Clinical Trial Protocol

	Document Number:	**c23506058-03**
EudraCT No.	2018-004313-41	
BI Trial No.	1371-0021	
BI Investigational Medicinal Product	BI 894416	
Title	Relative bioavailability of BI 894416 as tablet formulation following a high-fat, high-calorie breakfast compared to administration in the fasting state in healthy male subjects (an open-label, randomised, single-dose, two-period, two-sequence crossover study)	
Lay Title	A study in healthy men to test whether food affects the amount of BI 894416 in the blood	
Clinical Phase	I	
Clinical Trial Leader	Phone: Fax:	
Principal Investigator	Phone: Fax:	
Status	Final Protocol (Revised Protocol (based on global amendment 2))	
Version and Date	Version: 3.0	Date: 15 May 2019

CLINICAL TRIAL PROTOCOL SYNOPSIS

Company name	Boehringer Ingelheim
Protocol date	15 May 2019
Revision date	Not applicable
BI trial number	1371-0021
Title of trial	Relative bioavailability of BI 894416 as tablet formulation following a high-fat, high-calorie breakfast compared to administration in the fasting state in healthy male subjects (an open-label, randomised, single-dose, two-period, two-sequence crossover study)
Principal Investigator:	
Trial site	
Clinical phase	I
Trial rationale	This clinical trial will be performed to investigate the effect of food on bioavailability (assessed as relative bioavailability comparison of fed vs. fasting state) of BI 894416 as tablet formulation.
Trial objective	The main objective of this trial is to investigate the relative bioavailability of BI 894416 as tablet formulation following a high-fat, high calorie breakfast (Test, T) compared with administration in the fasting state (Reference, R).
Trial design	Randomised, open-label, two-way crossover design
Trial endpoints:	Primary endpoints: AUC_{0-tz} and C_{max} of BI 894416 Secondary endpoints: $AUC_{0-\infty}$ of BI 894416
Number of subjects **total entered** **each treatment**	 14 14
Diagnosis	Not applicable
Main criteria for inclusion	Healthy male subjects, age of 18 to 50 years (inclusive), body mass index (BMI) of 18.5 to 29.9 kg/m^2 (inclusive)
Test product **dose**	BI 894416 10 mg tablet 30 mg

mode of admin.	Oral with 240 mL of water after an overnight fast of at least 10 h (treatment "Reference" (R)) or after a high-fat, high-calorie breakfast (treatment "Test" (T))
Duration of treatment	One day (single dose) for each treatment
Statistical methods	Relative bioavailability will be estimated by the ratios of the geometric means (test/reference) for the primary and secondary endpoints. Additionally, their two-sided 90% confidence intervals (CIs) will be provided. This method corresponds to the two one-sided t-test procedure, each at a 5% significance level. Since the main focus is on estimation and not testing, a formal hypothesis test and associated acceptance range is not specified. 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. Descriptive statistics will be calculated for all endpoints.

FLOW CHART

Period	Visit	Day	Planned time (relative to drug administration) [h:min]	Approximate clock time of actual day [h:min]	Event and comment	Safety laboratory[8]	PK blood	12-lead ECG	Neurological Examination[7]	Vital signs (BP, PR)	Questioning for AEs and concomitant therapy[6]
SCR	1	-21 to -1			Screening (SCR)[1]	A		x	x	x	
1/2 (two identical periods separated by a wash-out interval of at least 5 days)	2/3	-5 to -1	-122:00	06:00	Ambulatory visit[9]	C[9]					x[9]
		1	-2:00	06:00	Allocation to treatment[2] (visit 2 only)	x[2,5]	x[2]	x[2]		x[2]	x[2]
			-0:30	07:30	High fat, high calorie breakfast (treatment T, only)						
			0:00	08:00	Drug administration						
			0:15	08:15			x				
			0:30	08:30			x				
			0:45	08:45			x				
			1:00	09:00			x	x		x	x
			1:30	09:30			x				
			2:00	10:00	240 mL fluid intake		x	x		x	x
			2:30	10:30			x				
			3:00	11:00			x				
			4:00	12:00	240 mL fluid intake, thereafter lunch[3]		x				x
			5:00	13:00			x				
			6:00	14:00			x				
			7:00	15:00	Snack (voluntary)[3]						
			8:00	16:00			x				
			10:00	18:00	Dinner[3]		x				
			12:00	20:00			x				x
		2	24:00	08:00	Discharge from trial site, breakfast (voluntary)[3]	B	x	x		x	x
			34:00	18:00	Ambulatory visit		x				x
		3	48:00	08:00	Ambulatory visit		x				x
FU	4	8 to 15			End of trial (EoTrial) examination[4]	B		x	x	x	x

1. Subject must be informed and written informed consent obtained prior to starting any screening procedures. Screening procedures include physical examination, neurological examination, check of vital signs, ECG, safety laboratory (including drug screening), 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 3 h 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 trial (EoTrial) visit, the EoTrial examination includes physical examination, neurological examination, vital signs, ECG, safety laboratory, recording of AEs and concomitant therapies.
5. Only urine drug screening and alcohol breath test 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. Unscheduled neurological examinations may be added at any time during the trial for individual volunteers or the whole treatment group, e.g., in case of neurological adverse events, if assessed as necessary by the investigator.
8. Letters A, B, and C define different sets of safety laboratory examinations (see Section 5.2.3)
9. Safety laboratory to be taken and to be medically evaluated within 5 days (within ~122 hours) prior to administration of study drug; this ambulatory visit including safety laboratory and adverse event questioning can be omitted if the screening examination is performed on Days -5, -4, -3, -2, or -1. Only prior to visit 2.

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ABBREVIATIONS

ADME	Absorption, distribution, metabolism, and excretion
AE	Adverse event
AESI	Adverse events of special interest
ALCOA	Attributable, legible, contemporaneous, original, and accurate
ANOVA	Analysis of variance
AUC_{0-24}	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 to 24 h
$AUC_{0-\infty}$	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity
$\%AUC_{tz-\infty}$	Percentage of $AUC_{0-\infty}$ obtained by extrapolation
AUC_{t1-t2}	Area under the concentration-time curve of the analyte in plasma over the time interval t_1 to t_2
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
BCS	Biopharmaceutics classification system
BI	Boehringer Ingelheim
BMI	Body mass index (weight divided by height squared)
BP	Blood pressure
CA	Competent authority
CI	Confidence interval
CL/F	Apparent clearance of the analyte in plasma after extravascular administration
C_{max}	Maximum measured concentration of the analyte in plasma
CRF	Case Report Form, paper or electronic (sometimes referred to as ‘eCRF’)
CTP	Clinical trial protocol
CTR	Clinical trial report
CYP3A	Cytochrome P450 subfamily 3A
DILI	Drug induced liver injury
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
eCRF	Electronic case report form
eDC	Electronic data capture
EDTA	Ethylenediaminetetraacetic acid
EEG	Electroencephalography
EoTrial	End of trial
EudraCT	European Clinical Trials Database
FU	Follow-up

GCP	Good Clinical Practice
gCV	Geometric coefficient of variation
gMean	Geometric mean
HPC	Human Pharmacology Centre
IB	Investigator's brochure
IEC	Independent Ethics Committee
IPD	Important protocol deviation
IQRMP	Integrated quality and risk management plan
IRB	Institutional Review Board
ISF	Investigator site file
λ_z	Terminal rate constant of the analyte in plasma
LC-MS/MS	Liquid chromatography with tandem mass spectrometry
MDA	Methylenedioxyamphetamine
MDMA	Methylenedioxymethamphetamine
MedDRA	Medical Dictionary for Regulatory Activities
$MRT_{,ex}$	Mean residence time of the analyte in the body, extravascular
NK	Natural killer
PK	Pharmacokinetic(s)
PKS	Pharmacokinetic set
PP	Polypropylene
PR	Pulse rate
QT	Time between start of the Q-wave and the end of the T-wave in an electrocardiogram
QTc	QT interval corrected for heart rate using the method of Fridericia (QTcF) or Bazett (QTcB)
R	Reference treatment
REP	Residual effect period
SAE	Serious adverse event
SCR	Screening
SOP	Standard operating procedure
SRD	Single-rising dose
SYK	Spleen tyrosine kinase
T	Test product or treatment
$t_{1/2}$	Terminal half-life of the analyte in plasma
t_{max}	Time from dosing to maximum measured concentration of the analyte in plasma
TS	Treated set
t_z	Time of last measurable concentration of the analyte in plasma
TSAP	Trial statistical analysis plan

ULN	Upper limit of normal
UV	Ultraviolet
V_z/F	Apparent volume of distribution during the terminal phase after extravascular administration
WHO	World Health Organization
WOCBP	Woman of child bearing potential
XTC	Ecstasy
ZAP70	Zeta-chain-associated protein kinase of 70 kDa

1. INTRODUCTION

BI 894416 is an oral, selective non-receptor protein tyrosine kinase SYK (spleen tyrosine kinase) inhibitor under clinical development for the indication of uncontrolled severe asthma.

This trial will be performed to investigate the relative bioavailability of BI 894416 in plasma when given after a high-fat, high-calorie breakfast in comparison to when given in the fasting state.

1.1 MEDICAL BACKGROUND

Asthma is a heterogenous disease characterized by a chronic inflammatory process of the airways and driven by both the innate and adaptive immune pathways [R14-4230, P08-01263]. In severe asthma, the T type 2 inflammation (T2) -high and T2-low, and the non-T2 pathways are involved associated with a mixed pattern of inflammation involving eosinophil, basophil, mast, neutrophil, innate lymphoid and dendritic cells [R15-5888, R16-0945].

SYK is a non-receptor cytoplasmic tyrosine kinase that is predominantly expressed in cells of hematopoietic lineage, including B cells, T cells, monocytes, NK cells, mast cells, basophils, and neutrophils [R15-5470]. SYK is a key component of the signal transduction associated with the T2-high and T2-low, and non-T2 asthma pathways that is activated through interaction with allergens and a number of innate and adaptive immune receptors including Fc receptors on basophils, mast, B- and T cells. SYK is essential for the FcεR1-mediated activation and degranulation of mast cells and basophils. SYK is also important in the signal propagation of the dectin family of innate receptors, present on macrophages, dendritic cells and neutrophils. Furthermore, SYK has important roles in B-cell and T-cell development, with partially redundant functions with Zeta-chain-associated protein kinase of 70 kDa (ZAP70) [R15-5470, R16-5298].

For more details on medical background see the current version of the Investigator's Brochure (IB) [c03536505].

1.2 DRUG PROFILE

BI 894416 is a potent and selective inhibitor of SYK. Based on pre-clinical *in vitro* and *in vivo* data, SYK inhibition is expected to have effect on the non-T2 and T2 inflammatory pathway components of severe asthma.

So far, BI 894416 was investigated in one clinical phase I first-in-man trial (BI study number 1371-0001) in healthy male volunteers. Trial 1371-0001 consisted of two trial parts, a single-rising dose (SRD) part and a relative bioavailability part. Single-dose treatment with up to 70 mg BI 894416 or placebo as oral solution in the SRD part of trial 1371-0001 as well as administration of three single doses (10, 10, and 40 mg BI 894416) as tablet or oral solution in the relative bioavailability part was safe and well tolerated.

For details on preliminary safety and tolerability as well as on pharmacokinetics and biomarker data of trial 1371-0001 refer to the IB [c03536505].

For a more detailed description of the BI 894416 profile, please refer to the current Investigator's Brochure (IB) [c03536505].

1.2.1 Residual Effect Period

The Residual Effect Period (REP, i.e., the period after the last dose with measurable drug levels and/or pharmacodynamic effects still likely to be present) of BI 894416 has not been defined yet. However, the elimination half-life of BI 894416 is short (gMean apparent terminal half-life between 3.0 and 5.8 h in the SRD part of trial 1371-0001), the mode of action is reversible, and safety and tolerability in trial 1371-0001 were good. This suggests that the occurrence of any potential adverse effects would likely be limited to a low number of days.

The End-of-Trial visit is earliest on Day 8 following BI 894416 dosing in period 2. This is expected to cover the period during which any adverse effects could reasonably occur.

1.3 RATIONALE FOR PERFORMING THE TRIAL

So far, BI 894416 has been administered to humans in the fasting state, only. In future trials, e.g., in multiple-dosing trials in patients, BI 894416 will be administered also in the non-fasting state. However, so far it has not been investigated whether oral bioavailability of BI 894416 could be affected by food.

This clinical trial will be performed to investigate the effect of food on bioavailability (assessed as relative bioavailability comparison of fed vs. fasting state) of BI 894416 as tablet formulation.

1.4 BENEFIT - RISK ASSESSMENT

Participation in this clinical trial is without any (therapeutic) benefit for healthy subjects. Their participation, however, is of major importance for the development of BI 894416. Subjects are exposed to risks of study procedures and risks related to the exposure to the trial medication.

1.4.1 Expected benefit to the target population

Asthma is a heterogeneous disease that is driven by the innate and adaptive immune pathway. In severe asthma, both the T2-high and T2-low, and the non-T2 inflammation pathways are involved, and associated with a mixed pattern of inflammation involving eosinophil, basophil, mast, neutrophil, innate lymphoid and dendritic cells. Up to 50% of severe asthma is driven by the non T2 and/or T2-low alone or in combination with the T2-high pathway. This non T2 / T2-low component represents an area of unmet medical need that does not respond to high dose inhaled corticosteroids or other current controller therapy, and is unlikely to respond to the T2-high monoclonal antibodies targeted therapies.

SYK is a key component of signal transduction associated with the T2-high and T2-low, and non-T2 asthma pathways that is activated through interaction with allergens and a number of innate and adaptive immune receptors including Fc receptors on basophils, mast, B and T

cells. SYK is also important in the signal propagation of the dectin family of innate receptors, present on macrophages, dendritic cells and neutrophils.

Such a therapy would meet a substantial unmet need for severe asthma patients, especially those with a non T2 and/or T2-low component, whether early/late-onset or steroid resistant, and could become a safe and effective substitute used before high dose inhaled corticosteroids, oral systemic corticosteroids or T2-high biological monoclonal antibodies.

1.4.2 Procedure-related risks

The use of an indwelling venous catheter or venepuncture for e.g. blood sampling may result in mild bruising, and in rare cases, in transient inflammation of the wall of the vein, or nerve injury, potentially resulting in paraesthesia, reduced sensibility, and/or pain for an indefinite period.

ECG electrodes may cause local and typically transient skin reactions.

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

1.4.3 Drug-related risks and safety measures

Potential effects on immune cells

SYK is involved in the function of basophil, mast, neutrophil and dendritic cells. Moreover, SYK is implicated in the development and function of both T cells and B cells. For details refer to the IB [c03536505].

The risk for healthy volunteers due to effects of BI 894416 on immune cells is expected to be minimal, for the following reasons:

- Inhibition of SYK is not expected to have a negative effect with regards to the immune response of innate immune cells to viral or bacterial infections due to redundancy in the infection immune response. The key neutrophil and dendritic cell functions most likely will be triggered by alternative pathways.
- Safety and tolerability data of trial 1371-0001 are not suggestive of an increased risk of infectious adverse events or of any relevant BI 894416-related findings in WBC, differential blood count, immunoglobulins, or lymphocyte subpopulations after single doses up to 70 mg BI 894416 (see IB [c03536505]).
- Due to the reversible mode of action of BI 894416 with regards to SYK inhibition, any potential effects on immune cells are expected to be of transient nature.

Risk mitigation and monitoring: Subjects with a history or diagnosis of relevant immunological disease will be excluded from trial participation (see Section 3.3.3). Adverse events will be monitored for an increase in infectious adverse events. Safety laboratory contains WBC, differential blood count, and CRP.

Tumour biology and carcinogenicity

The SYK pathway has been hypothesized to act as both a tumour suppressor and a tumour promoter in different types of human cancers [R16-4459]. An increased risk of carcinogenic/metastatic potential in epithelial cancers has been reported in the literature related to SYK knock-out, but not related to SYK inhibition. Allelic deletion of SYK has been associated with breast adenocarcinoma [R15-4770]. However, there is no evidence that pharmacologic inhibition of SYK will increase carcinogenicity or metastatic risk. Preclinical data with a potent and selective tool SYK inhibitor, BI 1002494, are in line with an absence of a carcinogenic effect due to inhibition of SYK enzymatic function [n00243171].

Risk mitigation and monitoring: Only male subjects are included in this trial. In view of the extended time necessary to induce a carcinogenic effect, two single doses of BI 894416 are not considered a relevant carcinogenic risk to male subjects participating in this study. Accordingly, no further risk mitigation is required in this study.

Platelet aggregation and bleeding risk

A role of SYK in platelet function has been demonstrated in literature [R15-5470]. Several platelet functions rely on SYK signalling (e.g. collagen receptor GPVI) but others are independent of SYK [R16-5240]. *In vitro* studies using human platelets demonstrated that at concentrations up to 100 µM, BI 894416 had no effect on extrinsic or intrinsic coagulation pathways. Also, BI 894416 did not inhibit ADP-induced platelet aggregation up to 100 µM. However, BI 894416 inhibited collagen- and arachidonic acid-induced platelet aggregation at 3 µM and 5 µM. However, platelet function as measured by bleeding time is not affected by a drug unless all the platelet pathways are inhibited due to redundancy within the system. Therefore, no risk for bleeding exists with regard to platelet inhibition unless a subject is also on another antiplatelet drug that blocks these other pathways.

Risk mitigation and monitoring: Use of any other concomitant drug that could reasonably inhibit platelet aggregation or coagulation (e.g. acetylsalicylic acid) will be prohibited (see Section 4.2.2.1). Adverse events will be monitored for any signs of bleeding or bleeding-related adverse events.

Bone density

SYK is reported to be involved in osteoclast differentiation, development and function. For details see the IB [c03536505]. In this trial, each subject is treated with two single doses of BI 894416. Due to comparatively slow turnover of bone tissue, no relevant effect on bone is expected due to two single-dose administrations with BI 894416 in this trial, and no specific monitoring of bone density is necessary or reasonable in this trial.

Genotoxicity, reproductive and developmental toxicity

Genetic toxicology results by weight of evidence indicate that BI 894416 is not mutagenic or clastogenic. In the 2-week repeat dose range finding study in male rats [n00240179], degeneration of spermatids of the testes was observed at ≥400 mg/kg/day, which is considered a secondary effect, related to overt toxicity and morbidity.

It is unknown whether BI 894416 or its metabolites are distributed into male semen. Theoretically there is therefore a risk for exposure of a study subject's female partner who is a woman of child bearing potential (WOCBP) to subtherapeutic exposures of BI 894416 or its metabolites via male semen. Developmental and reproductive studies have not yet been

conducted, therefore the effect of subtherapeutic concentrations of BI 894416 or its metabolites with regards to embryofetal risk has not been explored so far.

Risk mitigation: In order to address the risk of exposure of a subject's female WOCBP partner to BI 894416 or its metabolites via the subject's seminal fluid, subjects need to use barrier contraception (condom) or abstinence (see Section 3.3.3).

Phototoxicity

Subjects will be advised to avoid direct exposure to sun and UV light during the entire study (see Section 4.2.2.2). Further protective measures would not be necessary given the low phototoxic potential of BI 894416.

Potential effects on QT interval

Preclinical studies suggested no proarrhythmic potential or cardiovascular liability with BI 894416. However, statistical results of first-in-man trial 1371-0001 showed a most-likely dose- and concentration-dependent increase of QTcF interval. At gMean C_{max} of the 70 mg dose group, placebo- and baseline-corrected predicted mean QTcF increase was 5.9 ms (upper limit of the 90% CI was 10.5 ms). A dose- or concentration-dependent effect on heart rate was not observed. It is expected that plasma concentrations reached in current trial 1371-0021 are lower than the maximal plasma concentrations reached in trial 1371-0001.

Risk mitigation: Subjects with cardiovascular disorders (Section 3.3.3, exclusion criterion 5), subjects who used drugs that cause QT/QTc prolongation (Section 3.3.3, exclusion criterion 11), subjects that show a marked baseline prolongation of QT/QTc interval or any other relevant ECG finding at screening (Section 3.3.3, exclusion criterion 19), and subjects with a history of additional risk factors for Torsade de Pointes arrhythmia (Section 3.3.3, exclusion criterion 20) are excluded from trial participation. Moreover, subjects are in-house under close observation for 24 h following drug administration, and ECGs are done pre- and post-dose at the time points given in the Flow Chart. Considering these risk-mitigating measures, the risks to subjects participating at trial 1371-0021 due to potential effects on QT interval are considered minimal.

Drug-induced liver injury

Although rare, a potential for drug-induced liver injury (DILI) is under constant surveillance by sponsors and regulators. Therefore, this trial requires timely detection, evaluation, and follow-up of laboratory alterations in selected liver laboratory parameters to ensure subjects´ safety; see also section 5.2.6.1.4, adverse events of special interest.

1.4.4 Overall assessment of benefit-risk ratio

BI 894416 is a highly specific SYK inhibitor that has been adequately characterised in pre-clinical studies. The non-clinical safety package supports administration of BI 894416 for up to 4 weeks duration to men.

Data of trial 1371-0001 indicate good safety and tolerability of single oral doses of BI 894416 at all dose levels, i.e. up to 70 mg. In addition, data from oral administration of three SYK inhibitors are available and provide additional information on safety and tolerability of this class of drug in man. Published data indicate acceptable safety and tolerability of these three SYK inhibitors in healthy volunteers (see IB [c03536505]).

Plasma concentrations of BI 894416 in current trial 1371-0021 are expected to be in the range of the plasma concentrations that were measured in previous trial 1371-0001 and that were associated with good safety and tolerability.

Inhibition of SYK would meet a substantial unmet need for severe asthma patients, especially those with a non T2 and/or T2-low component, whether early/late-onset or steroid resistant, and could become a safe and effective substitute used before high dose inhaled corticosteroids, oral systemic corticosteroids or T2-high biological monoclonal antibodies.

This trial is required for the development of BI 894416. It is designed to assess the effect of food on bioavailability of BI 894416 as tablet formulation (in terms of relative bioavailability in fed vs. fasting state). The resulting data are planned to inform future trials regarding the administration of BI 894416 in relation to food intake.

Considering the medical need for an effective and safe treatment of uncontrolled severe asthma, the benefit of this trial is assessed to outweigh the potential risks.

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 investigate the relative bioavailability of BI 894416 as tablet formulation following a high-fat, high calorie breakfast (Test, T) compared with administration in the fasting state (Reference, R).

2.1.2 Primary endpoints

The following pharmacokinetic parameters will be determined for BI 894416:

- $AUC_{0\text{-}tz}$ (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 BI 894416:

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

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

The study will be performed as a randomised, open-label, two-way crossover trial in healthy male subjects in order to compare the test treatment (T) to the reference treatment (R). The treatments will be 30 mg BI 894416 as tablet formulation (3 tablets à 10 mg) following a high-fat, high-calorie breakfast (T) or 30 mg BI 894416 as tablet formulation (3 tablets à 10 mg) administered in the fasting state (R). 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 5 days between the treatments.

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

The open-label treatment is not expected to bias results, since the study endpoints are derived from measurement of plasma concentrations of the analyte, which are not expected to be influenced by the knowledge of treatment received.

3.3 SELECTION OF TRIAL POPULATION

It is planned that 14 healthy male subjects will enter the study. They will be recruited from the volunteers' pool of the trial site.

Only male subjects will be included in the study because no data on reproductive toxicology are available at this time and because, until availability of data from the 26-week Tg.rasH2 carcinogenicity study, study populations are restricted to male volunteers or patients (see IB [c03536505]).

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 study will be performed in healthy subjects.

3.3.2 Inclusion criteria

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

1. Healthy male 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 50 years (inclusive)
3. BMI of 18.5 to 29.9 kg/m^2 (inclusive)
4. Signed and dated written informed consent prior to admission to the study, in accordance with GCP and local legislation

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 and including the neurological examination) 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. Chronic or relevant acute infections
10. History of relevant allergy or hypersensitivity (including allergy to the trial medication or its excipients)
11. 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)
12. 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
13. Smoker (unless the subject quit smoking for at least 3 months prior to first planned administration of trial medication)
14. Alcohol abuse (consumption of more than 24 g per day)
15. Drug abuse or positive drug screening
16. Blood donation of more than 100 mL within 30 days of planned administration of trial medication or intended blood donation during the trial

17. Intention to perform excessive physical activities within one week prior to the administration of trial medication or during the trial
18. Inability to comply with the dietary regimen of the trial site
19. A marked baseline prolongation of QT/QTc interval (such as QTc intervals that are repeatedly greater than 450 ms) or any other relevant ECG finding at screening
20. A history of additional risk factors for *Torsade de Pointes* (such as heart failure, hypokalaemia, or family history of Long QT Syndrome)
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

In addition, the following trial-specific exclusion criteria apply:

22. History of relevant neurological disorder affecting the peripheral or central nervous system (this includes, but is not limited to: stroke, epilepsy, inflammatory or atrophic diseases affecting the nervous system, cluster headache or any cancer of the nervous system). Febrile seizures in childhood or adolescence, recovered carpal tunnel syndrome, recovered uncomplicated meningitis, recovered herpes zoster, tension headache, occasional benign tics (e.g. due to stress) or minor par- or dysesthesia (e.g. as a side effect of prior blood withdrawal) do not constitute a history of relevant neurological disorder.
23. History of immunological disease except allergy not relevant to the trial (such as mild hay fever or dust mite allergy) and except asthma in childhood or adolescence
24. History of cancer (other than successfully treated basal cell carcinoma)
25. Male subjects with WOCBP partner who are unwilling to use male contraception (condom or sexual abstinence) from time point of first administration of trial medication until 30 days after the last administration of trial medication
26. ALT (alanine transaminase), AST (aspartate transaminase), or creatinine exceed upper limit of normal range at screening, confirmed by a repeat test
27. Within 10 days prior to administration of trial medication, use of any drug that could reasonably inhibit platelet aggregation or coagulation (e.g., acetylsalicylic acid)

For study restrictions, refer to Section 4.2.2.

3.3.4 Withdrawal of subjects from treatment or assessments

Subjects may discontinue trial treatment or 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, the data will be included in the CRF and will be reported in the CTR. At the time of

discontinuation, a complete end of trial examination will be performed, if possible, and the information will be recorded in the CRF.

3.3.4.1 Discontinuation of trial treatment

An individual subject will discontinue trial treatment if:

1. The subject wants to discontinue trial treatment, without the need to justify the decision
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, 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 surgery, adverse events [AEs], or diseases)
5. The subject has an elevation of AST and/or ALT ≥3-fold ULN and an elevation of total bilirubin ≥2-fold ULN (measured in the same blood sample) and/or needs to be followed up according to the DILI checklist provided in the ISF
6. The subject experiences a drug-related AE of severe intensity or a serious AE.

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

Even if the trial treatment is discontinued, the subject remains in the trial and, given his agreement, will undergo the procedures for early treatment discontinuation and follow up as outlined in the Flow Chart and section 6.2.3.

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:

1. Failure to meet expected enrolment goals overall or at a particular trial site
2. New toxicological findings, serious adverse events, or any safety information invalidating the earlier positive benefit-risk-assessment. More specifically, the trial will be terminated if more than 50% of the subjects have drug-related and clinically relevant adverse events of moderate or severe intensity, or if at least 1 drug-related serious adverse event is reported
3. Violation of GCP or the CTP impairing the appropriate conduct of the trial

4. The sponsor decides to discontinue the further development of the investigational product.

3.3.5 Replacement of subjects

In case more than 2 subjects do not complete the trial, the Clinical Trial Leader together with the Trial Pharmacokineticist and the Trial Statistician are to decide, if and how many subjects will be replaced. A replacement subject will be assigned a unique trial subject number, and will be assigned to the same treatment sequence as the subject he replaces.

4. TREATMENTS

4.1 INVESTIGATIONAL TREATMENTS

The investigational product has been manufactured by BI Pharma GmbH & Co. KG.

4.1.1 Identity of the Investigational Medicinal Products

The characteristics of the test product are given below:

Substance:	BI 894416
Pharmaceutical formulation:	Tablet
Source:	BI Pharma GmbH & Co. KG, Germany
Unit strength:	10 mg
Posology:	3-0-0
Route of administration:	oral
Duration of use:	1 day (in treatment R and T)

4.1.2 Selection of doses in the trial

For the current trial a dose of 30 mg BI 894416 is selected to ensure that, in case administration with food increases the bioavailability of BI 894416, BI 894416 plasma concentrations are in the range that were reached in previous first-in-man trial 1371-0001 and that were safe and well-tolerated.

BI 894416 is a BCS class I compound. As such, no relevant food effect is expected, however, until food effect results in man are available, we assume as a worst-case that an up to 2-fold increase of BI 894416 bioavailability when given with food cannot be fully excluded.

In first-in-man trial 1371-0001, single oral doses of 3 to 70 mg BI 894416 were given as oral solution, and doses of 10 and 40 mg were given as tablets. All doses in trial 1371-0001 were assessed as safe and well-tolerated. In trial 1371-0001, BI 894416 gMean plasma exposure at a dose of 30 mg was 527 nM for C_{max} and 3140 nM*h for AUC_{0-24}, and BI 894416 gMean plasma exposure at a dose of 70 mg was 2190 nM for C_{max} and 11200 nM*h for AUC_{0-24} (preliminary data, see c03536505). That means, the ratios of gMean plasma exposure parameters at 70 mg and at 30 mg were approximately 4 for both C_{max} and AUC_{0-24}. These ratios are sufficient for the current trial to cover potential BI 894416 plasma exposure increases when given with food.

4.1.3 Method of assigning subjects to treatment groups

The randomisation list 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

list will be allocated to the subjects by drawing lots. Subjects are then assigned to a treatment sequence according to the randomisation list.

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

The randomisation procedure is described in Section 7.6.

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. Treatment of all subjects on the same calendar day is acceptable from a safety point of view (for safety margin to exposure in previous SRD trial 1371-0001 refer to Section 4.1.2; for discussion of study-associated risks and safety measures see Section 1.4).

4.1.4 Drug assignment and administration of doses for each subject

This trial is a 2-way crossover study. All subjects will receive the 2 treatments in randomised order. The treatments to be evaluated are outlined 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)	BI 894416	Tablet	10 mg	3 tablets (30 mg) as one single dose on Day 1 following a high-fat, high-calorie breakfast	30 mg
R (Reference)	BI 894416	Tablet	10 mg	3 tablets (30 mg) as one single dose on Day 1 in the fasting state	30 mg

Administration of investigational medicinal product: 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 sitting/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, and – if applicable – its preparation (e.g. reconstitution), if correct dosage cannot be ensured otherwise.

Treatment R: 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.

Treatment T: Subjects are to fast overnight prior to administration. Fasting is to start no later than 10 h before the scheduled dosing. A high-fat, high-calorie meal will be served 30 min before drug administration. The subjects must completely consume the meal prior to drug intake. The composition of the standard high-fat, high-calorie meal is detailed in Table 4.1.4: 2; this meal is in compliance with the FDA guidance 'Food-Effect Bioavailability and Fed Bioequivalence Studies' [R03-2269]. For restrictions with regard to diet, see Section 4.2.2.2.

Table 4.1.4: 2 Composition of the high-fat, high-calorie meal

Ingredients	kcal
2 chicken eggs (whole content) for scrambled eggs[1]	192
10 g butter for frying scrambled eggs	75
35 g fried bacon	186
2 toasted slices of wheat bread	130
15 g butter for buttering toast slices	113
115 g hash brown potatoes	132
240 mL whole milk (3.5% fat)	156
Sum[2]	984

[1] Whole eggs or liquid egg may be used

[2] The total caloric content is supplied approximately as following: 150 kcal as protein, 250 kcal as carbohydrate, and 500 to 600 kcal as fat.

All treatments: Subjects will be kept under close medical surveillance until 24 h after drug administration. During the first 4 h after drug administration, subjects are not allowed to lie down (i.e. no declination of the upper body of more than 45 degrees from upright posture).

The treatments will be separated by a wash-out phase of at least 5 days.

4.1.5 Blinding and procedures for unblinding

This open label Phase I trial will be handled in an open fashion throughout (that is, during the conduct, including data cleaning and preparation of the analysis). This is considered acceptable because the potential for bias seems to be low and does not outweigh practical considerations.

Emergency envelopes will not be provided, because the dose of trial medication and food condition is known to investigators and subjects.

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 local law and the principles of Good Manufacturing Practice.

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

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 EudraCT 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 trial manager (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 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 medication to trial subjects. The trial medication must be administered in the manner specified in the CTP.

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. All concomitant or rescue therapies will be recorded (including time of intake on study days) on the appropriate pages of the CRF.

Acetylsalicylic acid or other drugs that may inhibit platelet aggregation or coagulation should be avoided during the entire study.

Known inhibitors/inducers of CYP3A and P-glycoprotein activity should be avoided during the entire study.

4.2.2.2 Restrictions on diet and life style

Poppy-seeds containing foods should not be consumed starting 3 days before drug administration in each treatment period, in order to avoid false-positive results in the drug screen.

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 milk served with breakfast (treatment T, only; see Table 4.1.4: 2), 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 3000 mL.

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 the second study period is collected.

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

Methylxanthine-containing drinks or foods (such as coffee, tea, cola, energy drinks, or chocolate) are not allowed from 10 h before until 24 h after each administration of trial medication.

Smoking is not allowed during the trial.

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.

Direct exposure to the sun or exposure to solarium radiation should be avoided during the entire study.

4.3 TREATMENT COMPLIANCE

Compliance will be assured by administration of all trial medication in the study 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, relevant medical history and concomitant therapy, review of inclusion and exclusion criteria, review of vital signs (BP, PR), 12-lead ECG, laboratory tests, a physical examination and a neurological 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) will be measured by a blood pressure monitor (Dinamap Pro 100, GE Medical Systems, Freiburg, Germany) 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 that will be determined are listed in Tables 5.2.3: 1 and 5.2.3: 2. Reference ranges will be provided in the ISF, Section 10.

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, respectively.

Table 5.2.3: 1 Routine laboratory tests

Functional lab group	BI test name [comment/abbreviation]	A[1]	B[1]	C[1]
Haematology	Haematocrit	X	X	X
	Haemoglobin	X	X	X
	Red Blood Cell Count/Erythrocytes	X	X	X
	White Blood Cells/Leucocytes	X	X	X
	Platelet Count/Thrombocytes (quant)	X	X	X
Automatic WBC differential, relative	Neutrophils/Leukocytes; Eosinophils/Leukocytes; Basophils/ Leukocytes; Monocytes/Leukocytes; Lymphocytes/Leukocytes	X	X	X
Automatic WBC differential, absolute	Neutrophil, absol.; Eosinophils, absol.; Basophils, absol.; Monocytes, absol.; Lymphocytes, absol.	X	X	X
Manual differential WBC (if automatic differential WBC is abnormal)	Neut. Poly (segs); Neut. Poly (segs), absol.; Neutrophils Bands; 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	X	X	--
	Prothrombin time – INR (International Normalization Ratio)	X	X	--
Enzymes	AST [Aspartate transaminase] /GOT, SGOT	X	X	X
	ALT [Alanine transaminase] /GPT, SGPT	X	X	X
	Alkaline Phosphatase	X	X	--
	Gamma-Glutamyl Transferase	X	X	--
Hormones	Thyroid Stimulating Hormone	X	--	--
Substrates	Glucose (Plasma)	X	X	--
	Creatinine	X	X	X
	Bilirubin, Total	X	X	X
	Bilirubin, Direct	X	X	--
	Protein, Total	X	X	--
	C-Reactive Protein (Quant)	X	X	X
Electrolytes	Sodium	X	X	X
	Potassium	X	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 RBC/Erythrocytes (qual)	X	X	--
	Urine WBC/Leucocytes (qual)	X	X	--
	Urine pH	X	X	--
Urine sediment (microscopic examination if erythrocytes, leukocytes nitrite or protein are abnormal in urine)	Only positive findings will be reported (for instance, the presence of sediment bacteria, casts in sediment, squamous epithelial cells, erythrocytes, leukocytes)			

[1] A, B, and C are different sets of laboratory values. The Flow Chart details at which time point which set is to be investigated.

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 drug screening, it is planned to perform these tests during screening only. 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/XTC Opiates Phencyclidine Tricyclic antidepressants
Cotinine test (urine)	Cotinine
Infectious serology (blood)	Hepatitis B surface antigen (qualitative) Hepatitis B core antibody (qualitative) Hepatitis C antibodies (qualitative) HIV-1 and HIV-2 antibody (qualitative)

To encourage compliance with alcoholic restrictions, a breath alcohol test (e.g. Alcotest® 7410, Dräger AG, Lübeck, Germany) will be performed prior to each treatment period, and may be repeated at any time during the study 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 MVZ Labor Ravensburg GbR, Elisabethenstraße 11, 88212 Ravensburg, Germany, with the exception of drug screening tests. These tests will be performed at the trial site using M-10/14-PDT multiline test, or comparable test systems.

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

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, GE Medical Systems, Freiburg, Germany) 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 study procedures scheduled for the same time to avoid compromising ECG quality.

All ECGs will be stored electronically on the Muse CV Cardiology System (GE Medical Systems, Freiburg, Germany). 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 (at screening) 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

5.2.5.1 Neurological examination

At Screening, a physical neurological examination will be performed. Upon investigator judgment, additional neurological examinations may be added at any time during the trial, for individual subjects or for the whole treatment group.

The neurological examination will include the following assessments:

- Eye movement
- Pupil size and pupil reactivity
- Reflexes
- Assessment of muscle strength
- Gait
- Romberg test
- Tremor
- Point-to-point movements
- Sensitivity

Documentation, Assessment, and Reporting

Results will be documented in source data at the clinical trial site and assessed for clinical relevance by an investigator, deputy investigator or sub-investigator. Clinically relevant findings of the neurological examination will be reported as Adverse Events (during the trial) or as baseline conditions (at screening). Case narratives may be written if necessary.

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 or not considered related to the medicinal product.

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
- Requires 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

5.2.6.1.3 AEs considered ‘Always Serious’

Cancers of new histology and exacerbations of existing cancer 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'**.

In accordance with the European Medicines Agency initiative on Important Medical Events, Boehringer Ingelheim has set up a list of further AEs, which, by their nature, can always be considered to be 'serious' even though they may not have met the criteria of an SAE as defined above.

The latest list of 'Always Serious AEs' can be found in the eDC system, an electronic data capture system which allows the entry of trial data at the trial site. These events should always be reported as SAEs as described above.

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.

The following are considered as AESIs:

- Hepatic injury
  A hepatic injury is defined by the following alterations of hepatic laboratory parameters:
  - An elevation of AST (aspartate transaminase) and/or ALT (alanine transaminase) ≥3-fold ULN combined with an elevation of total bilirubin ≥2-fold ULN measured in the same blood sample, or
  - Aminotransferase (ALT, and/or AST) elevations ≥10 fold ULN

  These lab findings constitute a hepatic injury alert and the subjects showing these lab abnormalities need to be followed up according to the 'DILI checklist' provided in the ISF. In case of clinical symptoms of hepatic injury (icterus, unexplained encephalopathy, unexplained coagulopathy, right upper quadrant abdominal pain, etc.) without lab results (ALT, AST, total bilirubin) available, the Investigator should make sure that these parameters are analysed, if necessary in an unscheduled blood test. Should the results meet the criteria of hepatic injury alert, the procedures described in the DILI checklist should be followed.

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 the relationship, considering all relevant factors, including pattern of reaction, temporal relationship, de-challenge or re-challenge, confounding factors such as concomitant medication, concomitant diseases and relevant history.

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

- The event is consistent with the known pharmacology of the drug
- The event is known to be caused by or attributed to the drug class
- A plausible time to onset of the event relative to the time of drug exposure
- Evidence that the event is reproducible when the drug is re-introduced
- No medically sound alternative aetiologies that could explain the event (e.g. pre-existing or concomitant diseases, or co-medications)
- The event is typically drug-related and infrequent in the general population not exposed to drugs (e.g. Stevens-Johnson syndrome)
- An indication of dose-response (i.e. greater effect size if the dose is increased, smaller effect size if dose is 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
- Additional arguments amongst those stated before, like alternative explanation (e.g. situations where other drugs or underlying diseases appear to provide a more likely explanation for the observed event than the drug concerned)
- Disappearance of the event even though the trial drug treatment continues or remains unchanged

5.2.6.2 Adverse event collection and reporting

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 as well as the time of onset, end time, and intensity of these events. 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:
    - 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 or trial database 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 AEs but should only report any occurrence of cancer and related SAEs and related AESIs of which the investigator may become aware of by any means of communication, e.g. phone call. Those AEs should, however, not be reported in the CRF.

5.2.6.2.2 AE reporting to the sponsor and timelines

The Investigator must report SAEs, AESIs, and non-serious AEs which are relevant for the reported SAE or AESI, on the BI SAE form via fax immediately (within 24 hours) to the sponsor's unique entry point (country specific contact details will be provided in the ISF). The same timeline applies if follow-up information becomes available. In specific occasions the Investigator could inform the sponsor upfront via telephone. This does not replace the requirement to complete and fax the BI SAE form.

With receipt of any further information to these events, a follow-up SAE form has to be provided. For follow-up information, the same rules and timeline apply as for initial information.

5.2.6.2.3 Information required

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 assessed as 'chronic' or 'stable', or no further information can be obtained.

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

For quantification of BI 894416 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 venepuncture with a metal needle.

The EDTA-anticoagulated blood samples will be centrifuged for approximately 10 min at approximately 2000 g to 4000 g and at 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 blood collection until transfer of plasma aliquots into the freezer should be completed within 90 min, with interim storage of blood samples and 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. Further information such as matrix may also be provided.

After completion of the quantification of BI 894416 in a plasma aliquot, the left-over and/or back-up aliquot may be used for further methodological investigations (e.g. for stability testing or assessment of metabolites. 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 study samples will be discarded after completion of the additional investigations but not later than 5 years after the CTR is archived.

5.3.3 Analytical determinations

5.3.3.1 Analytical determination of analyte plasma concentration

BI 894416 concentrations in plasma will be determined by a validated LC-MS/MS (liquid chromatography tandem mass spectrometry) assay. All details of the analytical method will be available prior to the start of sample analysis.

5.4 BIOBANKING

Not applicable.

5.5 OTHER ASSESSMENTS

5.5.1 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.

5.6 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, standard laboratory values, and ECG parameters 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 Sections 2.1.2, 2.1.3, 2.2.2.1, and 5.3 are generally used assessments of drug exposure.

Due to neurologic effects observed in dog studies, a neurological examination is performed at Screening to ensure that no subject with a clinically relevant finding in the neurological examination is included into the trial. Upon investigator judgment, additional neurological examinations may be added at any time during the trial, for individual subjects or for the whole treatment group.

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.

The acceptable deviation from the scheduled time for vital signs, ECG, and laboratory tests will be ± 1 h.

If scheduled in the Flow Chart at the same time as a meal, blood sampling, vital signs, and 12-lead ECG recordings have to be done first. Furthermore, if several measurements including venepuncture are scheduled for the same time, venepuncture 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.

Starting from 48 hours after BI 894416 administration a time window of ± 120 min will be allowed for all study activities.

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 study.

For information regarding laboratory tests (including drug and virus screening), ECG, vital signs, physical examination and neurological 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 5.5.1).

6.2.2 Treatment periods

Each subject is expected to participate in 2 treatment periods (Days -5 to 3 in period 1 and Days 1, 2, and 3 in period 2). At least 5 days will separate drug administrations in the first and second treatment periods.

On Day 1 of each treatment period, study participants will be admitted to the trial site and kept under close medical surveillance for at least 24 h following drug administration. The subjects will then be allowed to leave the trial site after formal assessment and confirmation of their fitness. On all other study days, subjects will be treated 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. For details on times of all other trial procedures, refer to the Flow Chart. AEs and concomitant therapy will be assessed continuously from screening until the end of trial examination.

6.2.3 Follow-up period and trial completion

For AE assessment, laboratory tests, recording of ECG and vital signs, physical examination and neurological examination during the follow-up period, see Sections 5.2.1 to 5.2.6. Subjects who discontinue treatment before the end of the planned treatment period should undergo the EoTrial Visit.

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 EoTrial 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 STATISTICAL DESIGN – MODEL

The main objective of this trial is to investigate the effect of food on the relative bioavailability of BI 894416 administered as a single dose of 30 mg to healthy male volunteers. The drug administration after a standardised high fat, high caloric meal is regarded as the test treatment (T) while the intake of BI 894416 tablets under fasted conditions is the reference treatment (R). The trial is designed to allow intra-subject comparisons between the fasted and fed condition and will be evaluated statistically by use of an appropriate linear model.

A further objective is to evaluate and compare further pharmacokinetic parameters between the treatments. These pharmacokinetic parameters will be assessed by descriptive statistics.

The assessment of safety and tolerability is a further objective of this trial, and will be evaluated by descriptive statistics for the parameters specified in Section 2.2.2.2.

7.2 NULL AND ALTERNATIVE HYPOTHESES

The relative bioavailability of BI 894416 formula tablet (30 mg) under fasted conditions (R) compared to BI 894416 formula tablets (30 mg) under fed conditions (T) will be estimated by the ratios of the geometric means (test/reference) for the primary and secondary PK endpoints. Additionally, their two-sided 90% confidence intervals (CIs) will be provided. This method corresponds to the two one-sided t-test procedure, each at the 5% significance level. Since the main focus is on estimation and not testing, a formal hypothesis test and associated acceptance range is not specified.

7.3 PLANNED ANALYSES

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 study 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 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 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.

Adherence to the protocol will be assessed by the trial team. Important protocol deviation (IPD) categories will be suggested in the Integrated Quality and Risk Management Plan

(IQRMP), IPDs will be identified no later than in the Report Planning Meeting, and the IPD categories will be updated as needed.

Pharmacokinetics

The pharmacokinetic parameters listed in Section 2.1 for drug BI 894416 will be calculated according to the relevant SOP of the Sponsor (001-MCS-36-472).

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.

Relevant 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 at or before two times median t_{max}. Median t_{max} is to be taken either from the median t_{max} for the reference treatment or from median t_{max} for the test treatment, depending on whether the subject had experienced emesis after taken the test or the reference treatment. Median t_{max} is to be determined excluding the subjects experiencing emesis.
- A predose concentration of BI 894416 is >5% C_{max} value of that subject in the respective treatment period
- Missing samples/concentration data at important phases of PK disposition curve

Plasma concentration data and parameters of a subject which is 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).

7.3.1 Primary endpoint analyses

Statistical model

The statistical model used for the analysis of the primary (AUC_{0-tz} and C_{max}) and secondary ($AUC_{0-\infty}$) endpoints will be an analysis of variance (ANOVA) model on the logarithmic scale. This model will include effects accounting for 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. For tests on subject, period, and treatment effects, the denominator sum of squares will be the sum of squares for error; while for tests on sequence effects, the denominator will be the sum of squares for subjects. 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 (AUC_{0-tz} , C_{max} and $AUC_{0-\infty}$) measured on subject m in sequence i receiving treatmentk 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.

Primary analysis

Point estimates of bioavailability, the ratios of the geometric means (test/reference) for the primary endpoints (see 2.1.2), and their two-sided 90% confidence intervals (CIs) will be provided.

The pharmacokinetic parameters (AUC_{0-tz} and C_{max}) will then be log transformed (natural logarithm) prior to fitting the ANOVA model. The difference between the expected means for test treatments and reference treatment log(T)-log(R), will be estimated by the difference in the corresponding Least Square Means (point estimate) and two-sided 90% confidence intervals based on the t-distribution will be computed. These quantities will then be back transformed to the original scale to give the point estimator (geometric mean) and interval estimates for the ratio between response under test/ fed condition and response under reference/ fasted condition.

Pharmacokinetic parameters of a subject will be included in the analysis unless the subject has an important protocol deviation relevant for the evaluation. If an important protocol deviation only affects one treatment period the analysis for the other period from this subject is included anyway. Whether a protocol deviation is important will be decided no later than in the Report Planning Meeting.

7.3.2 Secondary endpoint analyses

The secondary endpoints (refer to Section 2.1.3) will be calculated according to the BI SOP 'Standards and processes for analyses performed within Clinical Pharmacokinetics/ Pharmacodynamics' (001-MCS-36-472) and will be assessed statistically using the same methods as described for the primary endpoints.

7.3.4 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 under fed and under fasted condition 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 planned time of the measurement or on the recorded time of AE onset (concept of treatment emergent AEs). Therefore, measurements planned or AEs recorded prior to first intake of trial medication will be assigned to the screening period and those between trial medication intake and the trial medication intake in the next treatment period or the EoTrial Visit (whatever comes next) will be assigned to the respective treatment. In case of two or more treatments, the follow-up will be summarized according to the previous treatment. 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 final 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, AESIs (see Section 5.2.6.1), and other significant AEs (according to ICH E3) will be listed separately.

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

Laboratory data will be compared to their reference ranges. Values outside the reference range as well as values defined as possibly clinically significant will be highlighted in the listings. Additionally, differences from baseline will be evaluated.

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

Relevant ECG findings will be reported as AEs.

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7.4 INTERIM ANALYSES

A preliminary, exploratory analysis of the PK parameters (AUC_{0-tz}, $AUC_{0-\infty}$ and C_{max} of BI 894416) may be performed based on all evaluable data after last subject out and prior to data base lock. This may be necessary, e. g., in case the information is needed to inform other activities during the development of BI 894416 such as food intake in relation to BI 894416 intake in other studies. In contrast to the final PK calculations, the preliminary, exploratory analysis will be based on planned sampling times rather than on actual times, regardless of whether actual times were within the time windows or not. Therefore, minor deviations of preliminary and final results may occur. Results will be provided as individual values and geometric means as well as the adjusted gMean ratios determined according to the planned primary analysis described in Section 7.3.1. The preliminary, exploratory results will be distributed to the trial team.

7.5 HANDLING OF MISSING DATA

7.5.1 Safety

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

7.5.2 Pharmacokinetics

Handling of missing PK data will be performed according to the relevant Corporate Procedure (001-MCS-36-472).

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

7.6 RANDOMISATION

Subjects will be randomised to one of the two treatment sequences (RT or TR) 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 list 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 list will contain additional blocks to allow for subject replacement (refer to Section 3.3.5).

7.7 DETERMINATION OF SAMPLE SIZE

It is planned to enter a total of 14 subjects in the trial, including up to 2 non PK evaluable subjects. The planned sample size is not based on a power calculation but is considered sufficient to achieve the aims of this exploratory trial. With this sample size, the following precision in estimating the ratio of geometric means (test/reference) can be expected with 95% probability. Precision is defined as the ratio of upper CI limit to the relative BA estimate. Note that the precision is independent of the actual ratio of geometric means.

The intra-individual coefficient of variation (gCV) was estimated from inter-individual gCV from preliminary PK data of the SRD part of a previous trial using the 30 mg dose (data on file) which will also be used in this trial. The observed inter-individual gCV was roughly 31% for C_{max} and 26% for $AUC_{0\text{-}tz}$. Assuming a within-subject correlation of 0.6 for C_{max} and 0.8 for $AUC_{0\text{-}tz}$, the estimated upper 70% CI of the intra-individual gCV was roughly 27% for C_{max} and 15% for $AUC_{0\text{-}tz}$..

Assuming a gCV of 15% for BI 894416 and given a sample size of 12 subjects with evaluable data for primary analysis, the precision of the two-sided 90% confidence interval of the bioavailability ratio will be approximately 1.16 for a greater gCV of 27%, the precision would still be approximately 1.30. Table 7.7: 1 provides an overview of the achievable precision for estimating the ratio of geometric means (test/reference). For illustrative purposes, the expected 90% confidence intervals with 95% tolerance probability are displayed for different values of the ratios T/R of geometric means.

Table 7.7: 1 Precision that can be expected with 95% tolerance probability and illustrative two-sided 90% confidence intervals around the ratios of geometric means (T/R) for different gCVs in a 2x2 crossover trial (N=12)

gCV [%]	Precision upper CL / relative BA estimate	Ratio [%]*	Lower CL [%]	Upper CL [%]
21	1.23	100	81.22	123.12
21	1.23	150	121.83	184.68
21	1.23	200	162.44	246.24
21	1.23	400	324.89	492.47
27	1.30	100	76.68	130.42
27	1.30	150	115.02	195.63
27	1.30	200	153.35	260.84
27	1.30	400	306.71	521.67
33	1.38	100	72.48	137.97
33	1.38	150	108.72	206.96
33	1.38	200	144.96	275.94
33	1.38	400	289.91	551.89

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

The expected 90% confidence interval limits in the table were derived by

$$\text{CI limit}_{\text{upper,lower}} = \exp(\ln(\theta) \pm \omega),$$

with θ being the ratio (T/R) on original scale and ω the distance from the estimate θ to either confidence interval limit on the log-scale, which was obtained from the achievable precision on the original scale.

The calculation was performed as described by Julious [R11-5230] using R Version 3.5.1.

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.

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 archiving 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 (or the subject's legally accepted representative) according to ICH-GCP and to the regulatory and legal requirements of the participating country. Each signature must be personally dated by each signatory and the informed consent and any additional 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 or the subject's legally accepted representative.

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 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 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.

ClinBase™
In the Human Pharmacology Centre (HPC) – Boehringer Ingelheim's Phase I unit – the validated ClinBase™ system is used for processing information and controlling data collected in clinical studies. In addition to its function as a procedure control system, ClinBase™ serves as data base. 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.

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: sex, 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™ (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™ 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.

Sponsor:
The sponsor must retain the essential documents according to the sponsor's SOPs.

8.4 EXPEDITED REPORTING OF ADVERSE EVENTS

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

8.5 STATEMENT OF CONFIDENTIALITY AND SUBJECT PRIVACY

Individual subject data obtained as a result of this trial is considered confidential and disclosure to third parties is prohibited with the exceptions noted in section 8.7.

Data protection and data security measures are implemented for the collection, storage and processing of patient data in accordance with the principles 6 and 12 of the WHO GCP handbook.

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 has to be in accordance with the informed consent
- The BI-internal facilities storing biological samples from clinical trial participants as well as the external banking 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
- If applicable, 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 **start of the trial** is defined as the date of the enrolment of the first subject in the trial.

The **end of the trial** is defined as the 'date of the last visit of the last subject in whole trial' ('Last Subject Completed') or 'end date of the last open AE' or 'date of the last follow-up test' or 'date of an AE has been decided as sufficiently followed-up', whichever is latest.

Early termination of the trial is defined as the premature termination of the trial for 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 EC/competent authority in each participating EU member state will be notified about the trial milestones according to the laws of each member state.

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 patient (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 Human Pharmacology Centre (HPC) of BI Pharma GmbH & Co. KG, Biberach, Germany, 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.

BI has appointed a Clinical Trial 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 Clinical Trial Managers (CTM), Clinical Research Associates, and investigators of participating trial sites

The trial medication will be provided by the Clinical Trial Supplies Unit, BI Pharma GmbH & Co. KG, Biberach, Germany.

Safety laboratory tests will be performed by the local laboratory of the trial site (
).

Analyses of BI 894416 concentrations in plasma will be performed at

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 BI or a contract research organization appointed by BI 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

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9.2 UNPUBLISHED REFERENCES

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10. APPENDICES

Not applicable.

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

11.1 GLOBAL AMENDMENT 1

Date of amendment		19 Feb 2019
EudraCT number **EU number**		2018-004313-41
BI Trial number		1371-0021
BI Investigational Medicinal Product(s)		BI 894416
Title of protocol		Relative bioavailability of BI 894416 as tablet formulation following a high-fat, high-calorie breakfast compared to administration in the fasting state in healthy male subjects (an open-label, randomised, single-dose, two-period, two-sequence crossover study)
To be implemented only after approval of the IRB / IEC / Competent Authorities		☒
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		☐
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		☐
Section to be changed		1) Flow Chart 2) 3.3.3 3) 3.3.4.1 4) 4.1.3 5) 5.2.3 6) 6.2.2 7) 6.2.3
Description of change		1) Addition of safety laboratory and AE questioning within 5 days prior to administration in the first treatment period; change of post-dose ECG and VS time points post dose on Day 1 to +1:00 h and +2:00 h; addition of AE questioning on Day 1 at +1:00 h; addition of neurological examination to end-of-trial examination 2) Reduction of maximum allowable alcohol consumption to 24 g/day; addition of exclusion criteria 26 and 27 3) Addition of treatment discontinuation criterion 6 4) Clarification that all subjects may be treated on the same calendar day 5) Addition of safety laboratory parameter set C

		6) Adaption of treatment period 1 duration 7) Addition of neurological examination
Rationale for change		1) In response to IEC / Competent Authority objection 2) In response to IEC / Competent Authority objection 3) In response to IEC / Competent Authority objection 4) In response to IEC / Competent Authority objection 5) To detail parameters to be measured within 5 days prior to first administration of trial drug (see point 1 above) 6) To account for addition of a safety laboratory examination prior to treatment period 1 (see point 1 above) 7) In response to IEC / Competent Authority objection

11.2 GLOBAL AMENDMENT 2

Date of amendment		15 May 2019
EudraCT number **EU number**		2018-004313-41
BI Trial number		1371-0021
BI Investigational Medicinal Product(s)		BI 894416
Title of protocol		Relative bioavailability of BI 894416 as tablet formulation following a high-fat, high-calorie breakfast compared to administration in the fasting state in healthy male subjects (an open-label, randomised, single-dose, two-period, two-sequence crossover study)

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

Section to be changed		Title Page
Description of change		Change of Clinical Trial Leader (CTL) “

		” instead of “ ” and change of phone extension
Rationale for change		Change of Clinical Trial Leader (CTL)

APPROVAL / SIGNATURE PAGE

Document Number: c23506058 **Technical Version Number:3.0**

Document Name: clinical-trial-protocol-revision-2

Title: Relative bioavailability of BI 894416 as tablet formulation following a high-fat, high-calorie breakfast compared to administration in the fasting state in healthy male subjects (an open-label, randomised, single-dose, two-period, twosequence crossover study)

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Approval-Clinical Pharmacokinetics		16 May 2019 10:56 CEST
Author-Trial Statistician		16 May 2019 10:57 CEST
Approval-Therapeutic Area		16 May 2019 16:07 CEST
Author-Clinical Trial Manager		16 May 2019 16:14 CEST
Approval-Team Member Medicine		16 May 2019 21:23 CEST
Verification-Paper Signature Completion		27 May 2019 10:41 CEST

(Continued) Signatures (obtained electronically)

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