Clinical Trial Protocol

	Document Number: c12098812-09
EudraCT No.:	2016-003470-40
BI Trial No.:	1371-0001
BI Investigational Product:	BI 894416
Title:	Safety, tolerability, pharmacokinetics and pharmacodynamics of single rising oral doses of BI 894416 in healthy male subjects (single-blind, partially randomised, placebo-controlled parallel group design)
Lay Title:	This study in healthy men tests how different doses of BI 894416 are taken up in the body and how well BI 894416 is tolerated
Clinical Phase:	I
Trial Clinical Monitor:	Phone: Fax:
Principal Investigator:	Phone: Fax:
Status:	Final Protocol (Revised Protocol (based on global amendment 8))
Version and Date:	Version: 9.0 Date: 25 Jul 2018

CLINICAL TRIAL PROTOCOL SYNOPSIS

Name of company: Boehringer Ingelheim		**Tabulated Trial Protocol**	
Name of finished product: Not applicable			
Name of active ingredient: BI 894416			
Protocol date: 09 AUG 2017	**Trial number:** 1371-0001		**Revision date:** 25 JUL 2018

Title of trial:	Safety, tolerability, pharmacokinetics and pharmacodynamics of single rising oral doses of BI 894416 in healthy male subjects (single-blind, partially randomised, placebo-controlled parallel group design)
Principal Investigator:	
Trial site:	
Clinical phase:	I
Objectives:	To investigate safety, tolerability, pharmacokinetics and pharmacodynamics following single rising doses of BI 894416, to obtain pharmacokinetic data of BI 894416 after administration as tablet formulation and to investigate relative bioavailability of a tablet formulation as compared to oral solution
Methodology:	1) Single rising dose (SRD) part: Single-blind, partially randomised within dose groups, placebo-controlled, parallel-group design 2) Relative bioavailability (rel BA) part: Open-label, randomised two-way crossover followed by a fixed sequence design
No. of subjects:	
total entered:	76*
each treatment:	1) SRD part: 8 per dose group (6 on active drug and 2 on placebo) * Additional subjects may be entered in the SRD part to allow testing of additional doses on the basis of experience gained during the trial conduct (e.g., preliminary PK data), provided the planned and approved highest dose will not be exceeded. Thus, the actual number of subjects entered in the SRD part may exceed 64 (may exceed 76 subjects total entered into the trial), but will not exceed 80 subjects entered in the SRD part (will not exceed 92 subjects total entered). 2) Rel BA part: 12 (all on active drug)
Diagnosis:	Not applicable
Main criteria for inclusion:	Healthy male subjects, age of 18 to 45 years, body mass index (BMI) of 18.5 to 29.9 kg/m^2

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Name of finished product: Not applicable			
Name of active ingredient: BI 894416			
Protocol date: 09 AUG 2017	**Trial number:** 1371-0001		**Revision date:** 25 JUL 2018

Test products:	1) SRD part: BI 894416 as a powder for oral solution (PfOS 2) Rel BA part: BI 894416 as a tablet formulation (10 mg)
dose:	1) SRD part: 3 mg, 10 mg, 20 mg, 40 mg, 54 mg (interim dose 30 mg (interim dose), 70 mg, 110 mg, 160 mg, 220 mg 2) Rel BA part: 10 mg (1 tablet; treatment X; in period 1 or 2), 40 mg (4 tablets; treatment Z; in period 3)
mode of admin.:	Oral with 240 mL of water after an overnight fast of at least 10 h
Comparator product:	1) SRD part: Placebo solution 2) Rel BA part: BI 894416 as a powder for oral solution (PfOS
dose:	1) SRD part: Not applicable 2) Rel BA part: 10 mg (treatment Y; in period 1 or 2)
mode of admin.:	Oral with 240 mL of water after an overnight fast of at least 10 h
Duration of treatment:	1) SRD part: One single dose per subject 2) Rel BA part: One single dose per subject in each treatment period (3 single doses in total
Criteria for pharmacokinetics:	1) SRD part: Secondary endpoints: $AUC_{0-\infty}$ and C_{max} of BI 894416 2) Rel BA part: Secondary endpoints: AUC_{0-tz}, $AUC_{0-\infty}$ and C_{max} of BI 894416

Name of company: Boehringer Ingelheim		**Tabulated Trial Protocol**	
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Criteria for safety:

1) SRD part:

Primary endpoint to assess safety and tolerability of BI 894416 is the number [N (%)] of subjects with drug-related adverse events.

2) Rel BA part:

Statistical methods:

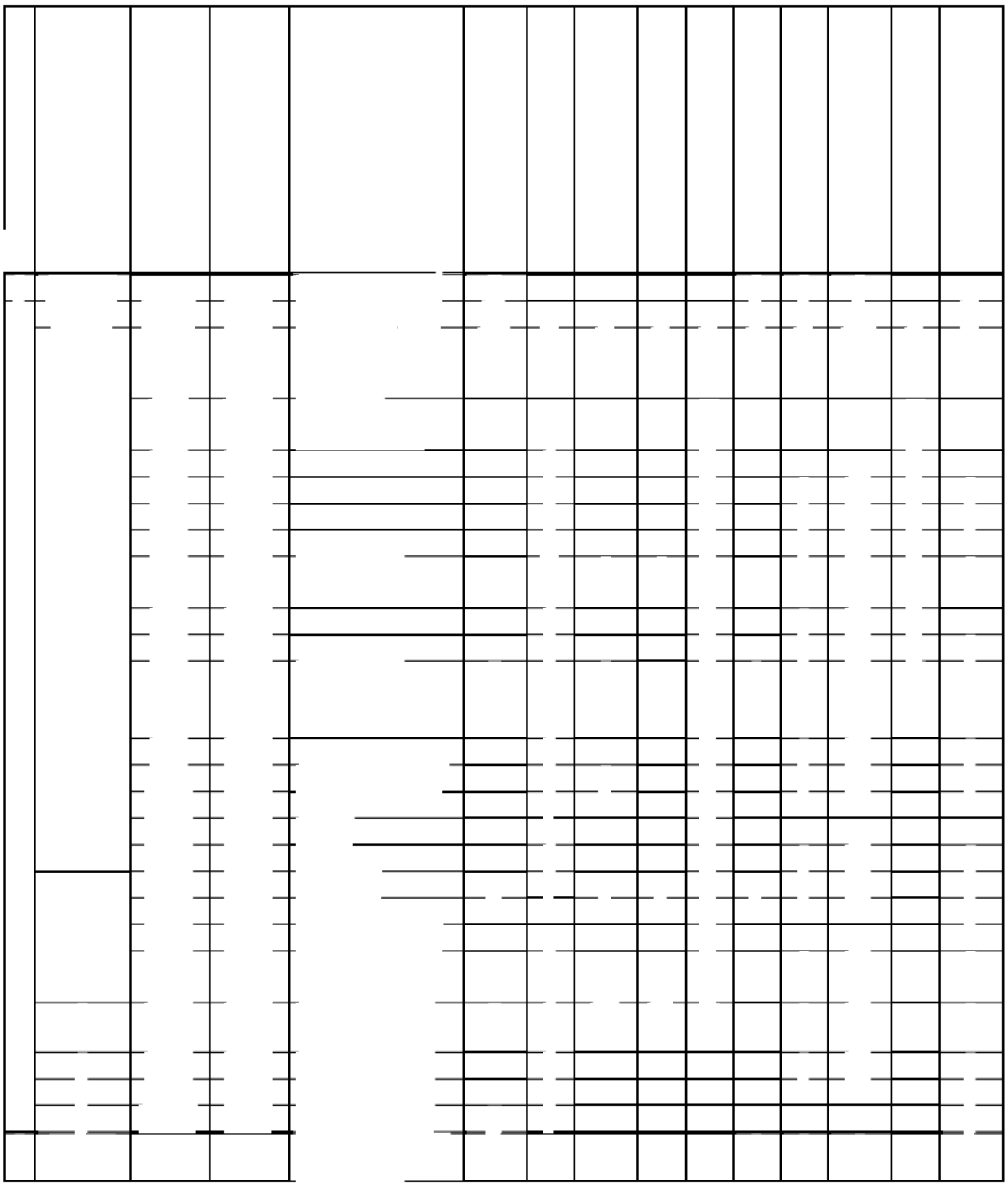
1) SRD part:

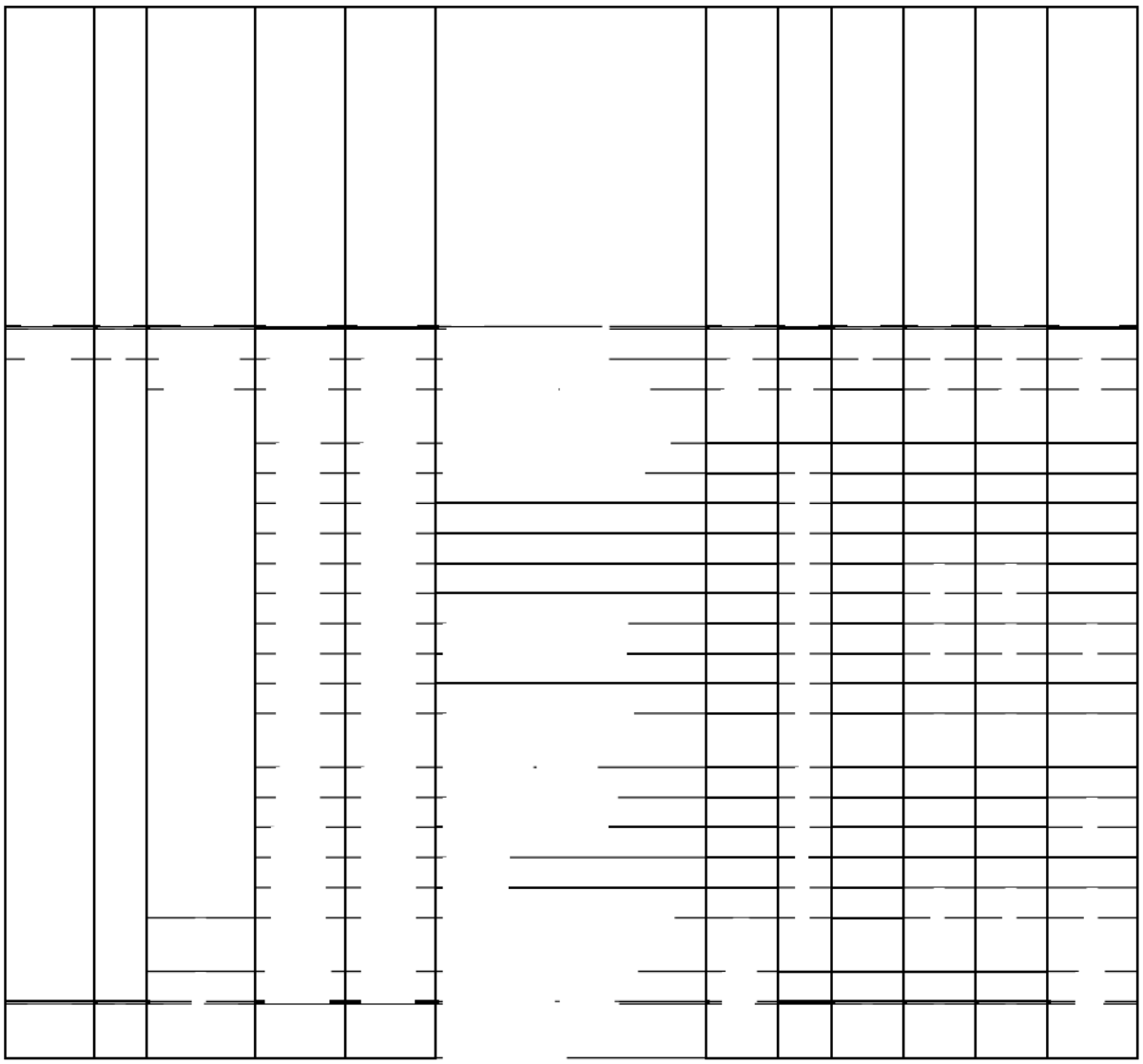
Descriptive statistics for safety, PK will be calculated.

2) Rel BA part:

Relative bioavailability will be estimated by the ratios of the geometric means (tablet 10 mg / PfOS 10 mg) for the secondary endpoints. Additionally, the two-sided 90% confidence intervals (CIs) will be provided. This method corresponds to the two one-sided t-tests procedure, each at the 5% significance level. Since the main focus is on estimation and not testing, an acceptance range was not specified. The statistical model will be an 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 ANOVA.

Descriptive statistics will be calculated for all endpoints.





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2. RATIONALE, OBJECTIVES, AND BENEFIT - RISK ASSESSMENT

2.1 RATIONALE FOR PERFORMING THE TRIAL

This First-in-Man trial is intended to start the clinical development of BI 894416

Single-rising dose (SRD) part

Effects of single rising doses of BI 894416 on safety, tolerability, pharmacokinetics, and will be assessed in healthy male volunteers. Within each dose group, all actively treated individuals will receive the same dose of BI 894416. The next higher dose will only be administered if the treatment in the preceding group was safe and showed acceptable tolerability and if the estimated systemic exposure of the next dose (guided by preliminary PK analyses) does not exceed the maximum acceptable systemic exposure (for details see Sections 2.1.2, 2.1.3, 3.1, 3.3.4.2 and 7.3.4).

Relative bioavailability (rel BA) part

Oral solution formulation of BI 894416 is used in the SRD part of the current trial, whereas further clinical trials with BI 894416 are planned for use with a tablet formulation. However, the relative bioavailability of BI 894416 as tablet formulation compared to oral solution is unknown. It is not excluded, that bioavailability of BI 894416 as tablet formulation may differ from oral solution. Therefore it is required to investigate relative bioavailability of BI 894416 as tablet formulation in comparison to oral solution, in order to plan the doses for further trials.

The rel BA part will be done after the 70 mg dose group was performed in the SRD part.

In the rel BA part, all subjects will be treated with 10 mg BI 894416 as tablet (treatment X) and as oral solution formulation (treatment Y) in a two-way randomized crossover fashion in visits 2 and 3 (periods 1 and 2, respectively). The resulting data will allow assessment of relative bioavailability at a dose of 10 mg.

After analysis of preliminary PK and safety data (see Sections 3.1 and7.3.4), the subjects that participate in the rel BA part will be dosed in visit 4 (period 3) with 40 mg BI 894416 as tablets (treatment Z).

2.1.4 Exploration of relative bioavailability

For the rationale for the relative bioavailability (rel BA) part, please refer to Section 2.1.

Following the 70 mg dose group in the SRD part, rel BA will be explored in the rel BA part. First, rel BA is investigated in two treatment periods (treatment X: tablet 10 mg; treatment Y: oral solution 10 mg) in an open-label, two-way, randomized crossover fashion.

Thereafter, subjects in the rel BA part will be treated in period 3 with 40 mg BI 894416 as tablets (treatment Z), if allowed after analysis of preliminary PK and safety data (see Sections 3.1 and 7.3.4).

2.2 TRIAL OBJECTIVES

The primary objective of this trial is to investigate the safety and tolerability of BI 894416 in healthy male subjects following oral administration of single rising doses of 3 mg, 10 mg, 20 mg, 40 mg, 70 mg, 110 mg, 160 mg, and 220 mg.

Secondary objectives are the exploration of the pharmacokinetics (PK) including dose proportionality after single dosing of BI 894416 as oral solution, the investigation of PK of BI 894416 as tablet formulation and the exploration of relative bioavailability of BI 894416 as tablet formulation compared to oral solution.

A description of the endpoints to be determined, and the observations along with specific information as how to collect the data for that information, is provided in Section 5.

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

The single-rising dose part of the trial is designed as single-blind, partially randomised, and placebo-controlled within parallel dose groups.

The relative bioavailability (rel BA) part of the trial is designed as open-label, two-way crossover followed by a fixed sequence.

A total of 76 healthy male subjects are planned to participate in the trial, thereof 64 in the SRD part and 12 in the rel BA part. Additional dose groups may be added to the SRD part (see below). Therefore the actual number of subjects entered into the trial may exceed 76, but will not exceed 92 subjects entered.

SRD part

A total of 64 healthy male subjects is planned to participate in the SRD trial part, according to 8 sequential groups comprising 8 subjects per group. However, additional subjects may be entered to allow testing of additional doses on the basis of experience gained during the trial conduct (e.g. preliminary PK data), provided the planned and approved highest dose will not be exceeded. Thus, the actual number of subjects entered into the SRD part may exceed 64, but will not exceed 80 subjects entered in the SRD part. Such changes may be implemented via non-substantial CTP Amendments.

Within each dose group, 6 subjects are planned to receive the active drug and 2 are planned to receive placebo. Only one dose is tested within each dose group. Each dose group will consist of 3 cohorts which will be treated subsequently for safety reasons. The 1st and 2nd cohorts will be treated in a fixed sequence and the 3rd cohort will be randomised.

The dose groups to be evaluated in the SRD part are outlined in Table 3.1: 1 below.

Table 3.1: 1 Dose groups of the SRD part

Dose Group	1	2	3	4	11*	9**	5	6	7	8
Dose [mg]	3	10	20	40	54	30	70	110	160	220
Number of subjects	8	8	8	8	8	8	8	8	8	8
Subjects receiving placebo	2	2	2	2	2	2	2	2	2	2
Subjects receiving active drug	6	6	6	6	6	6	6	6	6	6

* Interim dose group added with Global Amendment No. 4 following dose group 4

** Interim dose group added with Global Amendment No. 6 following interim dose group 11

On the first study day of each dose level of the SRD part, the 1st cohort will be treated in the following order: First subject (active) followed at least 10 min later by the second subject (placebo).

The 2nd cohort will be treated not earlier than 22 hours later (minimum time interval between 1st subject of 1st cohort and 1st subject of 2nd cohort). In the 2nd cohort, a time interval of at least 10 min will be maintained between dosings of individual subjects (active – active).

The 3rd cohort will be treated not earlier than 46 hours later (minimum time interval between 1st subject of 2nd cohort and 1st subject of 3rd cohort). In the 3rd cohort, a time interval of at least 10 min will be maintained between dosings of individual subjects (3 active, 1 placebo; randomized order).

The dose groups of the SRD part will be investigated consecutively in ascending order of dose

The decision to proceed to the next dose group will be based upon the safety, tolerability, and pharmacokinetic data of the preceding dose groups. The next dose will only be given if, in the opinion of the investigator and the trial clinical monitor (or authorised deputies), no safety concerns arose in the preceding dose group (i.e. no dose-limiting events occurred) and if none of the pre-specified trial-specific stopping criteria were met (refer to Section 3.3.4.2).

A documented Safety Review must take place prior to each dose escalation. Furthermore, an unscheduled safety review meeting can be requested anytime for any reasonable cause by the Principal Investigator (or an authorised deputy) or the Sponsor of the study, e.g. because of any unforeseen adverse events, etc. Dose escalation will only be permitted if no safety concerns exist in the opinion of the Principal Investigator (or an authorised deputy) and the trial clinical monitor (or an authorised deputy).

The investigator is allowed to alter the scheduled dose levels (e.g. add low and/or intermediate dose levels) on the basis of experience gained during the study, provided the planned and approved highest dose is not exceeded. In this case, the total number of subjects in this trial might increase. The investigator and/or the sponsor should stop dose escalation in case the safety evaluation leads to concerns that would not allow higher dosing.

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

Rel BA part

A total of 12 healthy male subjects is planned to participate in the rel BA trial part.

The rel BA trial part will be started (i.e., dosing in rel BA part will be started) after availability of preliminary PK and safety data of the 70 mg dose group of the SRD trial part.

The rel BA part consists of three treatment periods, and all entered subjects are planned to participate at all three treatment periods. Treatments are open-label. In periods 1 and 2, the subjects will receive the treatments X (one single dose of 10 mg BI 894416, tablet formulation, fasting conditions) and Y (one single dose of 10 mg BI 894416, oral solution formulation, fasting conditions) in a randomized two-way crossover fashion. These two periods are followed, after documented review of PK and safety data of periods 1 and 2 of the rel BA part, by treatment Z (one single dose of 40 mg BI 894416, tablet formulation, fasting conditions).

The subjects will be randomly allocated to the two treatment sequences (X-Y-Z or Y-X-Z).

The decision to start treatment in the rel BA part (i.e. to administer treatment in period 1) will be based upon the safety, tolerability, and pharmacokinetic data of the available dose groups of the SRD part including also the 70 mg dose group.

The decision to administer treatment in period 3 of the rel BA part will be based upon the safety, tolerability, and pharmacokinetic data of the SRD part including also the 70 mg dose group and of periods 1 and 2 of the rel BA part.

Treatment in the rel BA part (i.e. treatment in period 1) will only be started if, in the opinion of the investigator and the trial clinical monitor (or authorised deputies), no safety concerns arose in the preceding dose groups of the SRD part (i.e. no dose-limiting events occurred) and if none of the pre-specified trial-specific stopping criteria were met (refer to Section 3.3.4.2).

Treatment in period 3 of the rel BA part will only be started if, in the opinion of the investigator and the trial clinical monitor (or authorised deputies), no safety concerns arose in the preceding dose groups of the SRD part or in periods 1 and 2 of the rel BA part (i.e. no dose-limiting events occurred) and if none of the pre-specified trial-specific stopping criteria were met (refer to Section 3.3.4.2).

If it is decided, based on the criteria above, that treatment in period 3 is not given, no further procedures in period 3 are to be done;

A documented Safety Review must take place prior to starting treatment in the rel BA part in periods 1 and 3. Furthermore, an unscheduled safety review meeting can be requested anytime for any reasonable cause by the Principal Investigator (or an authorised deputy) or the Sponsor of the study, e.g. because of any unforeseen adverse events, etc. Treatments will only be started if no safety concerns exist in the opinion of the Principal Investigator (or an authorised deputy) and the trial clinical monitor (or an authorised deputy).

The investigator and/or the sponsor should decide to stop treatment of subjects in the rel BA part in case the safety evaluation leads to concerns.

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

3.1.1 Administrative structure of the trial

The trial is sponsored by Boehringer Ingelheim (BI) Pharma GmbH & Co. KG, Germany.

BI has appointed a Trial Clinical Monitor, responsible for coordinating all required activities, in order to

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

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

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.

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

The analyses of BI 894416 concentrations in plasma will be performed at

The digitally recorded 12-lead ECGs will be sent to a specialised contract research organisation ( ) for evaluation.

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 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.

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

For single-rising dose trials, the design described in Section 3.1 is viewed favourable under the provision not to expose the subjects involved to undue risks since the main study objective is to investigate safety and tolerability of BI 894416.

With the rising dose design, single-blind conditions regarding the subject's treatment (active or placebo) are maintained within each dose group. However, the current dose level will be known to subjects and investigators. The disadvantage of this trial design is a possible observer bias with regard to the dose-depending effects as well as time effects, but it has the virtue of minimizing subject risk by sequentially studying ascending doses. As time effects are expected to be small relative to the differences between the doses in the range investigated, unbiased comparisons between treatments can still be expected.

It is standard in trials involving healthy volunteers to include a placebo group as control for the evaluation of safety, tolerability and pharmacodynamic effects. Each dose group consists of 8 subjects with 6 on active treatment, and 2 on placebo. The placebo control group includes all subjects of all dose groups treated with placebo. 6 subjects per active treatment group are in general considered as sufficient for the exploratory evaluation of pharmacokinetics.

For the rel BA part, that is designed to assess relative bioavailability of tablet vs. oral solution formulation at a dose of 10 mg BI 894416 and to obtain pharmacokinetic data at a dose of 40 mg BI 894416 as tablet formulation, the crossover design is viewed favourable due to its efficiency: since each subject serves as his own control, the comparison between the treatments is based on a comparison within subjects rather than between subjects. Thus the inter-subject variability is removed from the comparison between treatments [R94-1529]. The first two periods that compare 10 mg oral solution with 10 mg tablet follow a two-way randomized crossover design, and the third treatment period, 40 mg BI 894416 as tablets, follows in a fixed-sequence crossover design. Subjects will only be treated in the third treatment period if allowed after analysis of preliminary PK and safety data of the preceding periods. This design is chosen to ensure that gMean plasma exposure values of BI 894416 in terms of C_{max} and AUC_{0-24} in the rel BA part do not exceed gMean plasma exposure values in terms of C_{max} and AUC_{0-24} that were observed previously in the SRD part of the trial and that were associated with acceptable safety and tolerability. Treatments in the rel BA part are open-label, as treatments are distinguishable and PK parameters are not expected to be influenced by knowledge of treatment.

3.3 SELECTION OF TRIAL POPULATION

It is planned that 76 healthy male subjects will enter the study. The actual number of subjects entered may exceed the total of 76 if additional intermediate doses will be tested in the SRD part (see Section 3.1), but will not exceed 92 subjects entered. Subjects will be recruited from the volunteers' pool of the trial site.

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

3.3.1 Main diagnosis for study entry

The study will be performed in healthy subjects.

3.3.2 Inclusion criteria

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

1. Healthy male subjects according to the assessment of the investigator, 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 45 years (incl.)
3. BMI of 18.5 to 29.9 kg/m^2 (incl.)
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) is deviating from normal and judged 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 50 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 judged as clinically relevant by the investigator
5. Gastrointestinal, hepatic, renal, respiratory, cardiovascular, metabolic, immunological or hormonal disorders

6. Cholecystectomy and/or surgery of the gastrointestinal tract that could interfere with the pharmacokinetics of the trial medication (except appendectomy and 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 prior to administration of trial medication if that might reasonably influence the results of the trial (incl. QT/QTc interval prolongation)
12. Participation in another trial where an investigational drug has been administered within 60 days prior to planned administration of trial medication, or current participation in another trial involving administration of investigational drug
13. Smoker (more than 10 cigarettes or 3 cigars or 3 pipes per day);
14. Inability to refrain from smoking on specified trial days
15. Alcohol abuse (consumption of more than 30 g per day)
16. Drug abuse or positive drug screening
17. Blood donation of more than 100 mL within 30 days prior to administration of trial medication or intended donation during the trial
18. Intention to perform excessive physical activities within one week prior to administration of trial medication or during the trial
19. Inability to comply with dietary regimen of trial site
20. 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
21. A history of additional risk factors for Torsades de Pointes (such as heart failure, hypokalemia, or family history of Long QT Syndrome)
22. Subject is assessed as unsuitable for inclusion by the investigator, for instance, because considered not 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:

23. 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) *
24. 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
25. History of cancer (other than successfully treated basal cell carcinoma)
26. 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)

27. Male subjects with WOCBP partner who are unwilling to use male contraception (condom or sexual abstinence) from time point of administration of trial medication until 30 days thereafter.

* 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.

For study restrictions, refer to Section 4.2.2.

3.3.4 Removal of subjects from therapy or assessments

3.3.4.1 Removal of individual subjects

An individual subject is to be removed from the trial if:

1. The subject withdraws consent for trial treatment or trial participation, without the need to justify the decision
2. The subject needs to take concomitant drugs that interfere with the investigational product or other trial medication
3. The subject is no longer able to participate for other medical reasons (such as surgery, adverse events (AEs), or diseases)
4. The subject shows an elevation of AST and/or ALT ≥3-fold ULN combined with 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.

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

A subject can also be removed from the trial if eligibility criteria are being violated or if the subject fails to comply with the protocol (for instance, by non-adherence to dietary rules, or non-attendance at study assessments).

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

If a subject is removed from or withdraws from the trial after first administration of trial medication, this will be documented and the reason for discontinuation must be recorded in the CRF. In this case, the data will be included in the CRF/trial database 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 CRFs. These discontinuations will be discussed in the CTR.

3.3.4.2 Discontinuation of the trial by the sponsor

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

1. New toxicological findings or serious adverse events invalidate the earlier positive benefit-risk assessment. More specifically, the trial will be terminated if more than 50% of the actively dosed subjects at one dose level show drug-related and clinically relevant adverse events of moderate or severe intensity, or if at least one drug-related serious adverse event is reported.
2. The expected enrolment goals overall or at a particular trial site are not met
3. Violation of GCP or the CTP by a trial site or investigator, disturbing the appropriate conduct of the trial
4. The sponsor decides to discontinue the further development of the investigational product.
5. Dose escalation will be stopped as soon as at least 2 subjects at one dose level on active drug showed relevant individual QT prolongation, i.e. absolute QT or QTc greater than 500 ms which has been confirmed by a repeat ECG recording or a QTc increase of greater 60 ms from baseline in connection with absolute QT or QTc greater than 500 ms, which has been confirmed by a repeat ECG recording.

3.3.5 Replacement of subjects

In case that one dose group in the SRD part of this trial is completed by less than 4 subjects on active treatment (due to e.g. drop-outs or recruitment reasons), or in case that the rel BA part of this trial is completed by less than 8 subjects (due to e.g. drop-outs or recruitment reasons) the trial clinical monitor 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 study subject number, and will be assigned to the same treatment or treatment sequence as the subject he replaces.

4. TREATMENTS

4.1 TREATMENTS TO BE ADMINISTERED

The investigational products have been manufactured by BI Pharma GmbH & Co. KG.

4.1.1 Identity of BI investigational product and comparator products

SRD part

The characteristics of the test product are given below:

Substance:	BI 894416
Pharmaceutical formulation:	Powder for oral solution
Source:	BI Pharma GmbH & Co. KG, Germany

Posology:	1-0-0
Route of administration:	p.o.
Duration of use:	Single dose

Rel BA part

The characteristics of the test product of the rel BA part are given below:

Substance:	BI 894416
Pharmaceutical formulation:	Tablet
Source:	BI Pharma GmbH & Co. KG, Germany
Unit strength:	10 mg
Posology:	- 1-0-0 (treatment X) *and*
	- 4-0-0 (treatment Z)
Route of administration:	p.o.
Duration of use:	One single dose per treatment

The characteristics of the reference product of the rel BA part are given below:

Substance:	BI 894416
Pharmaceutical formulation:	Powder for oral solution
Source:	BI Pharma GmbH & Co. KG, Germany
Posology:	(10 mg) -0-0 (treatment Y)
Route of administration:	p.o.
Duration of use:	Single dose

4.1.2 Method of assigning subjects to treatment groups

Prior to the screening visit, subjects will be contacted in writing and informed about the planned visit dates.

The subjects willing to participate in the SRD part will be recruited to dose groups and cohorts according to their temporal availability. As soon as enough subjects have been allocated to 1 of the dose cohorts (3 cohorts per dose group), the following subjects will be allocated to one of the other dose cohorts. Therefore, the allocation of subjects to dose cohorts is not influenced by trial personnel, but only by the subjects' temporal availability. As the study includes healthy subjects from a homogenous population, relevant imbalances between the dose groups are not expected.

The randomisation list with study subject numbers and allocated treatments (SRD part) or treatment sequences (rel BA part) will be provided to the trial site in advance. The allocation of subjects to study subject numbers will be performed prior to the first administration of trial medication. For this purpose, the subjects will be allocated to a study subject number by drawing lots. Once a subject number has been assigned, it cannot be reassigned to any other subject.

The randomisation procedure is described in Section 7.5.

4.1.4 Drug assignment and administration of doses for each subject

The treatments to be evaluated are outlined in Table 4.1.4: 1 (SRD part) and 4.1.4: 2 (rel BA part) below. The dose volume for placebo in the SRD part corresponds to the dose volume of the respective dose level.

The oral solutions for dosing (active drug and placebo) will be prepared according to the instruction given in Appendix 10.1 by pharmacists or qualified pharmacy staff members or qualified medical study personnel at the trial site under the responsibility of the investigator.

The trial medication will be administered to the subjects, while in a sitting or standing position, as an oral dose together with about 240 mL of water under supervision of the investigating physician or an authorised designee. The so-called four-eye principle (two-person rule) should be applied for administration of trial medication and – if applicable – its preparation (e.g. reconstitution), if correct dosage cannot be ensured otherwise.

Administration will be performed following an overnight fast, which is to start no later than 10 h before the scheduled dosing.

4.1.5 Blinding and procedures for unblinding

4.1.5.1 Blinding

The treatments administered in the SRD part (active or placebo) will be single-blind (that is, subjects will not know whether they receive active treatment or placebo). However, the current dose level will be known to the subjects. Treatments of the rel BA part will be open-label because the treatments are distinguishable from each other, and because knowledge of treatment is not expected to influence PK parameters.

For SRD part: Within the central ECG lab, the staff involved with interval measurements will be blinded with respect to the treatment and also with regard to the recording date and time as well as planned time points of the ECGs. The interval measurements for a given subject will be performed in a random and blinded sequence by a single technician.

For SRD part: If an interim safety analysis of ECG data is required, a part of the staff of the central ECG lab may be unblinded. This part of the staff will be strictly separated from the blinded staff members who are involved with ECG interval measurements and assessments of ECGs.

Furthermore, the trial bioanalyst, the trial biomarker analyst, the drug metabolism scientist and trial pharmacokineticist may receive the randomisation codes to perform the preliminary PK analysis. He or she will confirm in writing that the codes will be treated confidentially.

The database of this trial will be handled open-label, because no bias with regard to data cleaning of safety measures is expected.

4.1.5.2 Procedures for emergency unblinding

As this trial will be conducted single-blind in the SRD part and open-label in the rel BA part, the treatment information will be known to the investigator (SRD part) or to both investigator and subjects (rel BA part). Therefore, no emergency envelopes will be provided.

4.1.6 Packaging, labelling, and re-supply

Drug supplies will be provided by the Department of Pharmaceutical Development of Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach, Germany.

The clinical trial supply consists of containers holding the trial medication which are labelled with trial identification. The required information according to the German Drug Law as well as Annex 13/EU GMP Guideline will be provided on the containers.

Smaller boxes within the clinical trial supply containers will be labelled with:

- BI trial number
- Name of product and strengths or identification code
- Pharmaceutical dosage form, quantity of dosage units
- Route and mode of administration
- Term 'For Clinical Trial Use' (domestic language)
- Sponsor name and address
- Storage conditions
- Use-by date
- Medication number (not applicable for tablets)
- Batch number

The telephone number of the sponsor and name, address and telephone number of the trial site are given 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. Examples of the labels will be available in the ISF.

4.1.7 Storage conditions

Drug supplies will be kept in their original packaging and in a secure limited access storage area according to the recommended (labelled) storage conditions. Where 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 local clinical monitor (as provided in the list of contacts) is to be immediately contacted.

4.1.8 Drug accountability

The investigator will receive the investigational drugs delivered by the sponsor when the following requirements are fulfilled:

- Approval of the 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 as 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. All unused medication will be disposed locally by the trial site upon written authorisation by the clinical monitor. Receipt, usage and disposal must be documented on the respective forms. Account must be given for any discrepancies.

The investigator 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 products and trial subjects. The investigator will maintain records that document adequately that the subjects were provided

the doses specified by the CTP, and that reconcile all investigational products received from the sponsor. At the time of disposal, the investigator must verify that no remaining supplies are in the investigator's possession.

4.2 OTHER TREATMENTS, EMERGENCY PROCEDURES, RESTRICTIONS

4.2.1 Other treatments and emergency procedures

There are no special emergency procedures to be followed. No additional treatment is planned. However, in case of adverse events in need of 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 medical evaluation results have returned to an acceptable level.

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.

4.2.2.2 Restrictions on diet and life style

Poppy-seeds containing foods should not be consumed starting 3 days before trial drug administration until the last PK sampling of the respective treatment period.

While admitted to the trial site the subjects are restricted from consuming any other foods or drinks than those provided by the staff. Standardised meals will be served at the time points described in the Flow Chart. No food is allowed for at least 4 h after drug intake.

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

3000 mL.

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

Alcoholic beverages are not allowed starting 48 h before trial drug administration until after the last PK sample of the respective treatment period is collected.

Smoking is not allowed during in-house confinement at the trial site.

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

Excessive physical activity (such as competitive sport) should be avoided starting 7 days before the 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 and/or urinary excretion 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. VARIABLES AND THEIR ASSESSMENT

5.1 EFFICACY - CLINICAL PHARMACOLOGY

5.1.1 Endpoints of efficacy

No efficacy endpoints will be evaluated in this trial.

5.1.2 Assessment of efficacy

Not applicable.

5.2 SAFETY

5.2.1 Endpoints of safety

SRD part

Primary endpoint to assess safety and tolerability of BI 894416 is the number [N (%)] of subjects with drug-related adverse events.

Rel BA part

5.2.2 Assessment of adverse events

5.2.2.1 Definitions of adverse events

Adverse event

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

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

Serious adverse event

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

- results in death,
- is life-threatening, this refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if more severe,
- requires inpatient hospitalisation or prolongation of existing hospitalisation,
- results in persistent or significant disability or incapacity,
- is a congenital anomaly/birth defect,

  or
- is to be 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.

Medical and scientific judgement should be exercised in deciding whether other situations should be considered serious events, such as important medical events that might not be immediately life threatening or result in death or hospitalisation but might jeopardise the patient or might require intervention to prevent one of the other outcomes listed above. 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. Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse event.

AEs considered 'Always Serious'

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 given above.

The latest list of 'Always Serious AEs' can be found in the RDC system, a remote 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.

Cancers of new histology and exacerbations of existing cancer must be reported as a serious event regardless of the duration between discontinuation of the drug and the occurrence of the cancer.

Adverse events of special interest (AESIs)

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

The following are considered as AESIs in this trial:

- Hepatic injury, as defined by the following alterations of hepatic laboratory parameters:
  - o an elevation of AST and/or ALT ≥3-fold ULN combined with an elevation of total bilirubin ≥2-fold ULN measured in the same blood sample, and/or
  - o marked peak aminotransferase (ALT, and/or AST) elevations ≥10 fold ULN

  These lab findings constitute a hepatic injury alert and the patients 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 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.

Intensity of AEs

The intensity of the AE should be judged based on the following:

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

Causal relationship of AEs

The definition of an adverse reaction (i.e., a drug-related adverse event) implies at least a reasonable possibility of a causal relationship between a suspected medicinal product and an adverse event. An adverse reaction, in contrast to an adverse event, is characterised by the fact that a causal relationship between a medicinal product and an occurrence is suspected.

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 diminished).

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

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

5.2.2.2 Adverse event collection and reporting

AEs collection

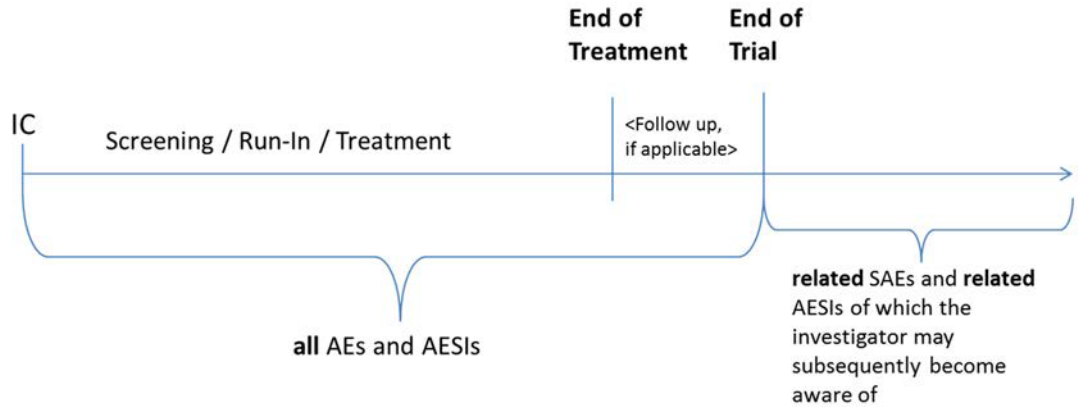
Upon enrolment into a trial, the subject's baseline condition is assessed (for instance, by documentation of medical history/concomitant diagnoses), and relevant changes from baseline are noted subsequently.

Subjects will be required to report spontaneously any AEs as well as the time of onset, end, 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, and intensity of the event as well as 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 through the residual effect period (REP), 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 related SAEs and related AESIs of which the investigator may become aware of by any means of communication, e.g. phone call.



The REP for BI 894416, when measurable drug levels or PD effects are still likely to be present after the last administration, is not known for this first-in-human trial. Therefore, all AEs reported until the end of trial examination (last per protocol contact) will be considered on treatment; please see Section 7.3.3.

AE reporting to 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 of awareness) 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.

Information required

For each AE, the investigator should provide the information requested on the appropriate CRF pages and the BI SAE form (if applicable). The investigator should determine the causal relationship to the trial medication.

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

- Worsening of the underlying disease or of other pre-existing conditions
- Changes in vital signs, ECG, physical examination, neurological 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 CRF only.

All (S)AEs, including those persisting after individual subject's end of trial must be followed up until they have resolved, have been sufficiently characterised, or no further information can be obtained.

5.4 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 and 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 Section 5.5 are generally used assessments of drug exposure.

5.5 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

Date and clock time of drug administration and pharmacokinetic sampling will be recorded.

Exact time points of plasma sampling will be derived from the study management system ClinBase™ and documented in the CRFs by the medical personnel or sent as electronic files to the trial data manager. The actual sampling times will be used for determination of pharmacokinetic parameters.

PK sampling times and periods may be adapted during the trial based on information obtained during trial conduct (e.g. preliminary PK data) including addition of samples and visits as long as the total blood volume taken per subject does not exceed 500 mL. Such changes would be implemented via non-substantial CTP Amendments.

5.5.1 Pharmacokinetic endpoints

The following pharmacokinetic parameters will be determined if feasible for BI 894416:

5.5.1.1 Secondary endpoints

SRD part

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

Rel BA part

- 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)
- $AUC_{0-\infty}$
- C_{max}

5.5.2 Methods of sample collection

5.5.2.1 Plasma sampling for pharmacokinetic analysis

For quantification of BI 894416 plasma concentrations, 2.7 mL of blood will be taken from an antecubital or forearm vein into a K_3-EDTA (tripotassium ethylenediaminetetraacetic acid)-anticoagulant blood drawing tube at the times indicated in the Flow Chart. Blood will be withdrawn by means of either an indwelling venous catheter or by venipuncture with a metal needle.

The EDTA-anticoagulated blood samples will be centrifuged for about 10 min at about 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 plasma. The second aliquot should contain remaining plasma. The process from blood collection until transfer of plasma aliquots into the freezer should be completed within 60 min, with interim storage of blood samples in ice water or on ice. For each aliquot the time when the sample was placed in the freezer will be documented. Until transfer on dry ice to the analytical laboratory, the aliquots will be stored upright at about -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 about -20°C or below until analysis.

At a minimum, the sample tube labels should list the following information: BI trial number, subject number, visit, and planned sampling time. Further information such as matrix and analyte may also be provided.

After completion of the quantification of BI 894416 concentrations in plasma samples of individual or all volunteers, left-over and back-up samples of these volunteers can be used for analysis of metabolites of BI 894416 (including, if applicable, re-analysis of parent compound).

After completion of the trial the plasma samples may be used for further methodological investigations**,** e.g. for stability testing, 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 upon the final study report has been signed.

5.5.3 Analytical determinations

5.5.3.1 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.

As described in Section 4.1.5, the bioanalyst will be unblinded during sample analysis.

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 end-of-trial examination are given 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-interval prior to the trial drug administration (including blank values for PK .

In the SRD part, the acceptable deviation from the scheduled time for vital signs, ECG and laboratory tests will be ± 15 min for the first 4 h after trial drug administration, ± 30 min thereafter on day 1, ± 90 min on day 2, and ± 120 min from 48 h post administration onwards.

In the rel BA part, the acceptable deviation from the scheduled time for vital signs, ECG and laboratory tests will be ± 45 min on day 1 for all time points after trial drug administration, ± 90 min on day 2, and ± 120 min from 48 h post administration onwards.

Starting from 48 h post administration a deviation from the scheduled time for PK sampling of ±120 min is acceptable.

If several activities are scheduled at the same time point in the Flow Chart, ECG should be the first and meal the last activity. Furthermore, if several measurements including venipuncture are scheduled for the same time, venipuncture should be the last of the measurements due to its inconvenience to the subject and possible influence on physiological parameters.

For planned individual plasma concentration 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 determination of pharmacokinetic parameters.

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

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

6.2.1 Screening period

After having been informed about the trial, all subjects will give their 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 refer to Sections 5.2.3 to 5.2.5.

6.2.2 Treatment period(s)

Trial medication will be taken orally by each subject under direct supervision of the investigator or his designee. Details on treatments and procedures of administration are described in Section 4.1.4.

Each subject that participates at the SRD part is expected to participate in one treatment period (i.e., visit 2).

Each subject that participates at the rel BA part is expected to participate in three treatment periods (i.e., visits 2, 3, and 4).

For details on time points and procedures for collection and processing of blood samples for PK , refer to Section 5.5.2 (PK) respectively, and to the Flow Chart.

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 time points for 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 End of trial period

For AE assessment, laboratory tests, recording of ECG and vital signs, physical examination and during the end of trial period, see Sections 5.2.2 to 5.2.5.

Subjects who discontinue treatment before the end of the planned treatment period should undergo the end of trial visit.

All abnormal values (including laboratory parameters) that are judged 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 subject's end of trial must be followed up until they have resolved, have been sufficiently characterised, or no further information can be obtained.

The end of the trial as a whole is defined by the 'last regular visit completed by last subject' 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.

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 STATISTICAL DESIGN – MODEL

7.1.1 Objectives

SRD part:

The primary objective of this trial is to investigate the safety and tolerability of BI 894416 by using descriptive statistics for all endpoints comparing active dose groups to placebo. The primary endpoint is defined in Section 5.2.1. Inferential statistics is not planned (as explained in Section 7.2).

Secondary objectives are the exploration of pharmacokinetics (PK) of BI 894416. Endpoints as specified in 5.5.1 will be analysed by descriptive statistics.

Rel BA part

Secondary objective of the rel BA part is to investigate the pharmacokinetics of BI 894416 as tablet formulation and to explore the relative bioavailability of 10 mg of BI 894416 tablet formulation (Test, T) compared to 10 mg of BI 894416 oral solution formulation (Reference, R). The rel BA part is designed to allow intra-subject comparisons and will be evaluated statistically by use of an appropriate linear model in an exploratory fashion.

The assessment of safety and tolerability will be an additional objective of the rel BA part of this trial, and will be evaluated by descriptive statistics.

7.2 NULL AND ALTERNATIVE HYPOTHESES

Safety and tolerability of the different dose groups of BI 894416 are to be determined on the basis of the investigated parameters in comparison to placebo. It is not planned to test any statistical hypotheses with regard to these variables in a confirmatory sense. Instead, they will be described in their entirety and evaluated by descriptive statistical methods.

Confidence intervals will be computed and will have to be interpreted in the perspective of the exploratory character of the study, i.e. confidence intervals are considered as interval estimates for effects.

7.3 PLANNED ANALYSES

All individual data will be listed.

Adherence to the protocol (such as inclusion/exclusion criteria, times of measurement, compliance with intake of trial medication, treatment dispensing errors, prohibited concomitant medication, completeness and consistency of data) will be checked. Important protocol violations (IPVs) will be identified no later than in the Report Planning Meeting and provided in the TSAP.

7.3.1 Primary analyses

The primary safety endpoint will be evaluated descriptively, for further information refer to the description of Analysis of safety and tolerability in Section 7.3.3.

7.3.2 Secondary analyses

The secondary parameters (refer to Section 5.5.1) will be calculated according to the BI Standard Operating Procedure (SOP) 'Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics' [001-MCS-36-472].

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

- the subject experienced emesis that occurred at or before two times median t_{max} of the respective treatment (Median t_{max} is to be determined excluding the subjects experiencing emesis),
- missing samples/concentration data at important phases of PK disposition curve.

The PK parameter analysis set (PKS) includes all subjects in the Treated Set (TS) who provide at least one PK parameter that was not excluded according to the description above.

Descriptive statistics will be provided.

Relative bioavailability

Relative bioavailability is to be determined on the basis of the secondary pharmacokinetic endpoints (see Section 5.5.1) for the rel BA part comparing 10 mg BI 894416 administered as tablet to PfOS. The statistical model used to assess the relative bioavailability will be an ANOVA (analysis of variance) model on the logarithmic scale. This model will include effects accounting for the following sources of variation: 'sequence', 'subjects within sequences', 'period' and 'treatment'. The effect 'subjects within sequences' will be considered as random, whereas the other effects will be considered as fixed. The model is described by the following equation:

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

where

y_{ijkm}	logarithm of response measured on subject m in sequence i receiving treatment k in period j,
μ	the overall mean,
ζ_i	the ith sequence effect, i = 1, 2,
s_{im}	the effect associated with the mth subject in the ith sequence, m=1, 2, ..., n_i
π_j	the jth period effect, j = 1, 2,
τ_k	the kth treatment effect, k = 1, 2,
e_{ijkm}	the random error associated with the mth subject in sequence i who received treatment k in period j.

7.3.3 Safety analyses

Safety will be assessed for the endpoints and parameters of interest listed in Section 5.2.1. All treated subjects (that is, all subjects who received at least one dose of study drug), will be included in the safety analysis. Safety analyses will be descriptive in nature and will be based on BI standards. No hypothesis testing is planned.

Treatments will be compared in a descriptive way. For the SRD part, the placebo control group in the safety evaluation will consist of all placebo treated subjects, regardless of the dose group in which they were treated. Treatment groups will be compared in a descriptive way. Tabulations of frequencies/proportions will be used for the evaluation of categorical (qualitative) data, and tabulations of descriptive statistics will be used to analyse continuous (quantitative) data.

The analyses will be done by 'treatment at onset'.

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 'screening', those between trial medication intake in a period until trial medication intake in the next period or the trial termination date will be assigned to the treatment period. These assignments including the corresponding time intervals will be

defined in detail in the TSAP. Please note that AEs occurring after the last per protocol contact but entered before database lock will be reported to drug safety only and will not be captured in the trial database.

Additionally, further treatment intervals (analysing treatments) may be defined 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, intensity and causal relationship of AEs will be tabulated by treatment, system organ class and preferred term. SAEs, AESIs (see Section 5.2.2.1) and other significant AEs (according to ICH E3) will be listed separately.

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

Vital signs or other safety-relevant data observed at screening, baseline, during the course of the trial and at the end-of-trial evaluation will be assessed with regard to possible changes compared to findings before start of treatment.

The ECG variables QT, HR, QTcF, QTcB, PR, QRS, and RR obtained from the centralised evaluation of 12-lead ECG recordings will be the basis for the derivation of quantitative and categorical ECG endpoints for the SRD part. These endpoints and their analyses will be described in the TSAP.

7.3.4 Preliminary analyses

Preliminary PK analyses

In contrast to the final PK calculations, the preliminary 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. The preliminary analysis will provide individual and mean concentration-time profiles and summary statistics of individual values. The preliminary results will be distributed to the Investigator and the trial team.

Depending on the results of available preliminary PK analyses, the tolerability and safety of the compound, and changes of dosing schedule (e.g. additional intermediate doses) additional PK preliminary analysis may be performed based on the request of the Trial Clinical Monitor, the investigator, or Trial Clinical Pharmacokineticist. No formal preliminary PK report will be written.

SRD part

A preliminary analysis of PK parameters (AUC_{0-24} and C_{max} of BI 894416) provided as individual values and geometric means will be performed for each dose level before proceeding to the next level.

Data from at least 4 actively dosed subjects at the current dose level (dose level N) are required in order to proceed to the next dose level (dose level N+1).

For escalation from Dose Group 1 to Dose Group 2, preliminary PK data are not required.

No inferential statistical interim analysis is planned. However, after each dose group the investigator (or his deputy) is allowed to postpone further dose progression until a preliminary analysis of the data already obtained has been performed.

Rel BA part

A preliminary analysis of PK parameters (AUC_{0-24} and C_{max} of BI 894416) provided as individual values and geometric means will be performed for the current dose group in the SRD part before proceeding to the rel BA part (i.e., before dosing of subjects in the rel BA part in period 1).

In addition, a preliminary analysis of PK parameters (AUC_{0-24} and C_{max} of BI 894416) of periods 1 and 2 of the rel BA part provided as individual values and geometric means will be performed before proceeding to dosing of subjects in period 3 of the rel BA part.

Data from at least 4 actively dosed subjects at the current dose level of the SRD part are required in order to proceed to the rel BA part, and data from at least 6 subjects dosed in periods 1 and 2 of the rel BA part need to be available in order to proceed to dosing in period 3 of the rel BA part.

Adjusted gMean ratios will be calculated for the preliminary PK parameters obtained for treatment 10 mg BI 894416 tablet compared to PfOS during treatment period 1 and 2 based on the statistical model for assessment of relative bioavailability described in Section 7.3.2.

Furthermore, expected gMean exposure values (C_{max} and AUC_{0-24}) will be predicted for treatment with 40 mg BI 894416 tablet.

No inferential statistical interim analysis is planned. However, the investigator (or his deputy) is allowed to postpone period 3 of the rel BA part until a preliminary analysis of the data already obtained has been performed.

7.3.5 Pharmacokinetic analyses

The pharmacokinetic parameters listed in Section 5.5.1 for drug BI 894416 will be calculated according to the BI SOP 'Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics' [001-MCS-36-472].

Subjects who are not included in the PKS (refer to Section 7.3.1.) will be reported with their individual plasma concentrations and individual pharmacokinetic parameters; however, they will not be included in descriptive statistics for plasma concentrations, pharmacokinetic parameters or other statistical assessment.

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).

7.4 HANDLING OF MISSING DATA

7.4.1 Safety

With respect to safety evaluations, it is not planned to impute missing values.

7.4.2 Plasma drug concentration - time profiles

Handling of missing PK data will be performed according to the relevant SOP of the Sponsor [001-MCS-36-472].

Drug concentration data identified with NOS (no sample available), NOR (no valid result), NOA (not analysed), BLQ (below the lower limit of quantification), or NOP (no peak detectable) will be displayed as such and not replaced by zero at any time point (this rule also applies also to the lag phase, including the predose values).

7.4.3 Pharmacokinetic parameters

Handling of missing PK data will be performed according to the relevant SOP of the Sponsor [001-MCS-36-472].

For the non-compartmental analysis, concentration data identified with NOS, NOR or NOA will generally not be considered. Concentration values in the lag phase identified as BLQ or NOP will be set to zero. All other BLQ/NOP values of the profile will be ignored. The lag phase is defined as the period between time zero and the first time point with a concentration above the quantification limit.

7.5 RANDOMISATION

For the SRD part, the first 4 subjects per dose level will not be randomised to maintain a treatment sequence of active-placebo-active-active due to safety reasons. The remaining 4 subjects of each dose level will be randomised in a 3:1 ratio, which reflects the ratio of subjects receiving active drug to placebo.

For the rel BA part, subjects will be randomised to one of the two treatment sequences 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, which involves 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 3.3.5).

7.6 DETERMINATION OF SAMPLE SIZE

A total of 76 healthy male subjects is planned to participate in the trial, thereof 64 in the SRD part and 12 in the rel BA part. Additional dose groups may be added to the SRD part (see below). Therefore the actual number of subjects entered into the trial may exceed 76, but will not exceed 92 subjects entered.

SRD part

It is planned to include a total of 64 subjects in this trial part. The planned sample size is not based on a power calculation. The size of 8 subjects per dose group (6 on active treatment, and 2 on placebo) is commonly used in single-rising dose studies of the present type and is in general considered as sufficient for the exploratory evaluation of single dose safety and pharmacokinetics [R95-0013].

Additional subjects may be entered to allow testing of additional doses on the basis of experience gained during the trial conduct (e.g. preliminary PK data), provided the planned and approved highest dose will not be exceeded. Thus, the actual number of subjects entered may exceed 64, but will not exceed 80 subjects entered.

Based on Global Amendment No. 4, following dose group 4 an intermediate dose group 11 with additional 8 subjects was added, i.e. planned sample size of this trial part is 72.

Based on Global Amendment No. 6, following dose group 11 an intermediate dose group 9 with additional 8 subjects was added, i.e. planned sample size of this trial part is 80.

Rel BA part

It is planned to include a total of 12 subjects in this trial part. The planned sample size is not based on a power calculation but is judged to be adequate to obtain reliable results and to fulfil the objectives and requirements of this exploratory trial part.

8. INFORMED CONSENT, DATA PROTECTION, TRIAL RECORDS

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

The investigator should inform the sponsor immediately of any urgent safety measures taken to protect the study subjects against any immediate hazard, and also of any serious breaches of the protocol or of ICH GCP.

As a general rule, no trial results should be published prior to finalisation of the CTR.

Insurance Coverage: The terms and conditions of the insurance coverage must be given to each subject and are made available to the investigator via documentation in the ISF.

8.1 STUDY APPROVAL, SUBJECT INFORMATION, AND 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 are to be retained by the investigator as part of the trial records. A copy of the signed and dated written informed consent and any additional subject information must be given to each subject or the subject's legally accepted representative.

The subject must be informed that his/her personal trial-related data will be used by Boehringer Ingelheim in accordance with the local data protection law. The level of disclosure must also be explained to the subject.

The subject must be informed that his or her medical records may be examined by authorised monitors (Clinical Monitor Local/Clinical Research Associate) or Clinical Quality Assurance auditors appointed by Boehringer Ingelheim, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

8.2 DATA QUALITY ASSURANCE

A quality assurance audit/inspection of this trial may be conducted by the sponsor or sponsor's designees, by IRBs/IECs, 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.

The data management procedures to ensure the quality of the data are described in detail in the trial data management and analysis plan (TDMAP) available in the TMF.

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 operated 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

Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

All data reported in the CRFs must be consistent with the source data or the discrepancies must be explained.

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

The investigator may need to request previous medical records or transfer records, depending on the trial.

8.3.2 Direct access to source data and documents

The investigator/institution will permit trial-related monitoring, audits, IRB/IEC review and regulatory inspection, providing direct access to all related source data/documents. CRFs and all source documents, including progress notes (if applicable) and copies of laboratory and medical test results must be available at all times for review by the sponsor's clinical trial monitor, auditor and inspection by health authorities (e.g. FDA). The Clinical Research Associate/on site monitor and auditor may review all CRFs, and written informed consents. The accuracy of the data will be verified by reviewing the documents described in Section 8.3.1.

8.3.3 Storage period of records

Trial site:
The trial site must retain the source and essential documents (including ISF) according to the national or local requirements (whatever is longer) 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 regulatory reporting obligation and in accordance to the requirements defined in this CTP.

8.5 STATEMENT OF CONFIDENTIALITY

Individual subject medical information obtained as a result of this trial is considered confidential and disclosure to third parties is prohibited with the exceptions noted below. Subject confidentiality will be ensured by using subject identification code numbers.

Treatment data may be provided to the subject's personal physician or to other appropriate medical personnel responsible for the subject's welfare. Data generated as a result of the trial need to be available for inspection on request by the participating physicians, the sponsor's representatives, by the IRB/IEC and the regulatory authorities, i.e. the CA.

8.6 COMPLETION OF TRIAL

The EC/competent authority in each participating EU member state needs to be notified about the end of the trial (last patient/subject out, unless specified differently in Section 6.2.3 of the CTP) or early termination of the trial.

Boehringer Ingelheim

APPROVAL / SIGNATURE PAGE

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Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Author-Trial Statistician		25 Jul 2018 17:00 CEST
Author-Trial Clinical Monitor		25 Jul 2018 17:18 CEST
Approval-Therapeutic Area Head		25 Jul 2018 19:42 CEST
Verification-Paper Signature Completion		26 Jul 2018 12:06 CEST
Approval-Team Member Medicine		30 Jul 2018 14:03 CEST
Author-Trial Clinical Pharmacokineticist		20 Aug 2018 08:14 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed