with advanced Parkinson's disease (PD). 9 Jul 2009

[U10-1341-01] . Long-term safety study of open-label pramipexole extended release (ER) in patients with early Parkinson's disease (PD). 248.633 Interim analysis. 18 February 2010.

[U10-1369-01] Long-term safety study of open-label pramipexole extended release (ER) in patients with advanced Parkinson's disease (PD). 248.634 Interim analysis. 26 February 2010.

[U10-1624-01] A double-blind, doubledummy, randomised, parallel-group study to investigate the safety, tolerability, trough plasma concentration, and efficacy of pramipexole ER versus pramipexole IR administered orally for 12 weeks in patients with Parkinson's disease (PD) on L-dopa therapy, followed by a 52-week openlabel long-term treatment period to evaluate the long-term safety and efficacy of pramipexole ER. 248.610. 16 April 2010.

[U10-2447-01] . A multiple dose study with increasing dose for pramipexole extended release (ER) tablet (0.375 mg q.d. to 1.5 mg q.d.) in two-way crossover comparison to investigate the bioequivalence of 1.5 mg ER x 1 tablet q.d. versus 0.375 mg ER x 4 tablets q.d. under fasted and fed conditions in Japanese healthy male volunteers. 248.677. 17 September 2010.

[U91-0026] et al. Pharmacokinetics and bioavailability of SND 919 CL 2 Y, comparison of the plasma levels after intravenous (infusion, 100 mcg), oral (tablets, 300 mcg) and oral (solution, 300 mcg) administration in 12 healthy volunteers (3-fold cross-over), 28 Sep 1990.

[U92-0018] et al. Investigations on the pharmacokinetics and metabolism of SND 919 CL 2 Y after administration of single radioactive doses of 0.100mg intravenously and 0.300 mg orally in 6 volunteers 30 Sep 1991.

[U95-0560] . Double-blind, placebocontrolled, parallel-group comparison to assess the safety, tolerance, and efficacy of Pramipexole in early Parkinson's disease. 2 November 1995.

[U95-0588] Parallel-group, placebocontrolled, dose-response tolerability, safety, and efficacy study of Pramipexole in early Parkinson's disease. TR No. 7217-95-037. 13 November 1995.

[U95-3150] Double-blind, Placebocontrolled, 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). BI trial No. 248.320. 11 July 1995.

[U96-0232] A double-blind, placebocontrolled, randomised, multicentre 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. BI trial No. 248.326. 9 August 1996.

10. APPENDICES

10.1 ESTIMATED GFR (EGFR) USING MODIFICATION OF DIET IN RENAL DISEASE (MDRD) FORMULA [R02-2529]

Simplified MDRD formulation:

eGFR=186X SCr (mg/dL) $^{-1.154}$ XAge $^{-0.203}$ X (0.742 if female)

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

11.1 GLOBAL AMENDMENT 1

Date of amendment		05 Feb 2018
EudraCT number **EU number**		Not applicable
BI Trial number		0248-0686
BI Investigational Product(s)		Pramipexole dihydrochloride monohydrate
Title of protocol		A two- stage multicenter, open-label, randomized, active controlled parallel group study comparing the efficacy and safety of Pramipexole SR versus Pramipexole IR administered orally over an 18-week treatment on nocturnal symptoms in L-Dopa^{+} treated patients with advanced Parkinson's disease (PD)

To be implemented only after approval of the IRB / IEC / Competent Authorities	X
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval	
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only	

Section to be changed		**CLINICAL TRIAL PROTOCOL**
Description of change		• Change the Lay Title from "SUSTAIN" to "The SUSTAIN study compares the effects of Sustained and immediate-release pramipexole on the noctUrnal Symptoms of paTients with Advanced ParkInsoN's diease who also take L-Dopa"
Rationale for change		• Added a longer title which includes details about the trial for patients
Section to be changed		**CLINICAL TRIAL PROTOCOL SYNOPSIS**
Description of change		Corrected typos: • Changed 'Parkinson' to 'Parkinson's' • Changed 'afflieted 'to 'affiliated'
Rationale for change		• Revised error in previous version.
Section to be changed		**CLINICAL TRIAL PROTOCOL SYNOPSIS**
Description of change		• Short summary of safety criteria
Rationale for change		• Summarized the safety criteria according to protocol template instruction
Section to be changed		**CLINICAL TRIAL PROTOCOL SYNOPSIS**
Description of change		• Clarified to have Pramipexole SR and the third dose of Pramipexole IR at 7- 9 pm before bedtime
Rationale for change		• Standardized the time to take the dose at night

Section to be changed		**CLINICAL TRIAL PROTOCOL SYNOPSIS**
Description of change		• Added NHQ as secondary efficacy endpoints
Rationale for change		• Added NHQ to evaluate the severity of nocturnal hypokinesia which was not covered by SCOPA scale.
Section to be changed		**FLOW CHART**
Description of change		• Added 'Assign patient number in eCRF' at visit 1 • Added 'Supply Trial identification card' at visit 1 • Added NHQ at all on-site visit(Visit 2-visit 7) • Added 'Instruct and supply health economics questionnaire' at on-site visit 1-6 • Added 'superscript 11' at TC3 and TC4 visit • Deleted 'safety lab tests' on visit 5 • Clarified the unit of the time window • Clarified the urine pregnancy test is not applicable for all patients • Clarified the twelfth comment • Revised the timeline scheduled for visit 1 • Revised days of Visit 2 • Replaced 'NA' by 'Not applicable' • Separated 'PDQ-8, EQ-5D-5L'from one line into two lines
Rationale for change		• Added NHQ to evaluate the severity of nocturnal hypokinesia which was not covered by SCOPA scale. • Added and deleted study processes in flow chart according to study needs • Clarified study process to avoid any confusion
Section to be changed		**ABBREVIATIONS**
Description of change		• Added NHQ abbreviation. • Added MCID abbreviation • Added EOT abbreviation
Rationale for change		• Added the abbreviation of 'NHQ' , 'MCID' and 'EOT' according to protocol template
Section to be changed		**2.1.3 Secondary endpoint(s)**
Description of change		• Added NHQ (change from baseline) • Deleted those endpoints from the secondary endpoints: Incidence of Adverse Events; Proportion of withdrawals due to Adverse Events; Change from baseline in vital signs (blood pressure and pulse rate) and weight; Change from baseline in Modified Minnesota Impulsive Disorders Interview (MMIDI); Safety laboratory parameters.
Rationale for change		• Added NHQ score to evaluate the severity of nocturnal hypokineisa which was not covered by SCOPA scale. • The original listed safety secondary endpoints are

		planned as safety criteria instead of secondary endpoints. Therefore, they need to be removed from this section.
Section to be changed		
Description of change		
Rationale for change		• Added it according to study design objective
Section to be changed		
Description of change		
Rationale for change		• Not required
Section to be changed		**3.1 OVERALL TRIAL DESIGN AND PLAN**
Description of change		• Changed from 'PDSS' to 'PDSS-2'
Rationale for change		• Revised error in previous version.
		3.3 TRANSITION FROM STAGE I TO STAGE II
Description of change		• Changed from 'Achieve MCID' to 'Achieve the minimal clinically important difference' • Changed from 'no statistical significance (P<0.05)' to ' no statistical significance (P>=0.05)'
Rationale for change		• Avoided to misunderstanding of 'MCID' • Revised error in previous version.
Section to be changed		**3.4 SELECTION OF TRIAL POPULATION**
Description of change		• Revised the patient No to be screened.
Rationale for change		• Revised error in previous version.
Section to be changed		**3.4.3 Exclusion criteria**
Description of change		• Modified exclusion criterion 1 • Added Exclusion criteria 6 and 11
Rationale for change		• Clarify exclusion criterions.
Section to be changed		**4.1.2 Selection of doses in the trial**
Description of change		• Changed from'7-11pm'to'7 -9pm' • Changed the usage of Pramipexole IR from '2.25 mg (1.0 mg *1/2 t.i.d. +0.25mg t.i.d.), and 3.75 mg (1.0 mg t.i.d. + 0.25 mg t.i.d.)' to '2.25 mg (1.0 mg *1/2 t.i.d. +1.0 mg *1/4mg t.i.d.), and 3.75 mg (1.0 mg t.i.d. + 1.0 mg *1/4mg t.i.d.).'
Rationale for change		• Revised error in previous version. • Changed the medication usage strategy according to medicine supply strategy.
Section to be changed		**4.1.4 Drug assignment and administration of doses for each patient**
Description of change		• Changed from '7-11pm'to'7 -9pm'

		• Clarified some patients who want to maintain their dosages, commercial Pramipexole IR/SR will be provided by themselves under the judgement of investigators. • Clarified the time window for on-site visit of visit 8
Rationale for change		• Revised error in previous version. • Clarified the study process and time window requirement for on-site visit after study completion
Section to be changed		**4.1.7.1 Storage conditions for IR**
Description of change		• Changed the storage conditions for Pramipexole IR • Clarified that STORM document will be used for temperature excursion
Rationale for change		• Keep the consistence with Pramipexole IR SmPC • Specified the process to manage site temperature excursion
Section to be changed		**5.1 ASSESSMENT OF EFFICACY**
Description of change		• Added NHQ.
Rationale for change		• Added NHQ to evaluate the severity of nocturnal hypokineisa which was not covered by SCOPA.
Section to be changed		**5.2 FURTHER EFFICACY ASSESSMENT PART**
Description of change		Deleted below two paragraphs. • Treatment compliance rate The investigator will be responsible for the assessment of patient compliance to study drug (see also section 4.3). • L-Dopa daily dose At study entry, the L-Dopa daily dose will be recorded in the eCRF on the specific page “L-Dopa concomitant therapy”. At each study visit, any change in the L-Dopa original daily dose will be recorded on the same specific eCRF page. The L-Dopa dose will be recorded as mg/day.
Rationale for change		• Not required.
Section to be changed		**5.2.5 Other safety parameters**
Description of change		• Clarified when to complete MMIDI
Rationale for change		• Kept the consistence with flow chart
Section to be changed		**5.5 OTHER ASSESSMENTST**
Description of change		• Added other assessments including demographics, height, baseline conditions, medical history, Modified Hoehn and Yahr scale, Patient Diary, MMSE, urine pregnancy test concomitant, therapy compliance. • Revised the description of Health Economics
Rationale for change		• Revised it according to protocol general template
Section to be changed		**5.6 APPROPRIATENESS OF MEASUREMENTS**
Description of change		• Added NHQ and EMO as “non standard” criterions.

Rationale for change		• Revised it according to protocol general template
Section to be changed		**6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS**
Description of change		• Revised the trial process according to follow chart
Rationale for change		• Kept the consistence with follow chart
Section to be changed		**7.1 STATISTICAL DESIGN - MODEL**
Description of change		• Changed from 'PDSS' to 'PDSS-2'
Rationale for change		• Revised error in previous version.
Section to be changed		**7.6 RANDOMISATION**
Description of change		• Changed from' and the packaging and labelling of trial medication will be done by the external vendor.' to' and the labelling of trial medication will be done by the external vendor.'
Rationale for change		• No repackage will be done by external vendor
Section to be changed		**8.3.1 Source documents**
Description of change		• Changed from 'Concomitant therapy (start date, changes)' to 'Concomitant therapy (start date, end dates ,changes)
Rationale for change		• End date is required to obtain.
Section to be changed		**8.7 ADMINISTRATIVE STRUCTURE OF THE TRIAL**
Description of change		• Clarified there are two coordinating Investigators are responsible to coordinate investigators at the different sites participating in this trial.
Rationale for change		• Revised error in previous version.
Section to be changed		**9.1 PUBLISHED REFERENCES**
Description of change		• Added publication information for NHQ
Rationale for change		• Added publication information according to protocol template.

11.2 GLOBAL AMENDMENT 2

Date of amendment		18 Dec 2018
EudraCT number **EU number**		Not applicable
BI Trial number		0248-0686
BI Investigational Product(s)		Pramipexole dihydrochloride monohydrate
Title of protocol		A two- stage multicenter, open-label, randomized, active controlled parallel group study comparing the efficacy and safety of Pramipexole SR versus Pramipexole IR administered orally over an 18-week treatment on nocturnal symptoms in L-Dopa^{+} treated patients with advanced Parkinson's disease (PD)
To be implemented only after approval of the IRB / IEC / Competent Authorities		X
To be implemented immediately in order to eliminate hazard –		

IRB / IEC / Competent Authority to be notified of change with request for approval	
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only	

Section to be changed		**CLINICAL TRIAL PROTOCOL SYNOPSIS**
Description of change		• Clarified the in-and exclusion critieria, i.e., patients diagnosed as idiopathic PD with at least 2 years' PD history.
Rationale for change		• Clarified the inclusion criteria.
Section to be changed		**FLOW CHART**
Description of change		• Added 'The flow chart applies only to Patients enrolled in Stage I. '
Rationale for change		• Clarified study process to avoid any confusion
Section to be changed		**ABBREVIATIONS**
Description of change		• Removed the abbreviation of ' Investigator's Brochure ' • Changed TCM to CTL. • Changed CML to CTM.
Rationale for change		• Not needed or revised according to company requirements.
Section to be changed		**1.2 DRUG PROFILE**
Description of change		• Added the expected adverse reactions 'inappropriate antidiuretic hormone secretion, delirium, mania, antecollis, spasms.' • Updated adverse events of Pramipexole observed in clinical trials • Deleted below sentence in protocol 'For a more detailed description of the Pramipexole profile, please refer to the current Investigator's Brochure (IB). '
Rationale for change		• Added the expected adverse reactions according to the update SmPCs. • Updated adverse events of Pramipexole observed in clinical trials • Deleted IB as a reference of the Pramipexole profile.
Section to be changed		**3.2 DISCUSSION OF TRIAL DESIGN, INCLUDING THE CHOICE OF CONTROL GROUP(S)**
Description of change		• Changed the 'exploration' to 'further evaluation'.
Rationale for change		• To keep the consistence between protocol synopsis and protocol main body.
Section to be changed		**3.4 SELECTION OF TRIAL POPULATION**
Description of change		• Revised 'two months' to 'three months' after trial initiation at each center may be excluded from the further participation.
Rationale for change		• Revised it according to study real situation.

Section to be changed		**3.4.2 Inclusion criteria**
Description of change		• ‘ Parkinson’s disease diagnosed for at least 2 years ’ changed to ‘ Diagnosed as Parkinson’s disease, with at least 2 years’ PD history. ’
Rationale for change		• Clarified the inclusion criteria.
Section to be changed		**3.4.4 Withdrawal of patients from therapy or assessments**
Description of change		• Corrected ‘ section 3.3.4.1 and 3.3.4.2 above ’ to ‘ section 3.4.4.1 and 3.4.4.2 below ’
Rationale for change		• Revised error in previous version.
Section to be changed		**3.4.4.2 Withdrawal of consent for trial participation**
Description of change		• Corrected ‘ section 3.3.4.1’ to ‘ section 3.4.4.1 ’
Rationale for change		• Revised error in previous version.
Section to be changed		**4.1.7.2 Storage conditions for SR**
Description of change		• Changed ’ Pramipexole SR must be stored in the original package according to the instructions on the label. Patients will be reminded to keep the study drug out of the reach of children’ to ’ Pramipexole SR must be store sealed in the room temperature. Keep out of the reach of children’
Rationale for change		• Updated wording according to Label Text Approval Form and kept consistence with label.
Section to be changed		**4.2.2.2 Restrictions on diet and life style**
Description of change		• Added restrictions on life style for somnolence.
Rationale for change		• Updated it according to SmPC.
Section to be changed		**6.2.2.3 Maintenance phase**
Description of change		• Visit 5 and Visit 7 Changed ’ Ask patient to complete MMIDI’ to ’ Perform MMIDI ’
Rationale for change		• MMIDI should be performed by investigator.
Section to be changed		**9.1 PUBLISHED REFERENCES**
Description of change		• Added reference in section 9.
Rationale for change		• Added reference.
Section to be changed		**11.1 Estimated GFR (eGFR) using Modification of Diet in Renal Disease (MDRD) formula. [R02-2529]**
Description of change		• Changed the header.
Rationale for change		• Added a reference.

APPROVAL / SIGNATURE PAGE

Document Number: c20307124 **Technical Version Number:3.0**

Document Name: clinical-trial-protocol-revision-02

Title: A two- stage multicenter, open-label, randomized, active controlled parallel group study comparing the efficacy and safety of Pramipexole SR versus Pramipexole IR administered orally over an 18-week treatment on nocturnal symptoms in L-Dopa+ treated patients with advanced Parkinson's disease (PD)

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Approval-Clinical Trial Leader		19 Dec 2018 08:51 CET
Approval-Biostatistics		19 Dec 2018 09:39 CET
Approval-Team Member Medical Affairs		19 Dec 2018 14:11 CET
Approval- Established Core Products		20 Dec 2018 09:46 CET

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed