Clinical Trial Protocol

	Document Number: **c43506074-02**
EU Trial No. **UTN**	2024-510764-23-00 U1111-1303-3852
BI Trial No.	0248-0689
BI Investigational Medicinal Product	Sifrol®, pramipexole
Title	Bioequivalence of two Sifrol® tablets following oral administration in healthy subjects (an open-label, randomised, single-dose, two-way crossover trial)
Lay Title	A study in healthy people to compare two different Sifrol® tablets
Clinical Phase	I
Clinical Trial Leader	[redacted] Phone: [redacted] Fax: [redacted]
[redacted] **Investigator**	[redacted] Phone: [redacted] / Fax: [redacted]
Current Version, Date	Version 2.0, 29 Apr 2024
Original Protocol Date	23 Feb 2024

CLINICAL TRIAL PROTOCOL SYNOPSIS

Company name	Boehringer Ingelheim
Original protocol date	23 February 2024
Revision date	29 April 2024
BI trial number	0248-0689
Title of trial	Bioequivalence of two Sifrol® tablets following oral administration in healthy subjects (an open-label, randomised, single-dose, two-way crossover trial)
[redacted] **Investigator**	[redacted]
Trial site	[redacted]
Clinical phase	I
Trial rationale	The manufacturing of Sifrol® tablets will be outsourced to [redacted] This trial targets to establish bioequivalence between Sifrol® tablets produced at the current (Ingelheim) and alternative (Ennigerloh) manufacturing site.
Trial objective	To establish the bioequivalence of Sifrol® tablets containing 0.088 mg pramipexole manufactured by BI in Ingelheim (reference) and by [redacted] (test).
Trial endpoints	Primary endpoints: AUC_{0-tz} and C_{max} of pramipexole Secondary endpoints: $AUC_{0-\infty}$ of pramipexole
Trial design	Randomised, open-label, two-way crossover design
Number of subjects **total entered** **on each treatment**	 28 28
Diagnosis	Not applicable
Main inclusion criteria	Healthy male and female subjects, age of 18 to 55 years (inclusive), body mass index (BMI) of 18.5 to 29.9 kg/m^2 (inclusive)
Test product **dose** **mode of administration**	Sifrol® 0.088 mg tablets (Ennigerloh) 1 x 1 tablet (= 0.088 mg pramipexole) Oral with 240 mL of water after an overnight fast of at least 10 h
Reference product **dose** **mode of administration**	Sifrol® 0.088 mg tablets (Ingelheim) 1 x 1 tablet (= 0.088 mg pramipexole) Oral with 240 mL of water after an overnight fast of at least 10 h

Duration of treatment	One day (single dose) for each treatment
Statistical methods	The assessment of bioequivalence will be based upon 2-sided 90% confidence intervals (CIs) for the ratios of the geometric means (test/reference) for the primary and secondary endpoints using an acceptance range of 80.00 to 125.00%. This method corresponds to the two one-sided t-tests procedure, each at a 5% significance level. The statistical model will be an analysis of variance (ANOVA) on the logarithmic scale including effects for sequence, subjects nested within sequences, period and treatment. CIs will be calculated based on the residual error from the ANOVA and quantiles from the t-distribution. The secondary endpoint will be analysed with the same statistical method as for the primary endpoints. Descriptive statistics will be calculated for all endpoints.

FLOW CHART

Period	Visit	Day	Planned time (relative to first drug administration) [h:min]	Approximate clock time of actual day [h:min]	Event and comment	Safety laboratory[8]	PK blood	12-lead ECG	Vital signs (BP, PR)	Questioning for AEs and concomitant therapy [6]
SCR	1	-21 to -1			Screening (SCR)[1]	A		x	x	
1/2 (two identical periods separated by a wash-out of at least 3 days between drug administrations	2/3	-1	-12:00	20:00	Admission to trial site[7]	x[5, 7]				x[7]
		1	-1:00	07:00	Allocation to treatment[2] (visit 2 only)		x[2]		x[2]	x[2]
			0:00	08:00	Drug administration, start bed rest					
			0:15	08:15			x			
			0:30	08:30			x			
			1:00	09:00			x			
			1:30	09:30			x			
			2:00	10:00	240 mL fluid intake		x		x	x
			3:00	11:00			x			
			4:00	12:00	240 mL fluid intake, end of bed rest, thereafter lunch[3]		x		x	x
			5:00	13:00			x			
			6:00	14:00			x			
			8:00	16:00			x			
			10:00	18:00			x			
			11:00	19:00	Dinner[3]					
			12:00	20:00			x			x
		2	24:00	08:00	Breakfast (voluntary) [3], discharge from trial site		x		x	x
			34:00	18:00	Ambulatory visit		x			x
		3	48:00	08:00	Ambulatory visit		x			x
FU	4	3-24			End of study (EoS) examination[4]	B		x	x	x

1. Subject must be informed and written informed consent obtained prior to starting any screening procedures. Screening procedures include physical examination, check of vital signs, ECG, safety laboratory (including drug screening and pregnancy test in women), demographics (including determination of body height and weight, smoking status and alcohol history), relevant medical history, concomitant therapy and review of inclusion/exclusion criteria. .Pharmacogenetic samples will be collected if needed.
2. The time is approximate; the procedure is to be performed and completed within the 3h prior to drug administration.
3. If several actions are indicated at the same time, the intake of meals will be the last action.
4. At the end of study (synonym for end of trial), the EoS examination includes physical examination, vital signs, ECG, safety laboratory, pregnancy test in women, recording of AEs and concomitant therapies.
5. Only urine drug screening and alcohol breath test as well as pregnancy test in women will be done at this time
6. AEs and concomitant therapies will be recorded throughout the trial, but will be specifically asked for at the times indicated in the Flow Chart above.
7. The time is approximate; all procedures must be completed no later than 10 hours before planned drug administration on Day 1.
8. The laboratory parameters to be determined in safety lab A and B are detailed in chapter 5.2.3.

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ABBREVIATIONS AND DEFINITIONS

AE	Adverse event
AESI	Adverse events of special interest
ANOVA	Analysis of variance
$AUC_{0-\infty}$	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity
[redacted]	
AUC_{0-tz}	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 to the last quantifiable data point
BA	Bioavailability
BI	Boehringer Ingelheim
BMI	Body mass index (weight divided by height squared)
BP	Blood pressure
CA	Competent authority
CI	Confidence interval
C_{max}	Maximum measured concentration of the analyte in plasma
CRF	Case Report Form, paper or electronic (sometimes referred to as ‘eCRF’)
CT Leader	Clinical Trial Leader
CT Manager	Clinical Trial Manager
CTP	Clinical trial protocol
CTR	Clinical trial report
CV	Arithmetic coefficient of variation
ECG	Electrocardiogram
eCRF	Electronic case report form
eDC	Electronic data capture
EDTA	Ethylenediaminetetraacetic acid
EoS	End of Study (synonym for End of Trial)
F	Absolute bioavailability factor
FAS	Full Analysis Set
FU	Follow-up
GCP	Good Clinical Practice
gCV	Geometric coefficient of variation
GI	Gastro-intestinal
gMean	Geometric mean
[redacted]	
HPLC-MS/MS	High performance liquid chromatography with tandem mass spectrometry
HR	Heart rate
IB	Investigator’s brochure

IEC	Independent Ethics Committee
IPD	Important protocol deviation
IRB	Institutional Review Board
ISF	Investigator site file
[redacted]	
LC-MS/MS	Liquid chromatography with tandem mass spectrometry
MDA	Methylenedioxyamphetamine
MDMA	Methylenedioxymethamphetamine
MedDRA	Medical Dictionary for Regulatory Activities
PK	Pharmacokinetic(s)
PKS	Pharmacokinetic set
PP	Polypropylene
PR	Pulse rate
QT interval	ECG interval from the start of the QRS complex to the end of the T wave
QTc interval	QT interval corrected for heart rate, e.g. using the method of Fridericia (QTcF) or Bazett (QTcB)
R	Reference treatment
REP	Residual effect period
RLS	Restless Legs Syndrome
SAE	Serious adverse event
SCR	Screening
SmPC	Summary of Product Characteristics
SOP	Standard operating procedure
T	Test product or treatment
TMF	Trial master file
[redacted]	
TS	Treated set
t_z	Time of last measurable concentration of the analyte in plasma
TSAP	Trial statistical analysis plan

1. INTRODUCTION

Pramipexole (Sifrol®) is a dopamine receptor agonist. The pramipexole immediate release (IR) tablets are an approved medicine for the treatment of signs and symptoms of Parkinson`s disease (either as monotherapy or in combination with levodopa) since 1997, and for the treatment of primary Restless Legs Syndrome since 2006 [U04-1242-08]. Boehringer Ingelheim intends to outsource the production of Sifrol® tablets to [redacted] This trial shall establish the bioequivalence of Sifrol® tablets manufactured by BI (reference) and by [redacted] (test).

1.1 MEDICAL BACKGROUND

Parkinson's disease is a neurodegenerative disorder manifested by abnormally slow movements (bradykinesia), diminished motor activity (hypokinesia), muscle rigidity, resting tremor, flexed posture, and the loss of postural reflexes. As the disease progresses, patients may develop clinical features partially augmented by levodopa (the usually prescribed therapy), such as motor complications (e.g. wearing off phenomenon and dyskinesia). Dopamine agonists are currently being used either in monotherapy for the treatment of Parkinson's disease in the early stage of the disease (as part of the levodopa sparing strategy to delay as much as possible the occurrence of levodopa-related motor fluctuations) or in the later phase of the disease to lessen motor complications caused by levodopa. The beneficial effects of dopamine agonists used as adjuvant therapy in patients experiencing response fluctuations or diminished response to levodopa are well documented [U04-1242-08]. The recommended dosing scheme in Parkinson's disease is a weekly up-titration from 0.25 mg to a maximum of 1.5 mg (t.i.d. dosing) resulting in a total daily exposure from 0.375 mg to a maximum of 4.5 mg (all doses refer to the salt). Abrupt discontinuation of pramipexole can lead to the development of a neuroleptic malignant syndrome. Therefore, pramipexole should be tapered off after the subject has received a dose of at least 0.75 mg [R24-1508, R24-1562].

Restless legs syndrome (RLS) is characterized by an uncomfortable urge to move the legs while at rest with a worsening of symptoms at night, which significantly impacts patient`s quality of life. RLS may be primary (idiopathic) or secondary pregnancy or various systemic disorders, especially iron deficiency, and chronic renal insufficiency. Although the patho-genesis of RLS remains unclear a central dopaminergic dysfunction is likely to be involved. Therapeutic options include iron-replacement (if body-iron stores are reduced) or prescription of gabapentin or pregabalin, and dopamine agonists such as pramipexole, ropinirole and rotigotine [P21-04108].

The recommended dosing scheme for the indication RLS (restless legs syndrome) is a weekly up-titration over the following once daily doses: 0.125 mg, 0.25 mg, 0.5 mg, 0.75 mg (all doses refer to the salt) [R24-1508, R24-1562].

1.2 DRUG PROFILE

Pramipexole is a non-ergot dopamine receptor agonist, i.e. it is structurally different from the ergot-derived drugs (e.g. bromocriptine, pergolide). It is a full agonist and has a high receptor selectivity for the D2 subfamily of dopamine receptors. [U04-1242-08]

1.2.1 Clinical pharmacokinetics (PK) of pramipexole

Pramipexole is rapidly and completely absorbed following oral administration. The absolute bioavailability is greater than 90% and the maximum plasma concentrations occur between 01:00 and 03:00 hours. Food intake reduces the rate of absorption but not the overall extent of absorption. Pramipexole shows linear kinetics and relatively small inter-patient variability of plasma levels [R24-1508, R24-1562].

Pramipexole is metabolised in man only to a small extent. Renal excretion of unchanged pramipexole is the major route of elimination and accounts for about 80% of dose. Approximately 90% of a ^{14}C labelled dose is excreted through the kidneys while less than 2% is found in the faeces. The elimination half-life ($t_{½}$ [h]) varies from 08:00 hours in the young to 12:00 hours in the elderly [U92-0018].

For a more detailed description of the pramipexole PK profile, please refer to the current SmPC [R24-1562].

1.2.2 Safety and tolerability of pramipexole

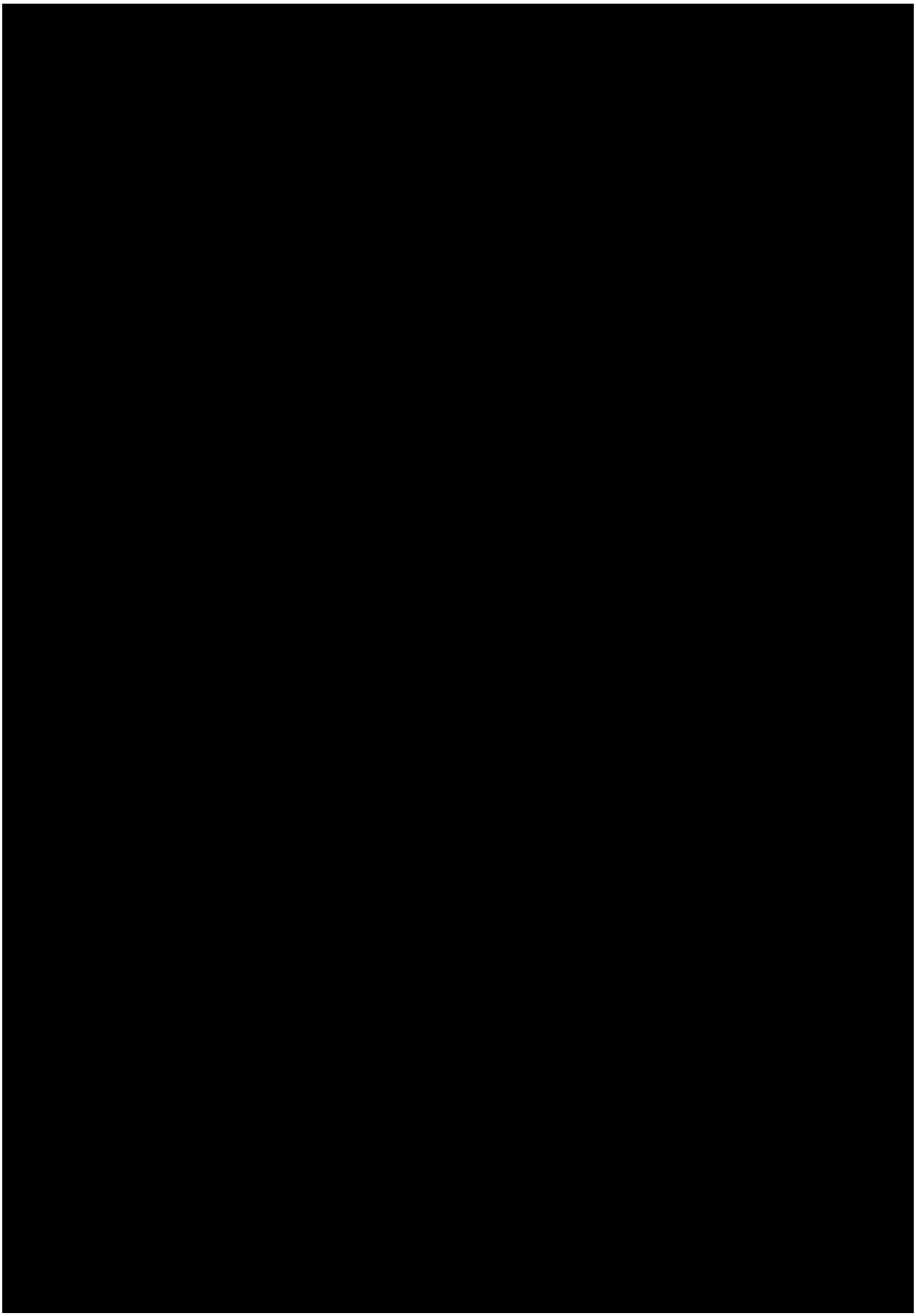
Safety and tolerability in patients

Based on the analysis of pooled placebo-controlled trials, comprising a total of 1,923 patients on pramipexole and 1,354 patients on placebo, adverse drug reactions were frequently reported for both groups. 63% of patients on pramipexole and 52% of patients on placebo reported at least one adverse drug reaction.

The most frequently (≥ 5%) reported adverse events in patients suffering from Morbus Parkinson were nausea, dyskinesia, hypotension, dizziness, somnolence, insomnia, constipation, hallucination, headache, and fatigue.

The most frequently (≥ 5%) reported adverse events in patients suffering from RLS were nausea, headache, dizziness, and fatigue [R24-1508, R24-1562].

[redacted]



[redacted]

For further description of the pramipexole safety profile, please refer to the current SmPC [R24-1562].

1.2.3 Residual Effect Period

The Residual Effect Period (REP) of pramipexole is 2 days. This is the period after the last dose during which measurable drug levels and/or pharmacodynamic effects are still likely to be present.

1.3 RATIONALE FOR PERFORMING THE TRIAL

Sifrol® is an approved medicinal product currently used in the treatment of Parkinson`s disease and Restless Legs Syndrome. To assure further market supply the manufacturing of Sifrol® tablets will be outsourced to [redacted]. This trial targets to establish bioequivalence between Sifrol® tablets produced at the current (Ingelheim) and alternative (Ennigerloh) manufacturing site.

1.4 BENEFIT - RISK ASSESSMENT

1.4.1 Benefits

Participation in this clinical trial is without any (therapeutic) benefit for healthy subjects. Their participation, however, is of major importance to assure further market supply with Sifrol® providing an effective treatment to patients suffering from Parkinson's disease and Restless Legs Syndrome.

1.4.2 Risks

Subjects are exposed to risks of trial procedures and risks related to the exposure to the trial medication. An overview of trial-related risks is given in Table 1.4.2: 1.

Table 1.4.2: 1 Overview of trial-related risks for this trial

Possible or known risks of clinical relevance	Summary of data, rationale for the risk	Mitigation strategy
Investigational Medicinal Product: pramipexole		
Cardiovascular effects including orthostatic dysregulation	Among the most frequently (≥ 5%) reported known side effects of dopamine receptor agonists (see 1.2.2)	Subjects are confined to bed until 4 h p.a. covering the time of maximum serum concentration. Vital signs will be monitored.
AEs related to gastro-intestinal tract and to the central nervous system	Known side effects of dopamine receptor agonists (see 1.2.2)	Reported AEs can be managed within the setting of a phase I trial.

Table 1.4.2: 1 Overview of trial-related risks for this trial (cont.)

Trial procedures		
Bruising and, in rare cases, phlebitis, or nerve injury, potentially resulting in paraesthesia, reduced sensibility, and/or pain	General risk by venipuncture for blood sampling, acceptable in the framework of trial participation.	Medical expertise of the trial site.

The total volume of blood withdrawn per subject during the entire trial will not exceed 150 ml (the volume of a normal blood donation is 500 mL). No health-related risk to healthy subjects is expected from withdrawal of this volume of blood.

[redacted]

1.4.3 Benefit risk assessment

Sifrol® is an approved medicine for more than 25 years. The nature of the target and the mechanism of action of pramipexole is well understood, its safety and tolerability are well characterised in patients as well as in healthy subjects.

In the current trial the lowest available clinical dose of Sifrol® is administered as a single dose on 2 occasions to healthy subjects, which is below the maximum daily dose used in the treatment of patients with Parkinson's disease or Restless Legs Syndrome. The trial will be performed to assure the further market supply with Sifrol®. It is therefore considered that the benefit of Sifrol® administration in this trial outweighs the potential risks for participating subjects.

2. TRIAL OBJECTIVES AND ENDPOINTS

2.1 MAIN OBJECTIVES, PRIMARY AND SECONDARY ENDPOINTS

2.1.1 Main objectives

The main objective of this trial is to establish the bioequivalence of Sifrol® tablets produced at the current (Ingelheim; Reference, R) and alternative (Ennigerloh; Test, T) manufacturing site following oral administration.

2.1.2 Primary endpoint

The following pharmacokinetic parameters will be determined for pramipexole:

- AUC_{0-tz} (area under the concentration-time curve of the analyte in plasma over the time interval from 0 to the last quantifiable data point)
- C_{max} (maximum measured concentration of the analyte in plasma)

2.1.3 Secondary endpoint

The following pharmacokinetic parameter will be determined for pramipexole:

- $AUC_{0-\infty}$ (area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity)

[redacted]

2.2.2.2 Safety and tolerability

Safety and tolerability of pramipexole will be assessed based on:

- Adverse events (including clinically relevant findings from the physical examination)

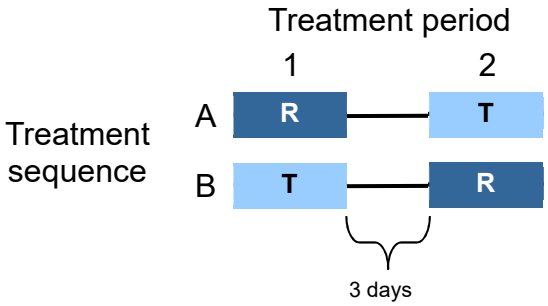
3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN

The trial will be performed as a randomised, open-label, two-way crossover trial in healthy male and female subjects in order to compare the test treatment (T) to the reference treatment (R). The treatments will be one Sifrol® 0.088 mg tablet (manufactured in Ennigerloh) as test treatment (T) and one Sifrol® 0.088 mg tablet (manufactured in Ingelheim) as reference treatment (R). Both treatments are administered to subjects in the fasting state. The subjects will be randomly allocated to the 2 treatment sequences (T-R or R-T). For details, refer to Section 4.1.

There will be a washout period of at least 3 days between the treatments.

Figure 3.1:1 trial design scheme



An overview of all relevant trial activities is provided in the Flow Chart. For visit schedule and details of trial procedures at selected visits, refer to Sections 6.1 and 6.2, respectively.

3.2 DISCUSSION OF TRIAL DESIGN, INCLUDING THE CHOICE OF CONTROL GROUP

For bioequivalence trials, the crossover design is preferred because of its efficiency: since each subject serves as his/her own control, the comparison between formulations is based on an intra-subject comparison, thus removing inter-subject variability from the comparison between formulations [R94-1529].

The open-label treatment is not expected to bias results, since the trial endpoints are derived from measurement of plasma concentrations of the analyte, which are provided by a bioanalytical laboratory that is blinded to treatment allocation.

3.3 SELECTION OF TRIAL POPULATION

It is planned that 28 healthy male and female subjects will enter the trial. They will be recruited from the volunteers' pool of the trial site.

A log of all subjects enrolled into the trial (i.e. who have signed informed consent) will be maintained in the ISF, irrespective of whether they have been treated with investigational drug or not.

3.3.1 Main diagnosis for trial entry

The trial will be performed in healthy subjects.

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

3.3.2 Inclusion criteria

Subjects will only be included in the trial if they meet the following criteria:

1. Healthy male or female subjects according to the assessment of the investigator, as based on a complete medical history including a physical examination, vital signs (BP, PR), 12-lead ECG, and clinical laboratory tests
2. Age of 18 to 55 years (inclusive)
3. BMI of 18.5 to 29.9 kg/m^2 (inclusive)
4. Signed and dated written informed consent in accordance with ICH-GCP and local legislation prior to admission to the trial
5. Either male subject, or female subject who meet any of the following criteria for a highly effective contraception from at least 15 days before the first administration of trial medication until 30 days after trial completion:
   - Use of combined (estrogen and progestogen containing) hormonal contraception that prevents ovulation (oral, intravaginal or transdermal), *plus condom*
   - Use of progestogen-only hormonal contraception that inhibits ovulation (only injectables or implants*), plus condom*
   - Use of intrauterine device (IUD) or intrauterine hormone-releasing system (IUS)
   - Sexually abstinent
   - A vasectomised sexual partner who received medical assessment of the surgical success (documented absence of sperm) and provided that partner is the sole sexual partner of the trial participant
   - Surgically sterilised (including hysterectomy)
   - Postmenopausal, defined as no menses for 1 year without an alternative medical cause (in questionable cases a blood sample with levels of FSH above 40 U/L and estradiol below 30 ng/L is confirmatory)

3.3.3 Exclusion criteria

Subjects will not be allowed to participate, if any of the following general criteria apply:

1. Any finding in the medical examination (including BP, PR or ECG) deviating from normal and assessed as clinically relevant by the investigator
2. Repeated measurement of systolic blood pressure outside the range of 90 to 140 mmHg, diastolic blood pressure outside the range of 50 to 90 mmHg, or pulse rate outside the range of 45 to 90 bpm
3. Any laboratory value outside the reference range that the investigator considers to be of clinical relevance
4. Any evidence of a concomitant disease assessed as clinically relevant by the investigator
5. Gastrointestinal, hepatic, renal, respiratory, cardiovascular, metabolic, immunological or hormonal disorders
6. Cholecystectomy or other surgery of the gastrointestinal tract that could interfere with the pharmacokinetics of the trial medication (except appendectomy or simple hernia repair)
7. Diseases of the central nervous system (including but not limited to any kind of seizures or stroke), and other relevant neurological or psychiatric disorders
8. History of relevant orthostatic hypotension, fainting spells, or blackouts
9. Relevant chronic or acute infections
10. 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
11. History of relevant allergy or hypersensitivity (including allergy to the trial medication or its excipients)
12. Use of drugs within 30 days of planned administration of trial medication that might reasonably influence the results of the trial (including drugs that cause QT/QTc interval prolongation)
13. Intake of an investigational drug in another clinical trial within 60 days of planned administration of investigational drug in the current trial, or concurrent participation in another clinical trial in which investigational drug is administered
14. Smoker (more than 10 cigarettes or 3 cigars or 3 pipes per day)
15. Inability to refrain from smoking on specified trial days
16. Alcohol abuse (consumption of more than 12 g per day for females and 24 g per day for males)
17. Drug abuse or positive drug screening
18. Blood donation of more than 100 mL within 30 days of planned administration of trial medication or intended blood donation during the trial
19. Intention to perform excessive physical activities within one week prior to the administration of trial medication or during the trial
20. Inability to comply with the dietary regimen of the trial site

21. Subject is assessed as unsuitable for inclusion by the investigator, for instance, because the subject is not considered able to understand and comply with study requirements, or has a condition that would not allow safe participation in the study
22. For female subjects: Lactation, pregnancy, or plans to become pregnant during the trial or within 30 days after trial completion
23. For female subjects: Positive pregnancy test

For restrictions of the trial, refer to Section 4.2.2.

3.3.4 Withdrawal of subjects from treatment or assessments

Subjects may withdraw or may be removed from trial treatment or may withdraw consent to trial participation as a whole ('withdrawal of consent') with very different implications; please see Sections 3.3.4.1 and 3.3.4.2 below.

If a subject is removed from or withdraws from the trial prior to the first administration of trial medication, the data of this subject will not be entered in the case report form (CRF) and will not be reported in the clinical trial report (CTR).

If a subject is removed from or withdraws from the trial after the first administration of trial medication, this will be documented and the reason for discontinuation must be recorded in the CRF; in addition, trial data will be included in the CRF and will be reported in the CTR.

Following removal or withdrawal, a complete end-of-trial examination should be performed. If the discontinuation or withdrawal occurs before the end of the REP (see Section 1.2.3), the discontinued subject should, if possible, be questioned for AEs and concomitant therapies at or after the end of the REP, in order to ensure collection of AEs and concomitant therapies throughout the REP, if not contrary to any consent withdrawal of the subject.

3.3.4.1 Withdrawal from trial treatment

An individual subject will be withdrawn from trial treatment if:

1. The subject wants to withdraw from trial treatment. The subject will be asked to explain the reasons but has the right to refuse to answer
2. The subject has repeatedly shown to be non-compliant with important trial procedures and, in the opinion of both, the investigator and sponsor representative, the safety of the subject cannot be guaranteed as he / she is not willing or able to adhere to the trial requirements in the future.
3. The subject needs to take concomitant medication that interferes with the investigational medicinal product or other trial treatment
4. The subject can no longer receive trial treatment for medical reasons (such as pregnancy, surgery, adverse events (AEs), or diseases)

In addition to these criteria, the investigator may discontinue subjects at any time based on his or her clinical judgment.

If it is known that a subject becomes pregnant during the trial, administration of the trial medication is to be stopped immediately, and the subject is to be removed from the trial. The subject is to be followed until she has given birth or until the end of the pregnancy. The subject's data are to be collected until the end of the trial (last visit of last subject) and reported in the CTR. For reporting of pregnancy and associated events, refer to Section 5.2.6.2.3.

If new efficacy or safety information becomes available, Boehringer Ingelheim will review the benefit-risk-assessment and, if needed, pause or discontinue the trial treatment for all subjects or take any other appropriate action to guarantee the safety of the trial subjects.

3.3.4.2 Withdrawal of consent to trial participation

Subjects may withdraw their consent to trial participation at any time without the need to justify the decision. If a subject wants to withdraw consent, the investigator should be involved in the discussion with the subject and explain the difference between trial treatment discontinuation and withdrawal of consent to trial participation, as well as explain the options for continued follow-up after trial treatment discontinuation, please see Section 3.3.4.1 above.

3.3.4.3 Discontinuation of the trial by the sponsor

Boehringer Ingelheim reserves the right to discontinue the trial at any time for any of the following reasons (if reason 2 is met, the trial must be discontinued immediately):

1. Deviation from GCP, or the CTP impairing the appropriate conduct of the trial
2. New toxicological findings, serious adverse events, or any safety information invalidating the earlier positive benefit-risk-assessment (see Section 3.3.4.1)
3. More than 50% of the subjects show drug-related and clinically relevant adverse events of moderate or severe intensity in one treatment period, or if at least one drug-related serious adverse event is reported

3.3.5 Replacement of subjects

In case more than 4 subjects do not complete the trial (including subjects non-evaluable for PK), subjects may be replaced if considered necessary to reach the objective of the trial. Subjects who withdraw or are withdrawn from treatment or assessments because of a drug-related adverse event will not be replaced. The Clinical Trial Leader together with the Trial Pharmacologist and the Trial Statistician are to decide, if and how many subjects will be replaced. The total number of replacements may not exceed 1/3 of the total number of evaluable subjects anticipated to complete the trial. A replacement subject will be assigned a unique trial subject number, and will be assigned to the same treatment sequence as the subject he or she replaces.

4. TREATMENTS

4.1 INVESTIGATIONAL TREATMENTS

Sifrol® tablets that are currently available on the market are produced in Ingelheim (reference treatment). In the future Sifrol® tablets will be manufactured by [redacted] (test treatment).

Each tablet contains 0.125 mg pramipexole dihydrochloride monohydrate (salt form) corresponding to 0.088 mg pramipexole (base) [R24-1562].

4.1.1 Identity of the Investigational Medicinal Products

The characteristics of the test product (manufactured in Ennigerloh) are given below:

Name:	Sifrol® Tabletten
Substance:	Pramipexole
Pharmaceutical formulation:	IR tablet
Source:	BI Pharma GmbH & Co. KG, Germany
Unit strength:	0.088 mg
Posology:	1-0-0
Mode of administration:	Oral

The characteristics of the reference product (manufactured in Ingelheim) are given below:

Name:	Sifrol® Tabletten
Substance:	Pramipexole
Pharmaceutical formulation:	IR tablet
Source:	BI Pharma GmbH & Co. KG, Germany
Unit strength:	0.088 mg
Posology:	1-0-0
Mode of administration:	Oral

4.1.2 Selection of doses in the trial

The dose selected for this trial is the starting dose used for up-titration in the clinic [R24-1562].

4.1.3 Method of assigning subjects to treatment groups

The randomisation scheme will be provided to the trial site in advance.

Subjects will be allocated to treatment sequences prior to the first administration of trial medication in the morning of Day 1 (Visit 2). For this purpose, numbers of the randomisation scheme will be allocated to the subjects by drawing lots. Subjects are then assigned to a treatment sequence according to the randomisation scheme.

Once a subject number has been assigned, it cannot be reassigned to any other subject.

All subjects may be treated in one cohort, i.e. all subjects may receive treatment on the same calendar day. In case this is not feasible (e.g., due to logistical or recruitment reasons), the group may be split into several cohorts as required.

The randomisation procedure is described in Section 7.4

4.1.4 Drug assignment and administration of doses for each subject

This is a 2-way crossover trial. All subjects will receive the 2 treatments in randomised order. The treatments to be evaluated are summarised in Table 4.1.4: 1 below.

Table 4.1.4: 1 Dosage and treatment schedule

Treatment	Substance	Formulation	Unit strength	Dosage	Total dose
T (Test)	Pramipexole	Tablet (Ennigerloh)	0.088 mg	1 tablet, single dose	0.088 mg
R (Reference)	Pramipexole	Tablet (Ingelheim)	0.088 mg	1 tablet, single dose	0.088 mg

Administration of trial medication will be performed after subjects have fasted overnight; fasting is to start no later than 10 h before the scheduled dosing. The investigator (or authorised designee) will administer the trial medication as an oral dose together with about 240 mL of water to subjects who are in a standing position. For drug administration, the so-called four-eye principle (two-person rule) should be applied. For this, one authorised employee of the trial site should witness the administration of trial medication.

Subjects will be kept under close medical surveillance until 24 h after drug administration. To avoid orthostatic dysregulation subjects are confined to bed for 4 hours after pramipexole dosing.

The treatments will be separated by a wash-out phase of at least 3 days.

4.1.5 Blinding and procedures for unblinding

This is an open trial and will be handled open throughout.

PK samples will be labelled in such a way that treatment allocation cannot be derived by the analytical site.

4.1.6 Packaging, labelling, and re-supply

The investigational medicinal products will be provided by BI. They will be packaged and labelled in accordance with the principles of Good Manufacturing Practice (GMP).

For details of packing and the description of the label, refer to the ISF.

The labels will be prepared according to Regulation (EU) No 536/2014, Annex 6 omitting certain particulars with the following justifications:

- The investigator name was omitted from the label because it is included on the Trial Identification Card, which will be issued to each trial participant.
- The "keep out of reach of children" statement was omitted from the label because the product will remain at the clinical site.

The telephone number of the sponsor and the name, address and telephone number of the trial site are provided in the subject information form. The EU Trial number is indicated on the title page of this protocol as well as on the subject information and informed consent forms.

No re-supply is planned.

4.1.7 Storage conditions

Drug supplies will be kept in their original packaging and in a secure limited access storage area in accordance with the recommended (labelled) storage conditions. If necessary, a temperature log must be maintained to make certain that the drug supplies are stored at the correct temperature. If the storage conditions are found to be outside the specified range, the Clinical Research Associate (as provided in the list of contacts) is to be contacted immediately.

4.1.8 Drug accountability

The investigator or designee will receive the investigational drugs delivered from the sponsor when the following requirements are fulfilled:

- Approval of the clinical trial protocol by the IRB / ethics committee
- 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

Only authorised personnel documented in the form 'Trial Staff List' may dispense investigational drugs to trial subjects. Investigational drugs are not allowed to be used outside of this protocol.

The investigator or designee must maintain records of the product’s delivery to the trial site, the inventory at the site, the use by each subject, and the disposal of unused products. These records will include dates, quantities, batch / serial numbers, expiry ('use-by') dates, and the unique code numbers assigned to the investigational medicinal product and trial subjects. The investigator or designee will maintain records that document adequately that the subjects were provided the doses specified by the CTP and reconcile all investigational medicinal

products received from the sponsor. At the time of disposal of remaining trial medication, the investigator or designee must verify that no remaining supplies are in the investigator's possession.

All unused medication will be disposed of locally by the trial site upon written authorisation of the Clinical Trial Leader. Receipt, usage and disposal of trial medication must be documented on the appropriate forms. Account must be given for any discrepancies.

4.2 OTHER TREATMENTS, EMERGENCY PROCEDURES, RESTRICTIONS

4.2.1 Other treatments and emergency procedures

There are no special emergency procedures to be followed. No additional treatment is planned. However, if adverse events require treatment, the investigator can authorise symptomatic therapy. In those cases, subjects will be treated as necessary and, if required, kept under supervision at the trial site or transferred to a hospital until all results of medical evaluations are acceptable.

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

In principle, no concomitant therapy is allowed except for hormonal contraceptives or ovary hormone replacement. All concomitant or rescue therapies will be recorded (including time of intake on trial days) on the appropriate pages of the CRF.

4.2.2.2 Restrictions on diet and life style

While admitted to the trial site, the subjects will be instructed not to consume any foods or drinks other than those provided by the staff. Standardised meals will be served at the times indicated in the Flow Chart. No food is allowed for at least 4 h after drug intake.

From 1 h before drug intake until lunch, fluid intake is restricted to the water administered with the drug, and an additional 240 mL of water at 2 h and 4 h post-dose (mandatory for all subjects). From lunch until 24 h post-dose, total fluid intake is restricted to 3500 mL.

Green tea, grapefruits, Seville oranges (sour or bitter oranges) and their juices, and dietary supplements and products containing St. John's wort (*Hypericum perforatum*) are not permitted from 7 days before the first administration of trial medication until after the last PK sample of each trial period is collected.

Alcoholic beverages are not permitted from 2 days before the first administration of trial medication until after the last PK sample of each trial period is collected.

Methylxanthine-containing drinks or foods (such as coffee, tea, cola, energy drinks, or chocolate) are not allowed during in-house confinement.

Smoking is not allowed during in-house confinement.

Excessive physical activity (such as competitive sport) should be avoided from 7 days before the first administration of trial medication until the end of trial examination.

4.2.2.3 Contraception requirements

If female subjects of child-bearing potential are included in the trial, adequate contraception is to be maintained throughout the course of the trial (see Section 3.3.2 for the definition of adequate measures).

4.3 TREATMENT COMPLIANCE

Compliance will be assured by administration of all trial medication in the trial centre under supervision of the investigating physician or a designee. The measured plasma concentrations of trial medication will provide additional confirmation of compliance.

Subjects who are non-compliant (for instance, who do not appear for scheduled visits or violate trial restrictions) may be removed from the trial and the CRF will be completed accordingly (for further procedures, please see Section 3.3.4.1).

5. ASSESSMENTS

5.1 ASSESSMENT OF EFFICACY

Not applicable.

5.2 ASSESSMENT OF SAFETY

5.2.1 Physical examination

At screening, the medical examination will include demographics, height and body weight, smoking and alcohol history (alcohol history not mandatory to be entered into CRF or to be reported), relevant medical history and concomitant therapy, review of inclusion and exclusion criteria, review of vital signs (BP, PR), 12-lead ECG, laboratory tests, and a physical examination. At the end of trial examination, it will include review of vital signs, 12-lead ECG, laboratory tests, and a physical examination.

5.2.2 Vital signs

Systolic and diastolic blood pressures (BP) as well as pulse rate (PR) or heart rate (heart rate is considered to be equal to pulse rate) will be measured by a blood pressure monitor (Dinamap Pro 100, [redacted] at the times indicated in the Flow Chart, after subjects have rested for at least 5 min in a supine position. All recordings should be made using the same type of blood pressure recording instrument on the same arm, if possible.

5.2.3 Safety laboratory parameters

For the assessment of laboratory parameters, blood and urine samples will be collected by the trial site at the times indicated in the Flow Chart after the subjects have fasted for at least 10 h. For retests, at the discretion of the investigator or designee, overnight fasting is not required.

The parameters to be assessed are listed in Tables 5.2.3: 1 and 5.2.3: 2. Reference ranges will be provided in the ISF.

Manual differential white blood cell count or urine sediment examinations will only be performed if there is an abnormality in the automatic blood cell count or in the urinalysis (if erythrocytes, leukocytes, nitrite or protein are abnormal in urine), respectively.

Table 5.2.3: 1 Routine laboratory tests

Functional lab group	BI test name [comment/abbreviation]	A	B
Haematology	Haematocrit	X	X
	Haemoglobin	X	X
	Red Blood Cell Count/Erythrocytes	X	X
	White Blood Cells/Leucocytes	X	X
	Platelet Count/Thrombocytes (quant)	X	X
Automatic WBC differential, relative	Neutrophils/Leukocytes; Eosinophils/Leukocytes; Basophils/ Leukocytes; Monocytes/Leukocytes; Lymphocytes/Leukocytes	X	X
Automatic WBC differential, absolute	Neutrophil, absol.; Eosinophils, absol.; Basophils, absol.; Monocytes, absol.; Lymphocytes, absol.	X	X
Manual differential WBC (if automatic differential WBC is abnormal)	Neut. Poly (segs)/Leukocytes; Neut. Poly (segs), absol.; Neutrophils Bands/Leukocytes; Neutrophils Bands, absol.; Eosinophils/Leukocytes; Eosinophils, absol.; Basophils/ Leukocytes; Basophils, absol.; Monocytes/Leukocytes; Monocytes, absol.; Lymphocytes/Leukocytes; Lymphocytes, absol.		
Coagulation	Activated Partial Thromboplastin Time	X	X
	Prothrombin time (Quick)	X	X
	Prothrombin time – INR (International Normalization Ratio)	X	X
Enzymes	AST [Aspartate aminotransferase] /GOT, SGOT	X	X
	ALT [Alanine aminotransferase] /GPT, SGPT	X	X
	Gamma-Glutamyl Transferase	X	X
Hormones	Thyroid Stimulating Hormone	X	--
Substrates	Glucose (Plasma)	X	X
	Creatinine	X	X
	Bilirubin, Total	X	X
	Bilirubin, Direct	X	X
	Protein, Total	X	X
	C-Reactive Protein (Quant)	X	X
Electrolytes	Sodium	X	X
	Potassium	X	X
	Calcium	X	X
Urinalysis (Stix)	Urine Nitrite (qual)	X	X
	Urine Protein (qual)	X	X
	Urine Glucose (qual)	X	X
	Urine Ketone (qual)	X	X
	Urobilinogen (qual)	X	X
	Urine Bilirubin (qual)	X	X
	Urine HGB (qual)	X	X
	Urine Leucocyte esterase (qual)	X	X
	Urine pH	X	X
Urine sediment (microscopic examination)	Only positive findings will be reported (for instance, the presence of sediment bacteria, casts in sediment, squamous epithelial cells, erythrocytes, leukocytes)		

A: parameters to be determined at Visit 1 (screening examination)
B: parameters to be determined at Visit 4 (end of trial examination)

The tests listed in Table 5.2.3: 2 are exclusionary laboratory tests that may be repeated as required. The results will not be entered in the CRF/database and will not be reported in the CTR. Except for pregnancy tests and drug screening, it is planned to perform these tests during screening only. Pregnancy testing in women will be performed at screening, prior to each treatment period, and as part of the end of trial examination. Drug screening will be performed at screening and prior to each treatment period.

Table 5.2.3: 2 Exclusionary laboratory tests

Functional lab group	Test name
Drug screening (urine)	Amphetamine/MDA Barbiturates Benzodiazepine Cannabis Cocaine Methadone Methamphetamines/MDMA/Ecstasy Opiates Phencyclidine Tricyclic antidepressants
Infectious serology (blood)	Hepatitis B surface antigen (qualitative) Hepatitis B core antibody (qualitative) Hepatitis C antibodies (qualitative) HIV-1 and HIV-2 antibody (qualitative)
Pregnancy test (urine)	Beta human chorionic gonadotropin (beta-HCG)

To encourage compliance with alcoholic restrictions, a breath alcohol test (e.g. AlcoTrue® M, [redacted]) will be performed prior to each treatment period, and may be repeated at any time during the trial at the discretion of an investigator or designee. The results will not be included in the CTR.

The laboratory tests listed in Tables 5.2.3: 1 and 5.2.3: 2 will be performed at [redacted], with the exception of drug screening and pregnancy tests. These tests will be performed at the trial site using M-10/14-PDT Surestep Multiline test and Cleartest® Diagnostik HCG test, respectively, or comparable test systems. In case of positive drug screen, a confirmatory test may be done at [redacted]

Laboratory data will be transmitted electronically from the laboratory to the trial site.

It is the responsibility of the Investigator to evaluate the laboratory results. Clinically relevant abnormal findings as judged by the Investigator are to be reported as adverse events (please refer to Section 5.2.6).

In case the criteria for hepatic injury are fulfilled, a number of additional measures will be performed (please see Section 5.2.6.1.4).

5.2.4 Electrocardiogram

Twelve-lead ECGs (I, II, III, aVR, aVL, aVF, V1 - V6) will be recorded using a computerised electrocardiograph (CardioSoft EKG System, [redacted]) at the times provided in the Flow Chart.

To achieve a stable heart rate at rest and to assure high quality recordings, the site personnel will be instructed to assure a relaxed and quiet environment, so that all subjects are at complete rest.

All ECGs will be recorded for a 10 sec duration after subjects have rested for at least 5 min in a supine position. ECG assessment will always precede all other trial procedures scheduled for the same time to avoid compromising ECG quality.

All ECGs will be stored electronically on the Muse CV Cardiology System ([redacted]). Electrode placement will be performed according to the method of Wilson, Goldberger and Einthoven modified by Mason and Likar (hips and shoulders instead of ankles and wrists).

All locally printed ECGs will be evaluated by the investigator or a designee. Abnormal findings will be reported as AEs (during the trial) or baseline conditions (if identified at the screening visit) if assessed to be clinically relevant by the investigator. Any ECG abnormalities will be carefully monitored and, if necessary, the subject will be removed from the trial and will receive the appropriate medical treatment.

ECGs may be repeated for quality reasons (for instance, due to alternating current artefacts, muscle movements, or electrode dislocation) and the repeated ECG will be used for analysis. Additional (unscheduled) ECGs may be collected by the investigator for safety reasons.

5.2.5 Other safety parameters

Not applicable.

5.2.6 Assessment of adverse events

5.2.6.1 Definitions of adverse events

5.2.6.1.1 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 considered related or not.

The following should also be recorded as an 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.

5.2.6.1.2 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 prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly/birth defect
- Is deemed serious for any other reason if it is an important medical event when based upon appropriate medical judgment 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

A suspected unexpected serious adverse reaction (SUSAR) is an untoward and unintended response to a study drug. A SUSAR should be considered as unexpected if the nature, seriousness, severity, or outcome of the reaction is not consistent with the reference safety information of the investigational drug (e.g. the investigator's brochure, or the corresponding defined local label such as the summary of product characteristics).

5.2.6.1.3 AEs considered ‘Always Serious’

In accordance with the European Medicines Agency initiative on Important Medical Events, Boehringer Ingelheim has set up a list of 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 eDC system, an electronic data capture system which allows the entry of trial data at the trial site. A copy of the latest list of ‘Always Serious AEs’ will be provided upon request. These events should always be reported as SAEs as described in Section 5.2.6.2.

Cancers of new histology must be classified as a serious event regardless of the time since discontinuation of the trial medication and must be reported as described in 5.2.6.2, subsections ‘AE Collection’ and ‘**AE reporting to sponsor and timelines’**.

5.2.6.1.4 Adverse events of special interest

The term adverse events of special interest (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 Section 5.2.6.2.2.

No AESIs have been defined for this trial.

5.2.6.1.5 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

5.2.6.1.6 Causal relationship of AEs

Medical judgment should be used to determine whether there is a reasonable possibility of a causal relationship between the AE and the given trial treatment, 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 reduced)

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
- There is an 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

5.2.6.2.1 AE collection

Upon enrolment into a trial, the subject's baseline condition is assessed (for instance, by documentation of medical history/concomitant diagnoses), and relevant changes from baseline are noted subsequently.

Subjects will be required to report spontaneously any AEs. In addition, each subject will be regularly assessed by the medical staff throughout the clinical trial and whenever the investigator deems necessary. As a minimum, subjects will be questioned for AEs (and concomitant therapies) at the time points indicated in the Flow Chart. Assessment will be made using non-specific questions such as 'How do you feel?'. Specific questions will be asked wherever necessary in order to more precisely describe an AE.

A carefully written record of all AEs shall be kept by the investigator in charge of the trial. Records of AEs shall include data on the time of onset, end time, intensity of the event, and any treatment or action required for the event and its outcome.

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

- From signing the informed consent onwards until an individual subject's end of trial (the End of Study (EoS) visit):
    - All AEs (serious and non-serious) and all AESIs
    - The only exception to this rule are AEs (serious and non-serious) and AESIs in Phase I trials in healthy volunteers, when subjects discontinue from the trial due to screening failures prior to administration of any trial medication. In these cases, the subjects' data must be collected at trial site but will not be entered in the CRF and will not be reported in the CTR.
- After the individual subject's end of trial:
    - The investigator does not need to actively monitor the subject for new AEs but should only report any occurrence of cancer and trial treatment related SAEs and trial treatment related AESIs of which the investigator may become aware of by any means of communication, e.g. phone call. Those AEs should be reported on the BI SAE form (see Section 5.2.6.2.2), but not on the CRF.

5.2.6.2.2 AE reporting to the sponsor and timelines

The Investigator must report SAEs, SUSARs, AESIs, and non-serious AEs which are relevant for the reported SAE, SUSAR or AESI, on the BI SAE form to the sponsor's unique entry point within 24 hours of becoming aware of the event (the only exception to this rule are SAEs and AESIs in phase I trials in healthy volunteers, when subjects discontinue from the trial due to screening failures prior to administration of any trial medication), the country specific reporting process will be provided in the ISF. The same timeline applies if follow-up information becomes available. On specific occasions, the Investigator could inform the sponsor upfront via telephone. This does not replace the requirement to complete and send 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. All (S)AEs, including those persisting after the individual subject's end of trial, must be followed up until they have resolved, have been sufficiently characterized (e.g. as 'chronic' or 'stable'), or no further information can be obtained.

5.2.6.2.3 Pregnancy

In rare cases, pregnancy might occur in a clinical trial. Once a subject 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.

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 Studies (Part B). The ISF will contain the Pregnancy Monitoring Form for Clinical Studies (Part A and Part B).

As pregnancy itself is not to be reported as an AE, in the absence of an accompanying SAE and/or AESI, only the Pregnancy Monitoring Form for Clinical Studies and not the SAE form is to be completed. If there is an SAE and/or AESI 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

For the assessment of pharmacokinetics, blood samples will be collected at the time points indicated in the Flow Chart. The actual sampling times will be recorded and used for determination of pharmacokinetic parameters.

5.3.2 Methods of sample collection

5.3.2.1 Blood sampling for pharmacokinetic analysis of pramipexole

For quantification of pramipexole concentrations in plasma, 2.7 mL of blood will be drawn from an antecubital or forearm vein into a K_2-EDTA (dipotassium ethylenediaminetetraacetic acid)-anticoagulant blood drawing tube at the times indicated in the Flow Chart. Blood will be withdrawn by means of either an indwelling venous catheter or by venipuncture with a metal needle.

The EDTA-anticoagulated blood samples will be centrifuged for approximately 10 min at approximately 2000 x g to 4000 x g and 4 to 8 °C. Two plasma aliquots will be obtained and stored in polypropylene tubes. The first aliquot should contain at least 0.5 mL of plasma. The process from plasma sample production from collection of whole blood samples should be completed within 60 min of blood sample collection. The resulting plasma samples should be transferred into the freezer within 60 min from plasma sample generation, with interim storage of blood samples and plasma aliquots at room temperature. The time each aliquot was placed in the freezer will be documented. Until transfer on dry ice to the analytical laboratory, the aliquots will be stored upright at approximately -20°C or below at the trial site. The second aliquot will be transferred to the analytical laboratory after the bioanalyst has acknowledged safe arrival of the first aliquot. At the analytical laboratory, the plasma samples will be stored at approximately -20°C or below until analysis.

At a minimum, the sample tube labels should list BI trial number, subject number, visit, and planned sampling time.

After analysis, the plasma samples may be used for further methodological investigations (e.g. for stability testing or assessment of metabolites) or to address Health Authority questions regarding the results/methodology. However, only data related to the analyte and/or its metabolite(s) including anti-drug antibodies (if applicable) will be generated by these additional investigations. The trial samples will be discarded after completion of the additional investigations but not later than 5 years after the CTR is archived.

[redacted]

5.3.4 Pharmacokinetic - pharmacodynamic relationship

No analysis of the relationship between pharmacokinetic and pharmacodynamic parameters is planned for this trial.

5.4 ASSESSMENT OF BIOMARKERS

Not applicable.

5.5 BIOBANKING

Not applicable.

5.6 OTHER ASSESSMENTS

5.6.1 Pharmacogenomic evaluation

Pharmacogenomic investigations explore the role of genetic variation in determining an individual's response to drugs. For this purpose, a sample of at most 10 mL of blood will be obtained at the screening examination from each subject whose genotype has not been previously determined. Separate informed consent for genotyping will be obtained from each volunteer prior to sampling.

DNA will be extracted from the blood sample in order to sequence genes coding for proteins that are involved in the absorption, distribution, metabolism, and excretion (ADME) of drugs. The gene sequences to be determined include known and likely functional variations of key ADME genes and incorporate more than 90% of ADME-related genetic markers identified by the PharmaADME group (weblink.pharmaadme.org). It is not intended to include the pharmacogenomic data in the CTR. However, the data may be part of the CTR, if necessary.

5.7 APPROPRIATENESS OF MEASUREMENTS

All measurements performed during this trial are standard measurements and will be performed in order to monitor subjects' safety and to determine pharmacokinetic parameters in an appropriate way. The scheduled measurements will allow monitoring of changes in vital signs and standard laboratory values, that might occur as a result of administration of trial medication. The safety assessments are standard, are accepted for evaluation of safety and tolerability of an orally administered drug, and are widely used in clinical trials. The pharmacokinetic parameters and measurements outlined in Section 5.3 are generally used assessments of drug exposure.

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

Exact times of measurements outside the permitted time windows will be documented. The acceptable time windows for screening and the end of trial examination are provided in the Flow Chart.

Study measurements and assessments scheduled to occur 'before' trial medication administration on Day 1 are to be performed and completed within a 3 h-period prior to the trial drug administration.

If not stated otherwise in the Flow Chart, the acceptable deviation from the scheduled time for vital signs and AE/CT questioning will be ± 60 min.

If scheduled in the Flow Chart at the same time as a meal, blood sampling and vital signs recordings have to be done first. Furthermore, if several measurements including venipuncture are scheduled for the same time, venipuncture should be the last of the measurements due to its inconvenience to the subject and possible influence on physiological parameters.

For planned blood sampling times, refer to the Flow Chart. While these nominal times should be adhered to as closely as possible, the actual sampling times will be recorded and used for the determination of pharmacokinetic parameters.

If a subject misses an appointment, it will be rescheduled if possible. The relevance of measurements outside the permitted time windows will be assessed no later than at the Report Planning Meeting.

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

6.2.1 Screening period

After having been informed about the trial, all subjects will provide written informed consent in accordance with GCP and local legislation prior to enrolment in the trial.

For information regarding laboratory tests (including drug and virus screening, pregnancy test), ECG, vital signs, and physical examination, refer to Sections 5.2.1 to 5.2.5.

Genotyping will be performed in those volunteers whose genotypes have not been previously determined (for details, see Section 5.6).

6.2.2 Treatment periods

Each subject is expected to participate in 2 treatment periods. At least 3 days will separate drug administrations in the first and second treatment period.

In the evening of Day -1 of each treatment period, trial participants will be admitted to the trial site and kept under close medical surveillance for at least 24 h following drug administration in the morning of Day 1. The subjects will then be allowed to leave the trial site after formal assessment and confirmation of their fitness in the morning of Day 2. Further PK samplings on Day 2 and 3 will be performed in an ambulatory fashion.

For details on time points and procedures for collection of plasma samples for PK analysis, refer to Flow Chart and Section 5.3.2.

The safety measurements performed during the treatment period are specified in Section 5.2 of this protocol and in the Flow Chart. AEs and concomitant therapy will be assessed continuously from obtaining subject's written informed consent until the end of trial examination.

For details on times of all other trial procedures, refer to the Flow Chart.

6.2.3 Follow-up period and trial completion

For AE assessment, laboratory tests, pregnancy test in females, recording of ECG and vital signs, and physical examination during the follow-up period, see Section 5.2.

Subjects who discontinue treatment before the end of the planned treatment period should undergo the EoS Visit.

If needed in the opinion of the investigator, additional visits may be scheduled after the EoS Visit for continued safety monitoring.

All abnormal values (including laboratory parameters) that are assessed as clinically relevant by the investigator will be monitored using the appropriate tests until a return to a medically acceptable level is achieved. (S)AEs persisting after a subject's EoS Visit must be followed until they have resolved, have been sufficiently characterised, or no further information can be obtained.

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 NULL AND ALTERNATIVE HYPOTHESES

Although there are multiple primary endpoints, an alpha adjustment is not needed because it is required that all primary endpoints meet the equivalence criterion as described below simultaneously. Therefore, a one-sided alpha of 5% will be used for testing.

The assessment of bioequivalence will be based upon two-sided 90% confidence intervals (CIs) for the ratio of the geometric means (test/reference) for the primary endpoints using an acceptance range of 80.00 - to 125.00%. This method is equivalent to the two-sided t-test procedure, each at the 5% significance level.

The following hypotheses are tested:

Null hypothesis H_0 (Inequivalence): $\mu_T - \mu_R \leq -\delta \quad or \quad \mu_T - \mu_R \geq \delta$

where μ_T and μ_R are the means of the log-transformed endpoint for the test and reference treatments, respectively, and δ is the bioequivalence limit that defines the acceptance range on the logarithmic scale. Alternative hypothesis H_a (Equivalence): $-\delta < \mu_T - \mu_R < \delta$

In this trial, the bioequivalence limit δ is ln(1.25). By back-transforming (exponentiating), this translates to an acceptance range of 80.00 to 125.00% for the ratio of the geometric means (test/reference) for endpoints on the original scale.

The rejection of the null hypothesis at the $\alpha = 0.05$ level is equivalent to the inclusion of the 90% confidence interval for $\mu_T - \mu_R$ in the acceptance range $(-\delta, \delta)$.

7.2 PLANNED ANALYSES

7.2.1 General considerations

7.2.1.1 Analysis sets

Statistical analyses will be based on the following analysis sets:

- Treated set (TS): The treated set includes all subjects who were treated with at least one dose of trial drug. The treated set will be used for safety analyses.
- Pharmacokinetic parameter analysis set (PKS): This set includes all subjects in the treated set (TS) who provide at least one PK endpoint that was defined as primary or secondary and was not excluded due to a protocol deviation relevant to the evaluation of PK or due to PK non-evaluability (as specified in the following subsection 'Pharmacokinetics'). Thus, a subject will be included in the PKS, even if he/she contributes only one PK parameter value for one period to the statistical assessment. Descriptive and model-based analyses of PK parameters will be based on the PKS.

Descriptions of additional analysis sets may be provided in the TSAP.

Adherence to the protocol will be assessed by the trial team. Important protocol deviation (IPD) categories will be suggested in the IPD specification file. IPDs will be identified no later than in the Report Planning Meeting, and the IPD categories will be updated as needed.

7.2.1.2 Pharmacokinetics

The pharmacokinetic parameters listed in Section 2.1 and 2.2.2 for pramipexole will be calculated according to the relevant BI internal procedures.

Plasma concentration data and parameters of a subject will be included in the statistical pharmacokinetic (PK) analyses if they are not flagged for exclusion due to a protocol deviation relevant to the evaluation of PK (to be decided no later than in the Report Planning Meeting) or due to PK non-evaluability (as revealed during data analysis, based on the criteria specified below). Exclusion of a subject's data will be documented in the CTR.

Important protocol deviations may be

- Incorrect trial medication taken, i.e. the subject received at least one dose of trial medication the subject was not assigned to
- Incorrect dose of trial medication taken
- Use of restricted medications

Plasma concentrations and/or parameters of a subject will be considered as non-evaluable, if for example

- The subject experienced emesis that occurred at or before two times median t_{max} of the respective treatment (Median t_{max} is to be determined excluding the subjects experiencing emesis),
- A predose concentration is >5% C_{max} value of that subject
- Missing samples/concentration data at important phases of PK disposition curve

Plasma concentration data and parameters of a subject which are flagged for exclusion will be reported with its individual values but will not be included in the statistical analyses. Descriptive and inferential statistics of PK parameters will be based on the PKS.

Only concentration values within the validated concentration range and actual sampling times will be used for the calculation of pharmacokinetic parameters. Concentrations used in the pharmacokinetic calculations will be in the same format provided in the bioanalytical report, (that is, to the same number of decimal places provided in the bioanalytical report).

7.2.2 Primary endpoint analyses

Primary analyses

The statistical model used for the analysis of the primary endpoints will be an analysis of variance (ANOVA) model on the logarithmic scale. That is, the PK endpoints will be log-transformed (natural logarithm) prior to fitting the ANOVA model. This model will include

effects accounting for the following sources of variation: sequence, subjects within sequences, period and treatment. The effect 'subjects within sequences' will be considered as random, whereas the other effects will be considered as fixed. The model is described by the following equation:

$y_{ijkm} = \mu + \zeta_i + s_{im} + \pi_j + \tau_k + e_{ijkm}$, where

y_{ijkm} = logarithm of response measured on subject m in sequence i receiving treatment k in period j,

μ = the overall mean,

ζ_i = the i^{th} sequence effect, i = 1, 2,

s_{im} = the effect associated with the m^{th} subject in the i^{th} sequence, m = 1, 2, ..., n_i

π_j = the j^{th} period effect, j = 1, 2,

τ_k = the k^{th} treatment effect, k = 1, 2,

e_{ijkm} = the random error associated with the m^{th} subject in sequence i who received treatment k in period j.

where $s_{im} \sim N(0, \sigma_B^2)$ i.i.d., $e_{ijkm} \sim N(0, \sigma_W^2)$ i.i.d. and s_{im}, e_{ijkm} are independent random variables.

Point estimates for the ratios of the geometric means (test/reference) for the primary endpoints (see Section 2.1) and their two-sided 90% confidence intervals (CIs) will be provided.

For each endpoint, the difference between the expected means for log(T)-log(R) will be estimated by the difference in the corresponding adjusted means (Least Squares Means). Additionally, their two-sided 90% confidence intervals will be calculated based on the residual error from the ANOVA and quantiles from the t-distribution. These quantities will then be back-transformed to the original scale to provide the point estimate and 90% CIs for each endpoint.

Bioequivalence is considered established if the 90% confidence intervals of the geometric means for the primary endpoints are contained in the pre-defined acceptance range, see Section 7.1.

Further exploratory analyses

The statistical model as stated above will be repeated for the primary endpoints but with all sources of variation ('sequence', 'subjects within sequences', 'period', 'treatment') considered as fixed effects.

In addition to the model based approach, the endpoints will be analysed descriptively.

7.2.3 Secondary endpoint analyses

The secondary endpoint (refer to Section 2.1.3) will be calculated according to the relevant BI internal procedures and will be assessed statistically using the same methods as described for the primary endpoints.

7.2.5 Safety analyses

Safety will be analysed based on the assessments described in Section 2.2.2.2. All treated subjects (TS, refer to Section 7.2) will be included in the safety analysis. Safety analyses will be descriptive in nature and based on BI standards. No hypothesis testing is planned.

For all analyses, the treatment actually administered (= treatment at onset) to the subject will be used (any deviations from the randomised treatment will be discussed in the minutes of the Report Planning Meeting).

Treatments will be compared in a descriptive way. Tabulations of frequencies/proportions will be used to evaluate categorical (qualitative) data, and tabulations of descriptive statistics will be used to analyse continuous (quantitative) data.

Measurements (such as ECG, vital signs, or laboratory parameters) or AEs will be assigned to treatments (see Section 4.1) based on the actual treatment at the time of the measurement or on the recorded time of AE onset (concept of treatment emergent AEs). Therefore, measurements performed or AEs recorded prior to first intake of trial medication will be assigned to the screening period, those between trial medication intake and end of REP (see Section 1.2.3) will be assigned to the respective treatment period. Events occurring after the REP but prior to next intake or end of trial termination date will be assigned to 'follow-up'. These assignments including the corresponding time intervals will be defined in detail in the TSAP. Note that AEs occurring after the last per protocol contact but entered before database lock will be reported to Pharmacovigilance only and will not be captured in the trial database.

Additionally, further treatment intervals (analysing treatments) may be defined in the TSAP in order to provide summary statistics for time intervals, such as combined treatments, on-treatment totals, or periods without treatment effects (such as screening and follow-up intervals).

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Frequency, severity, and causal relationship of AEs will be tabulated by treatment, system organ class, and preferred term. SAEs and other significant AEs (according to ICH E3) will be listed separately.

Relevant ECG findings will be reported as AEs.

Previous and concomitant therapies will be presented per treatment without consideration of treatment periods.

Laboratory data will be compared to their reference ranges. Clinically relevant values outside the reference range will be highlighted in the listings.

Vital signs or other safety-relevant data will be assessed with regard to possible on-treatment changes from baseline.

For vital signs, baseline is defined per period as the last measurement prior to trial drug administration.

7.2.6 Interim analyses

No interim analysis is planned.

7.3 HANDLING OF MISSING DATA

7.3.1 Safety

It is not planned to impute missing values for safety parameters.

7.3.2 Pharmacokinetics

Handling of missing PK data will be performed according to the relevant BI internal procedures.

PK parameters that cannot be reasonably calculated based on the available drug concentration-time data will not be imputed.

7.4 RANDOMISATION

Subjects will be randomised to one of the 2 treatment sequences (R-T, T-R) in a 1:1 ratio. The block size will be documented in the CTR.

The sponsor will arrange for the randomisation as well as packaging and labelling of trial medication. The randomisation scheme will be generated using a validated system that uses a pseudo-random number generator and a supplied seed number so that the resulting allocation is both reproducible and non-predictable.

The randomisation scheme will contain additional blocks to allow for subject replacement (refer to Section 3.3.5).

7.5 DETERMINATION OF SAMPLE SIZE

It is planned to enter a total of 28 subjects in the trial with the aim of at least 24 PK evaluable subjects, because this sample size is considered sufficient to achieve the aims of this trial.

The sample size was determined using assumptions on the intra-individual variability of the primary endpoints based on trial 248.560 (U06-1598-01) investigating pharmacology of 0.375 mg pramipexole for various tablet formulations in healthy male volunteers. For C_{max} and various AUCs up to 30 hours post drug administration, the intra-individual geometric coefficient of variation (gCV) ranged from 12.5 – 13.6%. Hence, the assumed intra-individual gCVs in this trial are for C_{max} and $AUC_{0\text{-}tz}$ about 15%.

Due to the high correlation between the primary endpoints, only C_{max} will be considered for power calculations. Using a sample size of 24 subjects (12 per sequence group), the power to reject both one-sided null hypotheses for one parameter each at the 5% level of significance in favour of bioequivalence is displayed in Table 7.5: 1, under various assumptions for the T/R gMean ratio. To account for the uncertainty of the assumed gCV, a range of gCVs around 15% is also presented.

Table 7.5: 1 Power for concluding bioequivalence (acceptance range 80-125%) based on a geometric coefficient of variation around 15% and for different expected ratios of geometric means (test/reference) in a 2x2 crossover trial (N=24)

gCV [%]	**gMean ratio (T/R) [%]***				
	92.5	**95**	**100**	**105**	**107.5**
12	99.2	99.9	99.9	99.9	99.5
15	94.7	98.7	99.9	98.9	96.0
20	79.2	89.6	96.7	90.3	81.8

**Ratio of geometric means (test/reference) for a PK endpoint is defined by $exp(\mu_T)/exp(\mu_R)$.*

From the above table, a sample size of 24 PK evaluable subjects will yield approximately 90% power to conclude bioequivalence for an assumed gCV of 20% if the ratio is not more than 5% different from the ratio of 100% which reflects no difference in exposure. In addition, this sample size still provides approximately 80% power in case the ratio is not more than 7.5% different from 100% and the gCV is 20%.

Accounting for a drop-out rate of approximately 15%, a total of N = 24 + 4 = 28 subjects are planned to be entered into the trial.

The calculations were performed as described by Diletti et al. [R94-1445] using the function power.TOST() of the R package PowerTOST Version 1.5-4 in R Version 4.1.2.

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 Guideline for Good Clinical Practice (GCP), relevant BI Standard Operating Procedures (SOPs), the EU regulation 536/2014, and other relevant regulations. Investigators and site staff must adhere to these principles. Deviation from the protocol, the principles of ICH GCP or applicable regulations will be treated as 'protocol deviation'.

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

The investigator will inform the sponsor immediately of any urgent safety measures taken to protect the trial subjects 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. As a general rule, no trial results should be published prior to finalisation of the CTR.

The terms and conditions of the insurance coverage are made available to the investigator and the subjects and are stored in the ISF.

8.1 TRIAL APPROVAL, SUBJECT 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 a subject's participation in the trial, written informed consent must be obtained from each subject 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 subject-information form retained by the investigator as part of the trial records. A signed copy of the informed consent and any additional subject information must be given to each subject.

The subject must be given sufficient time to consider participation in the trial. The investigator or delegate obtains written consent of the subject's own free will with the informed consent form after confirming that the subject understands the contents. The investigator or [redacted] delegate must sign (or place a seal on) and date the informed consent form. If a trial collaborator has given a supplementary explanation, the trial collaborator also signs (or places a seal on) and dates the informed consent.

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 risk-based approach is used for trial quality management. It is initiated by the assessment of critical data and processes for trial subject protection and reliability of the results as well as identification and assessment of associated risks. An Integrated Quality and Risk Management Plan or alternative plan, in line with the guidance provided by ICH Q9 and ICH-GCP E6, for fully outsourced trials, documents the rationale and strategies for risk management during trial conduct including monitoring approaches, vendor management and other processes focusing on areas of greatest risk.

Continuous risk review and assessment may lead to adjustments in trial conduct, trial design or monitoring approaches.

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 subjects will be provided by the sponsor. For drug accountability, refer to Section 4.1.8.

Electronic Study Documentation System:
In the [redacted] Boehringer Ingelheim's Phase I unit, a validated electronic study documentation system (ClinBase™ or successor Trial Complete Early Phase, TCEP) is used for processing information and controlling data collected in clinical trials. In addition to its function as a procedure control system, the study documentation system serves as databases. Instead of being entered into CRFs, selected data are directly entered into the system.

8.3.1 Source documents

In accordance with regulatory requirements, the investigator should prepare and maintain adequate and accurate source documents and trial records for each trial subject that include all observations and other data pertinent to the investigation. Source data as well as reported data should follow the 'ALCOA principles' 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 subject 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 at least one documented attempt to retrieve previous medical records. If this fails, a verbal history from the subject, documented in their medical records, would be acceptable.

Before providing any copy of subjects' source documents to the sponsor, the investigator must ensure that all subject identifiers (e.g., subject's name, initials, address, phone number,

and social security number) have properly been removed or redacted to ensure subject confidentiality.

If the subject is not compliant with the protocol, any corrective action (e.g. re-training) must be documented in the subject file.

For the CRF, data must be derived from source documents, for example:

- Subject identification: gender, year of birth (in accordance with local laws and regulations)
- Subject participation in the trial (substance, trial number, subject number, date subject was informed)
- Dates of subject's visits, including dispensing of trial medication
- Medical history (including trial indication and concomitant diseases, if applicable)
- Medication history
- AEs and outcome events (onset date [mandatory], and end date [if available])
- SAEs (onset date [mandatory], and end date [if available])
- Concomitant therapy (start date, changes)
- Originals or copies of laboratory results and other imaging or testing results, with proper documented medical evaluation (in validated electronic format, if available)
- ECG results (original or copies of printouts)
- Completion of subject's participation in the trial (end date; in case of premature discontinuation, document the reason for it, if known)
- Prior to allocation of a subject 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 subject or testing conducted specific for a protocol) to support inclusion/exclusion criteria does not make the subject eligible for the clinical trial.

Data directly entered into ClinBase™ or TCEP (that is, without prior written or electronic record) are considered to be source data. The place where data are entered first will be defined in a trial specific Source Data Agreement. The data in ClinBase™ or TCEP are available for inspection at any time.

8.3.2 Direct access to source data and documents

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 Clinical Research Associate, 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:
The trial site(s) must retain the source and essential documents (including ISF) according to 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.

Reporting suspected unexpected serious adverse reactions (SUSARs) to the EMA will be done via E2B transmission of Individual Case Safety Reports (ICSRs) to the Eudravigilance CT Module.

8.5 STATEMENT OF CONFIDENTIALITY AND SUBJECT PRIVACY

Data protection and data security measures are implemented for the collection, storage and processing of subject data in accordance with the principles 7 and 12 of the WHO GCP handbook.

Individual subject data obtained as a result of this trial is considered confidential and disclosure to third parties is prohibited with the following exceptions:
Personalised treatment data may be given to the subject's personal physician or to other appropriate medical personnel responsible for the subject's welfare. Data generated at the site 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 and clinical data, in particular

- Sample and data usage have to be in accordance with the informed consent
- The BI-internal facilities storing biological samples from clinical trial participants as well as the external storage facility are qualified for the storage of biological samples collected in clinical trials.
- An appropriate sample and data management system, incl. audit trail for clinical data and samples to identify and destroy such samples according to ICF is in place
- A fit for the purpose documentation (e.g. biomarker proposal, analysis plan and report) ensures compliant usage
- A fit for purpose approach will be used for assay/equipment validation depending on the intended use of the biomarker data

- Samples and/or data may be transferred to third parties and other countries as specified in the ICF

8.6 TRIAL MILESTONES

The first act of recruitment represents the start of the trial and is defined as the date when the first trial participant (subject) in the whole trial signs informed consent.

The end of the trial is defined as the date of the last visit of the last subject in the whole trial ('Last Subject Completed').

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.

The sponsor will notify the IEC/competent authority in each participating EU member state about all required trial milestones according to the respective laws.

A final report of the clinical trial data will be written only after all subjects have completed the trial in all countries (EU or non-EU), so that all data can be incorporated and considered in the report.

The sponsor will submit to the EU database a summary of the final trial results within one year from the end of a clinical trial as a whole, regardless of the country of the last subject (EU or non-EU).

8.7 ADMINISTRATIVE STRUCTURE OF THE TRIAL

The trial is sponsored by Boehringer Ingelheim (BI).

The trial will be conducted at the [redacted] under the supervision of the Principal Investigator. Relevant documentation on the participating (Principal) Investigators (e.g. their curricula vitae) will be filed in the ISF. The investigators will have access to the BI web portal Clinergize to access documents provided by the sponsor.

BI has appointed a Clinical Trial Leader (CT Leader), responsible for coordinating all required trial 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 local Clinical Trial Mangers (CT Managers), Clinical Research Associates (CRAs), and investigators of participating trial sites

The trial medication will be provided by the [redacted]

Safety laboratory tests will be performed by the local laboratory of the trial site ([redacted]

Analyses of pramipexole concentrations in plasma will be performed at [redacted]

On-site monitoring will be performed by BI or a contract research organisation appointed by BI.

Data management and statistical evaluation will be done by [redacted] according to BI SOPs.

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.

9. REFERENCES

9.1 PUBLISHED REFERENCES

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U95-0470 [redacted] A study in healthy volunteers to compare the bioavailability of pramipexole after thrice daily repeated per oral administration of either the formulation used in the main clinical studies or the final formulation intended for marketing (at strengths of 0.125 and 1.5 mg). 248.116. 24.08.1995

10. APPENDICES

Not applicable.

11. DESCRIPTION OF GLOBAL AMENDMENT

11.1 GLOBAL AMENDMENT 1

Date of amendment		29 April 2024
EudraCT number **EU number**		2024-510764-23-00
BI Trial number		0248-0689
BI Investigational Medicinal Product(s)		Sifrol®, pramipexole
Title of protocol		Bioequivalence of two Sifrol® tablets following oral administration in healthy subjects (an open-label, randomised, single-dose, two-way crossover trial)
Substantial Global Amendment due to urgent safety reasons		☐
Substantial Global Amendment		☒
Non-substantial Global Amendment		☐
Section to be changed		1) 1.1, 1.2.1, 1.2.2, 4.1, 4.1.2 2) 5.2.6.1.2 3) 5.2.6.2.2 4) 8.4
Description of change		1) New SmPCs (Jan 2024 and Mar 2024) added 2) SUSAR definition added 3) Reporting of SUSARs to sponsor added 4) Reporting of SUSARs to Eudravigilance database added
Rationale for change		1) Regulatory request (RFI part I) 2) Regulatory request (RFI part I) 3) Regulatory request (RFI part I) 4) Regulatory request (RFI part I)

APPROVAL / SIGNATURE PAGE

Document Number: c43506074 **Technical Version Number:2.0**

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

Title: Bioequivalence of two Sifrol® tablets following oral administration in healthy subjects (an open-label, randomised, single-dose, two-way crossover trial)

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Approval-Clinical Trial Leader	[redacted]	29 Apr 2024 14:31 CEST
Approval-Clinical Program [redacted]		29 Apr 2024 14:33 CEST
Author-Trial Statistician		29 Apr 2024 14:44 CEST
Verification-Paper Signature Completion		29 Apr 2024 17:11 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	**Signed by**	**Date Signed**