Clinical Trial Protocol

	Document Number:	**c28590127-04**
EudraCT No.	2019-003424-21	
BI Trial No.	1371-0022	
BI Investigational Medicinal Product	BI 894416	
Title	Formulation selection and subsequent optimization of two different oral formulations of BI 894416 in healthy male subjects (open-label, randomised, single-dose study in two parts; trial part 1: five-period crossover design with an additional sixth period in a fixed sequence; trial part 2: three-period crossover followed by a two-period crossover design)	
Lay Title	A study in healthy men to find the best formulation of BI 894416 and to test how this is taken up in the body	
Clinical Phase	I	
Clinical Trial Leader	[redacted] Phone: [redacted] Fax: [redacted]	
Principal Investigator	[redacted] Tel: [redacted] (day) Tel: [redacted] (out of hours emergency)	
Status	Final Protocol (Revised Protocol (based on global amendment 1))	
Version and Date	Version: 2.0	Date: 22 July 2020

CLINICAL TRIAL PROTOCOL SYNOPSIS

Company name	Boehringer Ingelheim
Protocol date	16 December 2019
Revision date	22 July 2020
BI trial number	1371-0022
Title of trial	Formulation selection and subsequent optimization of two different oral formulations of BI 894416 in healthy male subjects (open-label, randomised, single-dose study in two parts; trial part 1: five-period crossover design with an additional sixth period in a fixed sequence; trial part 2: three-period crossover followed by a two-period crossover design)
Principal Investigator:	[redacted]
Trial site	[redacted]
Clinical phase	I
Trial rationale	To optimize the oral formulation of BI 894416 in healthy subjects
Trial objective	To select a formulation principle (tablet vs. capsule) and to optimize the identified formulation of BI894416, if needed.
Trial design	Open-label, randomised, single-dose study in two parts; trial part 1: five-period crossover design with an additional sixth period in a fixed sequence; trial part 2: three-period crossover followed by a two-period crossover design
Trial endpoints:	Primary endpoint: $AUC_{0-\infty}$ of BI 894416 Secondary endpoint: AUC_{0-tz} of BI 894416
Number of subjects **total entered** **each treatment**	 42 Trial part 1: 24 Trial part 2: 18
Diagnosis	Not applicable
Main criteria for inclusion	Healthy male subjects, age of 18 to 55 years (inclusive), body mass index (BMI) of 18.5 to 29.9 kg/m^2 (inclusive)

Test product 1	**BI 894416 Prototype Formulation A2**
dose	62.5 mg (1 tablet)
mode of admin.	Oral with 240 mL of water after an overnight fast of at least 10 h
Test product 2	**BI 894416 Prototype Formulation C2**
dose	62.5 mg (1 tablet)
mode of admin.	- Oral with 240 mL of water after an overnight fast of at least 10 h *or* - Oral with 240 mL of water following a high-fat high-calorie breakfast
Test product 3	**BI 894416 Prototype Formulation D2**
dose	62.5 mg (1 capsule)
mode of admin.	Oral with 240 mL of water after an overnight fast of at least 10 h
Test product 4	**BI 894416 Prototype Formulation F2**
dose	62.5 mg (1 capsule)
mode of admin.	- Oral with 240 mL of water after an overnight fast of at least 10 h *or* - Oral with 240 mL of water following a high-fat high-calorie breakfast
Test product 5	**BI 894416 Prototype Formulations G or I**
dose	50 to 75 mg (1 tablet or capsule)
mode of admin.	- Oral with 240 mL of water after an overnight fast of at least 10 h or - Oral with 240 mL of water following a high-fat high-calorie breakfast
Test product 6	**BI 894416 Prototype Formulations H or K**
dose	50 to 75 mg (1 tablet or capsule)
mode of admin.	- Oral with 240 mL of water after an overnight fast of at least 10 h or - Oral with 240 mL of water following a high-fat high-calorie breakfast
Ref. product 1 & 2	**BI 894416 Reference Formulation**
dose	60 mg (6 x 10 mg tablets)
mode of admin.	Oral with 240 mL of water after an overnight fast of at least 10 h

Duration of treatment	One day (single dose) for each treatment Trial part 1 • R1 - Reference 1: 60 mg BI 894416, fasted (n=24) • T1 - Formulation A2: 62.5 mg BI 894416, fasted (n=24) • T2 - Formulation C2: 62.5 mg BI 894416, fasted (n=24) • T3 - Formulation D2: 62.5 mg BI 894416, fasted (n=24) • T4 - Formulation F2: 62.5 mg BI 894416, fasted (n=24) At least 10 subjects of part 1 (fixed sequence part) • T5 - Formulation C2: 62.5 mg BI 894416, after high-fat, high-calorie breakfast (n≥10) At least 10 of the other subjects of part 1 (fixed sequence part) • T6 - Formulation F2: 62.5 mg BI 894416, after high-fat, high-calorie breakfast (n≥10) *Decision point: either (a) stop here or (b) proceed to trial part 2A with one of the optimised formulations, G or I.* Trial part 2 (optional) Trial part 2A (only one, either G or I will be tested in the fasted and fed state) • R2 - Reference 2: 60 mg BI 894416, fasted (n=18) • T7 - Formulation G or I: 50-75 mg BI 894416, fasted (n=18) • T8 - Formulation G or I): 50-75 mg BI 894416, after high-fat, high-calorie breakfast (n=18) *Decision point: either (a) stop here or (b) proceed to trial part 2B with one of the optimised formulations, H or K* Trial part 2B (only one, either H or K will be tested in the fasted and fed state) • T9 - Formulation H or K: 50-75 mg BI 894416, fasted (n=18) • T10 - Formulation H or K: 50-75 mg BI 894416, after high-fat, high-calorie breakfast (n=18) There will be a washout period of at least 4 days between treatments, i.e. the dose in the preceding treatment period and the dose in the following treatment period will be separated by at least 4 days.
Statistical methods	Preliminary pharmacokinetic analyses and simulations will be performed between trial part 1 and trial part 2A as, well as between part 2A and 2B, if appropriate. Relative bioavailability will be estimated by the ratios of the geometric means (test/ reference) for primary, secondary and further selected 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. CIs will be calculated based on the residual error from the ANOVA. Descriptive statistics will be calculated for all endpoints.

FLOW CHART – TRIAL PART 1

Period	Visit	Day	Planned time (relative to drug administration) [h:min]	Approximate clock time of actual day [h:min]	Event and comment	Safety laboratory[7]	PK blood	Neurological examination[8]	12-lead ECG	Vital signs (BP, PR)	Questioning for AEs and concomitant therapy[6]
SCR	1	-28 to -1			Screening (SCR)[1]	A		x	x	x	
1/2/3/4/5/6 (six periods separated by a wash-out of at least 4 days)	2/3/4/5/6/7	-1	-12:00	20:00	**Admission to trial site**(visit 2 only)	x[5]					x
			-11:30	20:30	Snack (voluntary)						
		1	-1:30	06:30	Allocation to treatment[2] (visit 2 only)	B[2/9]	x[2]		x[2]	x[2]	x[2]
			-0:30	07:30	High fat, high calorie breakfast (Treatment T5 & T6 only)						
			0:00	**08:00**	**Drug administration** (with 240 mL fluid intake)						
			0:20	08:20			x				x
			0:40	08:40			x				x
			1:00	09:00			x		x	x	x
			2:00	10:00	240 mL fluid intake		x		x	x	x
			3:00	11:00			x				x
			4:00	12:00	240 mL fluid intake, thereafter lunch[3]		x		x	x	x
			5:00	13:00			x				x
			6:00	14:00			x				x
			8:00	16:00	Snack (voluntary)[3]		x		x	x	x
			10:00	18:00			x				x
			11:00	19:00	Dinner						
			12:00	20:00			x				x
			14:00	22:00			x				x
			16:00	24:00			x				x
		2	24:00	08:00		B	x		x	x	x
			34:00	18:00			x				x
		3	48:00	08:00			x				x
			58:00	18:00			x				x
		4	72:00	08:00	Breakfast (voluntary) **Discharge from trial site**(visit 7 only)	B[10]	x		x	x	x
EoT	8	8 to 15			End of trial (EoT) examination[4]	A		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, check of vital signs, ECG, safety laboratory (including drug screening, alcohol breath- and urine cotinine test), demographics (including determination of body height and weight, smoking status and alcohol history), relevant medical history, concomitant therapy and review of inclusion/exclusion criteria.
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 visit the EoT examination includes physical 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. A and B define different sets of safety laboratory examinations (see Section 5.2.3)

8. 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.
9. Pharmacogenetic samples will be collected at Day 1 prior to first drug administration in period 1.
10. Only to be taken before discharge from the trial site

FLOW CHART – TRIAL PARTS 2A & 2B (OPTIONAL)

Period	Visit	Day	Planned time (relative to drug administration) [h:min]	Approximate clock time of actual day [h:min]	Event and comment	Safety laboratory[7]	PK blood	Neurological examination[8]	12-lead ECG	Vital signs (BP, PR)	Questioning for AEs and concomitant therapy[6]
SCR	1	-28 to -1			Screening (SCR)[1]	A		x	x	x	
1/2/3/4/5 (five identical periods separated by a wash-out of at least 4 days – preliminary PK analysis between periods 3 and 4)	2/3/4/5/6	-1	-12:00	20:00	**Admission to trial site**(visit 2 only)	x[5]					x
			-11:30	20:30	Snack (voluntary)						
		1	-1:30	06:30	Allocation to treatment[2] (visit 2 only)	B[2/9]	x[2]		x[2]	x[2]	x[2]
			-0:30	07:30	High fat, high calorie breakfast (Treatments T8 & T10 only)						
			0:00	**08:00**	**Drug administration** (with 240 mL fluid intake)						
			0:20	08:20			x				x
			0:40	08:40			x				x
			1:00	09:00			x		x	x	x
			2:00	10:00	240 mL fluid intake		x		x	x	x
			3:00	11:00			x				x
			4:00	12:00	240 mL fluid intake, thereafter lunch[3]		x		x	x	x
			5:00	13:00			x				x
			6:00	14:00			x				x
			8:00	16:00	Snack (voluntary)[3]		x		x	x	x
			10:00	18:00			x				x
			11:00	19:00	Dinner						
			12:00	20:00			x				x
			14:00	22:00			x				x
			16:00	24:00			x				x
		2	24:00	08:00		B	x		x	x	x
			34:00	18:00			x				x
		3	48:00	08:00			x				x
			58:00	18:00			x				x
		4	72:00	08:00	Breakfast (voluntary) **Discharge from trial site**(visits 4 and/ or 6 only)	B[10]	x		x	x	x
EoT	8	8 to 15			End of trial (EoT) examination[4]	A		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, check of vital signs, ECG, safety laboratory (including drug screening, alcohol breath, and urine cotinine test), demographics (including determination of body height and weight, smoking status and alcohol history), relevant medical history, concomitant therapy and review of inclusion/ exclusion criteria.
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 part 2A (Visit 4) and/ or 2B (Visit 6), the EoT examination includes physical examination, vital signs, ECG, safety laboratory, recording of AEs and concomitant therapies. Should trial part 2B follow within 28 days after EoT examination of part 2A, no additional safety laboratory examination is needed.
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. A and B define different sets of safety laboratory examinations (see Section 5.2.3)

8. 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.
9. Pharmacogenetic samples will be collected at Day 1 prior to first drug administration in period 1.
10. Only to be taken before discharge from the trial site

TABLE OF CONTENTS

ABBREVIATIONS

ADME	Absorption, distribution, metabolism, and excretion
ADP	Adenosine diphosphate
AE	Adverse event
AESI	Adverse events of special interest
ALCOA	Attributable, legible, contemporaneous, original, and accurate
ANOVA	Analysis of variance
$AUC_{0-\infty}$	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity
AUC_{0-24}	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 to 24 h
[redacted]	
AUC_{0-tz}	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 to the last quantifiable data point
BA	Bioavailability
BI	Boehringer Ingelheim
BMI	Body mass index (weight divided by height squared)
BP	Blood pressure
CA	Competent authority
CI	Confidence interval
CL	Total clearance of the analyte in plasma after intravascular administration
[redacted]	
CRF	Case Report Form, paper or electronic (sometimes referred to as ‘eCRF’)
CTM	Clinical Trial Manager
CTP	Clinical trial protocol
CTR	Clinical trial report
CYP3A	Cytochrome P450 subfamily 3A
DILI	Drug induced liver injury
DNA	Deoxyribonucleic acid
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
eDC	Electronic data capture

EDTA	Ethylenediaminetetraacetic acid
EEG	Electroencephalography
EoT	End of trial
ER	Extended release
EudraCT	European Clinical Trials Database
F	Absolute bioavailability factor
FDA	Food and Drug Administration
FOB	Faecal occult blood
GCP	Good Clinical Practice
GI	Gastro-intestinal
gMean	Geometric mean
IB	Investigator's brochure
ICF	Informed Consent Form
IEC	Independent Ethics Committee
IMPD	Investigational Medicinal Product Documentation
IPD	Important protocol Deviation
IQRMP	Integrated Quality and Risk Management Plan
IR	Immediate release
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
LLOQ	Lower limit of quantification
MDA	Methylenedioxyamphetamine
MDMA	Methylenedioxymethamphetamine
MedDRA	Medical Dictionary for Regulatory Activities
MRD	Multiple-rising dose
[redacted]	
NK	Natural killer
PfOS	Powder for reconstitution of an oral solution
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
SUSAR	Suspected unexpected serious adverse reaction
SYK	Spleen tyrosine kinase
T	Test product or treatment
TDMAP	Trial Data Management and Analysis Plan
[redacted]	
TMF	Trial master file
[redacted]	
TS	Treated set
TSAP	Trial statistical analysis plan
t_z	Time of last measurable concentration of the analyte in plasma
ULN	Upper limit of normal
UV	Ultraviolet
WHO	World Health Organization
WOCBP	Woman of child bearing potential
V_z	Apparent volume of distribution during the terminal phase after intravascular administration
[redacted]	
XTC	Ecstasy
ZAP70	Zeta-chain-associated protein kinase of 70 kDa

1. INTRODUCTION

BI 894416 is an oral, selective, spleen tyrosine kinase (SYK) inhibitor being developed for the indication of uncontrolled, severe, and persistent asthma.

This trial will be performed to select one formulation principle (extended release (ER) tablet vs. ER capsule) and to optimize the selected ER formulation.

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 basophil-, mast-, B- and T cells. SYK is essential for the FcεR1-mediated activation and degranulation of mast- and basophil cells. 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- 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, refer to the most recent version of the Investigator's Brochure (IB) [c03536505].

1.2 DRUG PROFILE

[redacted]

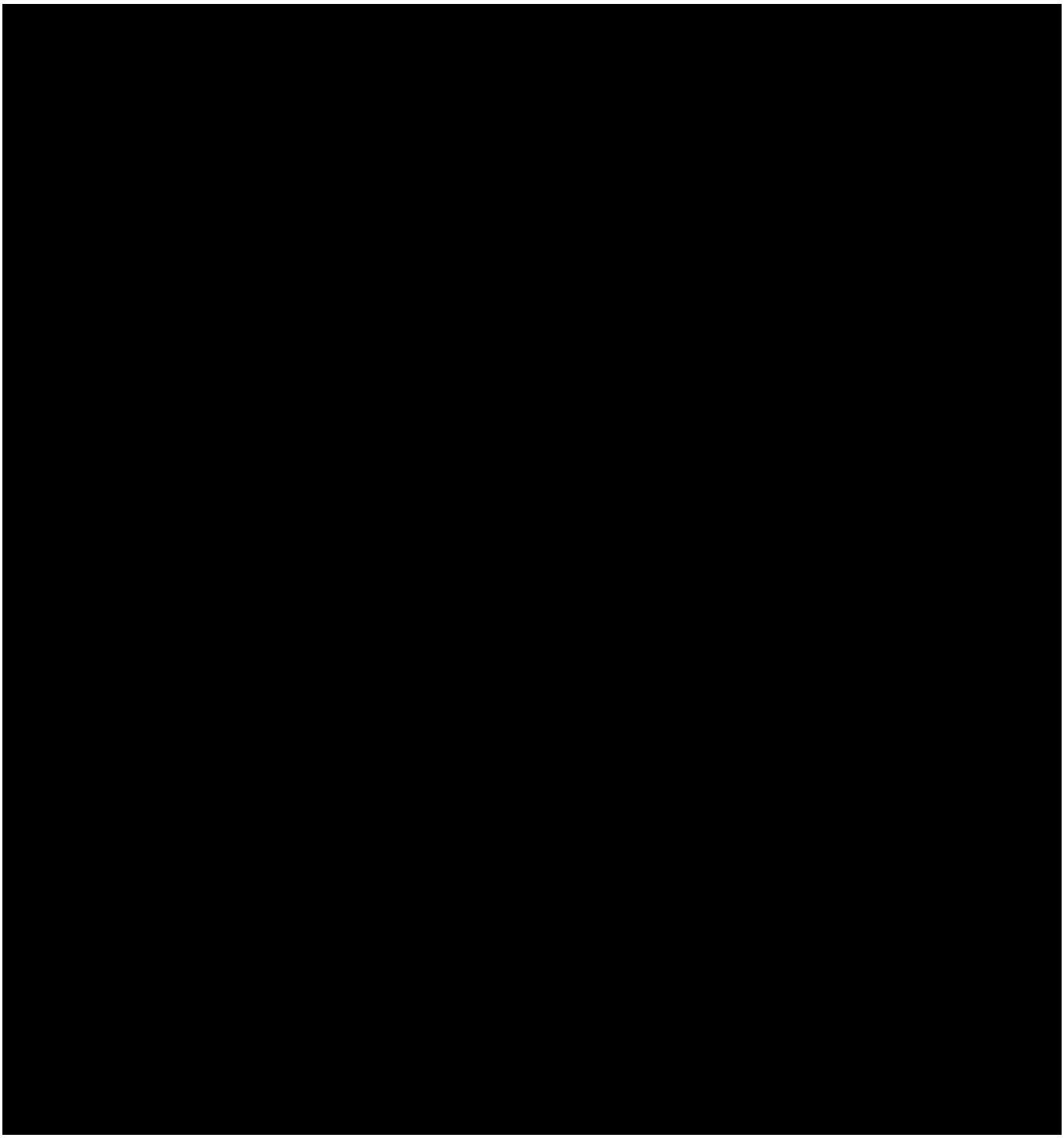

Table 1.2.1: 1 Study 1371-0008 –Adverse event (preliminary) listing of a single 75 mg dose of BI 894416

Subject	Term	Outcome	Severity	Relationship	Seriousness	Comment
[redacted]	Pressure sensation left parasternal; short episodes (10 seconds) for 30 minutes	Recovered/ Resolved	Mild	No	No	
	Nosebleed	Recovered/ Resolved	Mild	No	No	The subject had a nosebleed at home; not longer than 1 to 2 minutes
	Elevated serum CK	Not Recovered/ Not Resolved	Mild	No	No	
	Elevated serum [GOT/] GPT	Not Recovered/ Not Resolved	Mild	No	No	
	Elevated serum [GOT/] GPT	Not Recovered/ Not Resolved	Mild	No	No	
	Anemia (normochromic, normocytic)	Recovered/ Resolved	Mild	No	No	
	Headache	Recovered/ Resolved	Moderate	No	No	
	Headache	Recovered/ Resolved	Mild	No	No	
	Tension headache	Recovered/ Resolved	Mild	Yes	No	
	Orthostatic dysregulation	Recovered/ Resolved	Moderate	No	No	Orthostatic dysregulation during blood sampling prior to drug administration
	Headache	Recovered/ Resolved	Mild	Yes	No	
	Diarrhea	Recovered/ Resolved	Mild	Yes	No	

No SAEs and no AESI were observed in this dose group. Patient [redacted] with elevated liver and CK- values received placebo. All other adverse events as well as changes from base line of laboratory, ECG and vital sign parameters were of minor clinical relevance.

The corresponding pharmacokinetic geometric mean parameters were 2330 nM for C_{max} and 15100 nM*h for AUC_{0-24}. These values were slightly higher than those in the first-in-man study 1371-0001 after a single 70 mg dose of BI 894416 with a geometric mean C_{max} of 2,130 nM and a geometric mean AUC_{0-24} of 11,100 nM*h.

In conclusion, a single 75 mg dose of BI 894416 was well tolerated and safe. The systemic and peak exposure was similar to that seen in study 1371-0001 after a single dose of 70 mg.

1.2.2 Comparator

Not applicable

[redacted]

1.3 RATIONALE FOR PERFORMING THE TRIAL

Preclinical pharmacokinetic/ pharmacodynamic modelling showed that [redacted] is necessary to achieve full clinical efficacy in humans.

Based on data from trial 1371-0001, thrice daily administration of an immediate release formulation (IR) would be necessary to achieve this goal.

With an ER formulation a twice daily dosing regimen is expected to result in BI 894416 plasma concentrations corresponding to an [redacted] with a lower total daily systemic exposure compared to that of the IR formulation. Twice daily dosing might also be associated with higher patient convenience and compliance.

In trial part 1, oral ER tablet and capsule formulations, based on different release principles, will be tested, to identify the formulation that would most reliably lead to a therapeutically relevant exposure (i.e. concentrations corresponding to an [redacted] when single dose pharmacokinetics is simulated to steady state under fasted and fed conditions.

If necessary, the formulation selected in trial part 1 would be further optimized in trial part 2 with regards to dose and drug release. This could either result in (i) an increased [redacted] for better target inhibition and/ or (ii) a lower potential food effect to achieve a more stable target inhibition and/ or (iii) a reduced variability of the pharmacokinetics for a more consistent target inhibition in the study population.

The Clinical Trial Authorisation (CTA) application for this study describes a flexible protocol design using the concept of formulation design space /a bracketed dose approach to allow decision-making in response to interim pharmacokinetic observations. The principles of a flexible protocol were discussed and agreed with the Medicines and Healthcare products Regulatory Agency (MHRA) at a Scientific Advice Meeting between the MHRA and [redacted] (formerly [redacted]).

Based upon the concept of formulation design space/ a bracketed dose approach, specific IMPs are not detailed within the Investigational Medicinal Product Dossier (IMPD) but rather a defined dose range of formulation inputs and corresponding performance outputs are described and justified based on in vitro studies. The chosen formulation from within the approved design space for the first prototype to be dosed will be documented in a File Note and approved by the sponsor and a [redacted] representative ahead of manufacture.

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 medical 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 alternative to 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.

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.

Electrocardiogram stickers on the subjects' chests and limbs may cause some local irritation and may be uncomfortable to remove but subjects will be closely monitored to ensure any local irritation does not persist.

1.4.3 Risks related to BI 894416 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- and B cells. For further details, refer to the most recent 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. For further details, refer also to the most recent IB [c03536505]).

- Due to the reversible mode of action of BI 894416 with regard 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 (refer to Section 3.3.3,). Adverse events will be monitored for an increase in infectious adverse events. Safety laboratory will contain 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 mice, 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 will be included in this trial. In view of the extended time necessary to induce a carcinogenic effect, a maximum of 6 single doses of BI 894416 are not considered to be a relevant carcinogenic risk to male subjects, participating in this study. Accordingly, no further measures of risk mitigation are thought to be required in this study.

Platelet aggregation and bleeding risk

A role of SYK in platelet function has been demonstrated in the 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, respectively. In general, platelet function, as measured by bleeding time, should not be affected by a drug after the administration of a single dose. Therefore, the risk for bleeding is considered to be low with regard to platelet inhibition, unless a subject is also on other antiplatelet drugs that block other pathways. In line with this conclusion, data of previous trial 1371-0001 did not indicate any signs of an increased risk of bleeding.

Risk mitigation and monitoring: Use of any other concomitant drugs that could reasonably inhibit platelet aggregation or coagulation (e.g. acetylsalicylic acid) will be prohibited in this trial (refer also to Sections 3.3.3 and 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, refer to the most recent version of the IB [c03536505]. In this trial, each subject is treated with a maximum of 6 single doses of BI 894416. Due to comparatively slow turnover of bone tissue, no relevant effect on bone is expected, and no specific monitoring of bone density is necessary or reasonable in this trial.

Mortality/ morbidity in preclinical studies

Due to overt morbidity that occurred in toxicological studies with CByB6F1 non-transgenic mice and in Wistar Han rats, some animals died or had to be sacrificed. Clinical signs preceding morbidity were similar in both rodent species and included respiratory changes (rapid, shallow, and/ or laboured breathing), decreased motor activity, ruffled fur, hunched or prostrate posture, eye changes (squinting, discharge) and/ or hypothermia. These findings occurred at exposures of ≥723,000 nM*h which is equivalent to 20-fold of the human exposure cap. One dog of the 3-day escalation study was sacrificed due to overt neurotoxicity. For details, refer to the most recent IB [c03536505].

Risk mitigation and monitoring: Data of trial 1371-0001 indicate good safety and tolerability of BI 894416 at all investigated doses (single oral doses of up to 70 mg). Doses of BI 894416, given in trial 1371-0022 and expected plasma exposures are about the same as those previously given to and seen in healthy volunteers, respectively. Moreover, subjects will be in-house at the trial site and under close medical observation for 24 h after administration of BI 894416. Vital signs and ECGs will be recorded during the trial. Subjects will be instructed to report AEs spontaneously and will be asked at pre-defined time points for AEs. In case of AEs in need of treatment, the investigator can authorise symptomatic therapy and, if required, subjects will be kept under supervision at the trial site or transferred to a hospital, until all monitored results will have returned to an acceptable level.

Neurotoxicity

In dog toxicology studies, acute adverse neurological effects with tremor and movement disorder, assessed as dyskinesia (paresis/ rigidity), were observed at high exposures (for further detail, refer also to most recent IB [c03536505]). One dog was euthanized due to overt neurotoxicity in 3-day escalation study at 90 mg/kg/day [n00235423]. In another dose escalation study [n00245394], all clinical signs of neurotoxicity were reversible with the cessation of dosing. No structural changes were observed in histopathology. Peripheral nerve conduction velocity and EEG were unchanged. No specific mechanism causing these neurological effects in dogs was identified. Although it has not been determined whether or not these neurological changes are dog specific, an external expert review considered these findings most likely to be a channelopathy specific to dog and not likely to occur in man. For more detail, refer also to the most recent IB [c03536505].

Risk mitigation and monitoring: Subjects with relevant neurological disorder in the medical history will be excluded from trial participation (refer to Section 3.3.3). Neurological examinations, as described in Section 5.2.5.1, will be performed at screening, and subjects with clinically relevant findings in this neurological examination will be excluded from study participation (refer to Section 3.3.3). If necessary (investigator decision), unscheduled neurological examinations may be performed at any time during the trial. Relevant findings in the neurological examination during the trial will be reported as AEs. If necessary, subjects may be sent for further, more specific evaluation and treatment to a local neurologist.

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 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 a risk for exposure of a trial 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 (refer also to Section 3.3.3).

Phototoxicity

Subjects will be advised to avoid direct exposure to sun and UV light during the entire trial (refer to 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 pro-arrhythmic 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 QT_cF interval. At gMean C_{max} of the 70 mg dose group, placebo- and baseline-corrected predicted mean QT_cF increase was 5.9 ms (upper limit of the 90%-CI was 10.5 ms). In this study, the risk of QT prolongation may need differential considerations: While the risk might be similar after the administration of 60 mg of the IR reference formulation as compared to the trial 1371-0001 in which a single dose of 70 mg was administered, the risk might be lower after the administration of the ER formulations, due to the C_{max} of BI 894416 which is expected to be lower. Also, in trial 1371-0008 after a single dose of 75 mg, no ECG changes were noted.

Risk mitigation and monitoring: Subjects with cardiovascular disorders (refer also to Section 3.3.3), subjects who have been using drugs that cause QT/QT_c prolongation (refer also to Section 3.3.3), subjects who show a marked baseline prolongation of QT/QT_c interval or any other relevant ECG finding at screening (refer also to Section 3.3.3), and subjects with a history of additional risk factors for Torsade de Pointes arrhythmia (refer also to Section 3.3.3) will be excluded from trial participation. Moreover, subjects will be in-house under close observation for 72 h following drug administration, and ECGs are registered pre- and post-dose at the time points given in the Flow Chart. Considering these risk-mitigating measures, the risk to subjects participating in this trial due to potential effects on the QT interval are considered minimal.

1.4.4 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. For further information, refer to Section 5.2.6.1.4, adverse events of special interest.

1.4.5 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 of up to 4 weeks duration to man.

Data of previous trials 1371-0001 and 1371-0008 indicate good safety and tolerability of single oral doses of BI 894416 at all dose levels up to 70 mg and 75 mg, respectively. 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. For details, refer to the most recent IB [c03536505]).

BI 894416 plasma exposures in this trial are expected to be within the range of those values that were observed in the first-in-man trial 1371-0001 and that were associated with good safety and tolerability.

Considering the medical need for a better treatment in severe asthma and taking into account the (so far) known safety profile of BI 894416, characterised in trials 1371-0001 (single rising dose, first in man), 1371-0021 (food interaction), 1371-0004 (itraconazole interaction) and the ongoing 1371-0008, the expected benefit is likely to outweigh the potential risks and justifies exposure of healthy volunteers.

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 select a formulation principle (tablet vs. capsule) and to optimize the identified extended release formulation of BI894416, if needed.

2.1.2 Primary endpoint

The following pharmacokinetic parameters will be determined for BI 894416:

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

2.1.3 Secondary endpoint

The following pharmacokinetic parameter will be determined for BI 894416:

- 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)

[redacted]

2.2.2.2 Safety and tolerability

Safety and tolerability of BI 894416 will be assessed based on:

- Adverse events (including clinically relevant findings from the physical examination)
- Safety laboratory tests
- 12-lead ECG
- Vital signs (blood pressure, pulse rate)

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

The study will be performed in healthy male subjects as an open-label, randomised, single-dose study in two parts. For a depiction of the overall study design, refer to Figure 3.1: 1.

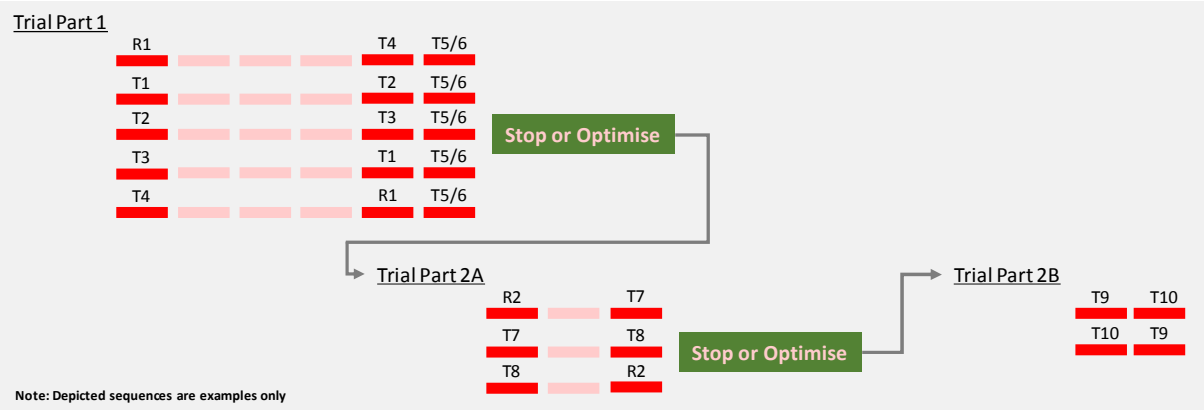

Figure 3.1: 1 Example of the overall study design

Trial part 1 (n=24) will be performed as a five-period crossover design in order to compare test treatments T1 to T4 to the reference treatment R1. These treatments will be administered under fasted conditions and in one of the following 5 sequences, T3-R1-T1-T4-T2, T2-T1-T3-R1-T4, T4-T3-R1-T2-T1, T1-T4-T2-T3-R1, R1-T2-T4-T1-T3. Test treatments T5 or T6 will be added as the sixth treatment period. These treatments will be administered under fed conditions.

Trial part 2 (n=18) is optional and will be split in two parts. Trial part 2A will be performed as a three-period crossover design, with sequences T7-T8-R2, R2-T7-T8 and T8-R2-T7, to compare treatments T7 and T8 to the reference treatment R2. If appropriate, trial part 2B will follow as a two-period crossover design, with sequences T9-T10 and T10-T9, in order to compare test treatments T9 and T10.

A single dose of each treatment will be administered as follows:

Trial part 1

- R1-Reference Formulation 1: 60 mg BI 894416, fasted (n=24)
- T1-Prototype Formulation A2: 62.5 mg BI 894416, fasted (n=24)
- T2- Prototype Formulation C2: 62.5 mg BI 894416, fasted (n=24)
- T3- Prototype Formulation D2: 62.5 mg BI 894416, fasted (n=24)
- T4- Prototype Formulation F2: 62.5 mg BI 894416, fasted (n=24)

At least 10 subjects of part 1 (fixed sequence part)

- T5- Prototype Formulation C2: 62.5 mg BI 894416, after high-fat, high-calorie breakfast (n≥10)

At least 10 of the other subjects of part 1 (fixed sequence part)

- T6- Prototype Formulation F2: 62.5 mg BI 894416, after high-fat, high-calorie breakfast (n≥10)

Decision point: either (a) stop here or (b) proceed to trial part 2A with either optimised formulations G (tablet) or I (capsule), as T7 under fasted conditions and T8 after a high-fat, high-calorie breakfast.

Decision rules:

The decision will be based on data of a minimum of 16 evaluable subjects and will include the assessment of (i) safety parameters (e.g. AE' ECG, vital signs and safety laboratory data) up to 72 h post-dose, (ii) preliminary pharmacokinetic analysis up to 58h post-dose, and (iii) pharmacokinetic simulations, using an existing model which was based on pharmacokinetic data of Phase I studies.

Criteria to stop after trial part 1 will be:

- Pharmacokinetic simulations to steady state demonstrate a C_{min} [redacted] under fasted and fed conditions and further optimization of the formulation with regards to dose and drug release is not expected to improve pharmacokinetic properties.
- Pharmacokinetic simulations to steady state indicate that C_{min} [redacted] cannot be achieved under fasted and/ or fed conditions even considering dose and drug release optimization.

For additional discontinuation criteria, refer to Section 3.3.4.3.

Criteria to continue after trial part 1 will be:

- Pharmacokinetic simulations to steady state demonstrate a $C_{min} \geq$ [redacted] under fasted and/ or fed conditions and further optimization of formulation with regards to dose and drug release is expected to improve pharmacokinetic properties
- Pharmacokinetic simulations to steady state demonstrate a C_{min} [redacted] under fasted and/ or fed conditions and further optimization of formulation with regards to dose and drug release is expected to improve to a C_{min} [redacted]

Improved pharmacokinetic properties would be (i) a reduced food effect, (ii) a higher [redacted] at a similar or even reduced dose, (iii) a smaller peak to trough ratio at simulated steady state pharmacokinetics, (iv) possibly reduced variability of pharmacokinetic parameters. The optimization would be guided by (i) the formulation principle (ER tablet vs. ER capsule), (ii) the release rate (and profile) and (iii) the dose.

If optimization is considered possible, formulations G (ER tablet) or I (ER capsule) will be developed and further tested in trial part 2A.

In case, both ER tablet formulation or ER capsule formulation would qualify for optimization, a decision will be made based on available data.

Trial part 2 (optional)

Trial part 2A (only one, either G or I will be tested in the fasted and fed state)

- R2-Reference Formulation 2: 60 mg BI 894416, fasted (n=18)

- T7- Prototype Formulation G or I: 50-75 mg BI 894416, fasted (n=18)
- T8- Prototype Formulation G or I: 50-75 mg BI 894416, after high-fat, high-calorie breakfast (n=18)

Decision point: either (i) stop here or (ii) proceed to trial part 2B with either optimised formulations H (tablet) or K (capsule), as T9 under fasted conditions and T10 after a high-fat, high-calorie breakfast.

Decision rules:

The decision will be based on data of a minimum of 12 evaluable subjects and will include the assessment of (i) safety parameters (e.g. AE' ECG, vital signs and safety laboratory data) up to 72 h post-dose, (ii) preliminary pharmacokinetic analysis up to 58h post-dose, and (iii) pharmacokinetic simulations, using an existing model which was based on pharmacokinetic data of Phase I studies.

Criteria to stop after trial part 2A will be:

- Pharmacokinetic simulations to steady state demonstrate a [redacted] under fasted and fed conditions and further optimization of the formulation with regards to dose and drug release is not expected to improve pharmacokinetic properties.
- Pharmacokinetic simulations to steady state indicate that [redacted] cannot be achieved under fasted and/ or fed conditions even considering dose and drug release optimization.

For additional discontinuation criteria, refer to Section 3.3.4.3.

Criteria to continue after trial part 2A will be:

- Pharmacokinetic simulations to steady state demonstrate a [redacted] under fasted and/ or fed conditions and further optimization of formulation with regards to dose and drug release is expected to improve pharmacokinetic properties
- Pharmacokinetic simulations to steady state demonstrate a [redacted] D63 under fasted and/ or fed conditions and further optimization of formulation with regards to dose and drug release is expected to improve to a [redacted]

Improved pharmacokinetic properties would be (i) a reduced food effect, (ii) a higher [redacted] at a similar or even reduced dose, (iii) a smaller peak to trough ratio at simulated steady state pharmacokinetics, (iv) possibly reduced variability of pharmacokinetic parameters. The optimization would be guided by (i) the release rate (and profile) and (ii) the dose.

If optimization is considered possible, formulations H (ER tablet) or K (ER capsule) will be developed and further tested in trial part 2B.

Trial part 2B (only one, either H or K will be tested in the fasted and fed state)

- T9- Prototype Formulation H or K : 50-75 mg BI 894416, fasted (n=18)
- T10- Prototype Formulation H or K : 50-75 mg BI 894416, after high-fat, high-calorie breakfast (n=18)

For details on decision making and procedures between trial parts, refer to Section 6.2.2.

There will be a washout period of at least 4 days between the treatments, i.e. the dose in the preceding treatment period and the dose in the following treatment period are separated by at least 4 days.

Subjects will be randomly allocated to the different treatment sequences. For details, refer to Section 4.1.

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 GROUPS

3.2.1 Discussion of study design

All trial parts

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 provided by a bioanalytical laboratory that is blinded to treatment allocation.

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

Period 6 of trial part 1 (fixed sequence)

A fixed-sequence design was selected in which BI 894416 Formulation C2 (T5) or Formulation F2 (T6) was administered in the sixth study period after a high-fat, high-calorie breakfast. The fixed-sequence design is not expected to lead to systematic errors in the estimation of the treatment effects since nonspecific time-effects are unlikely due to the short trial duration.

3.2.2 Rational for decision rules

The rational for performing this trial is to identify an ER formulation that results in therapeutically relevant exposures after twice daily dosing.

Rules, described in Section 3.1, allow to make a decision whether one of the tested formulations meets the requirements after trial part 1, or whether it can be improved within this trial in part 2A and/ or part 2B. Rules would also guide the termination of the process, either after trial part 1 or trial part 2A, if no successful formulation was to be achieved.

3.3 SELECTION OF TRIAL POPULATION

It is planned that a total of 42 healthy male subjects will enter the trial, 24 in trial part 1 and 18 in trial part 2. They will be recruited from the volunteers' pool of the trial site.

[redacted] must have a full medical history from each subject's general practitioner (GP) within the last 12 months, prior to enrolment in the study. Before subjects are admitted to the clinical unit, The Over Volunteering Prevention System (TOPS) will be checked to ensure that each subject has not participated in a study at another site within at least 90 days of the dosing date.

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 (refer also to the most recent 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 55 years (inclusive) at the time of signing informed consent
3. BMI of 18.5 to 29.9 kg/m^2 (inclusive) as measured at screening
4. Signed and dated written informed consent prior to admission to the study, in accordance with GCP and local legislation
5. Subjects who are sexually active must use, with their partner, highly effective contraception from the time of administration of trial medication until 30 days after administration of trial medication. Adequate methods are:
   - Condoms plus use of hormonal contraception by the female partner that started at least 2 months prior to administration of trial medication (e.g., implants, injectables, combined oral or vaginal contraceptives, intrauterine device) or
   - Condoms plus surgical sterilization (vasectomy at least 1 year prior to enrolment) or
   - Condoms plus surgically sterilised partner (including hysterectomy) or
   - Condoms plus intrauterine device or
   - Condoms plus partner of non-childbearing potential (including homosexual men)

   Subjects are required to use condoms to prevent unintended exposure of the partner (both, male and female) to the study drug via seminal fluid. Male subjects should use a condom throughout the study and for 30 days after last IMP administration. Alternatively, true abstinence is acceptable when it is in line with the subject's preferred and usual lifestyle.

If a subject is usually not sexually active but becomes active, with their partner, they must comply with the contraceptive requirements detailed above

Male subjects should not donate sperm for the duration of the study and for at least 30 days after last IMP administration

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, ECG, physical and 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 40 to 90 mmHg, or pulse rate outside the range of 40 to 100 bpm at screening and pre-dose of first period
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). Inactive hayfever is permitted
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/QT_c interval prolongation)
12. Intake of an investigational drug in another clinical trial within 90 days of planned first 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) as demonstrated by a positive urine cotinine test; this includes also the use of e-cigarettes and nicotine replacement products
14. Alcohol abuse (consumption of more than 21 units per week) or positive alcohol breath test
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 and pre-dose
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. Liver enzymes (ALT, AST, GGT, AP) above upper limit of normal at the screening examination
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 first administration of trial medication until 30 days after the last administration of trial medication
28. Subjects with pregnant or lactating partners

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. For details, refer to 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 including but not limited to:

   Corrected QT interval by Fridericia's formula (QTcF) interval of >500 msec or increase in QTcF interval of >60 msec from baseline (confirmed following a repeat ECG)

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. Refer also to 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 or the contract with BI impairing the appropriate conduct of the trial
4. The sponsor decides to discontinue the further development of the investigational product

The investigator/ trial site will be reimbursed for reasonable expenses incurred in case of trial termination (except, if item 3 applies).

Stopping Criteria

The study will be halted, and the risk to other subjects evaluated, if any of the following criteria are met:

- A serious adverse reaction (i.e., a serious AE considered at least possibly related to the IMP administration) in one subject.
- Severe non-serious adverse reactions (i.e., severe non-serious AE considered as, at least possibly related to the IMP administration) in two subjects in the same cohort (cohort refers to subjects receiving the same treatment), independent of within or not within the same system organ class.

3.3.5 Replacement of subjects

In case of more than 4 subjects in trial part 1 and 4 subjects in trial part 2 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 and which regimens they are required to complete. A total of maximum 8 subjects will be replaced in the whole trial. A replacement subject will be assigned a unique trial subject number, and will be assigned to the same treatment as the subject he replaces.

In trial part 1, up to 8 replacement subjects may be enrolled into the study. The maximum number of replacement subjects that may be dosed is 4.

In trial part 2, up to 8 replacement subjects may be enrolled into the study. The maximum number of replacement subjects that may be dosed is 4.

Subjects withdrawn due to an IMP-related AE or termination of the study will not be replaced.

Subjects who are withdrawn for other reasons may be replaced at the discretion of the investigator and sponsor to ensure sufficient evaluable subjects.

For trial part1 and 2, replacement subjects will complete the entire sequence.

4. TREATMENTS

4.1 INVESTIGATIONAL TREATMENTS

The investigational products are manufactured by two different manufacturers:

- IR reference tablet: [redacted]
- ER tablet and ER capsule: [redacted]

BI 894416 doses will be calculated and administered as a free base, so the conversion factor is 1. The molecular weight of BI 894416 is 382.46 g/mol.

4.1.1 Identity of the Investigational Medicinal Products

Trial part 1

The characteristics of the test product are given below:

Name:	***T1- Prototype Formulation A2 (ER tablet - fast release rate)***
Substance:	BI 894416
Pharmaceutical formulation:	Tablet
Source:	[redacted]
Unit strength:	62.5 mg
Posology:	1-0-0
Route of administration:	Oral with 240 mL of water after an overnight fast of at least 10 h
Duration of use:	One day (single dose) for each treatment
Name:	***T2 & T5/ Prototype Formulation C2(ER tablet – slow release rate)***
Substance:	BI 894416
Pharmaceutical formulation:	Tablet
Source:	[redacted]
Unit strength:	62.5 mg
Posology:	1-0-0
Route of administration:	Oral with 240 mL of water after an overnight fast of at least 10 h or (T2) Oral with 240 mL of water following a high-fat high-calorie breakfast (T5)
Duration of use:	One day (single dose) for each treatment

Name:	***T3- Prototype Formulation D2(ER capsule – fast release rate)***
Substance:	BI 894416
Pharmaceutical formulation:	Capsule
Source:	[redacted]
Unit strength:	62.5 mg
Posology:	1-0-0
Route of administration:	Oral with 240 mL of water after an overnight fast of at least 10 h
Duration of use:	One day (single dose) for each treatment

Name:	***T4 & T6- Prototype Formulation F2 (ER capsule – slow release rate)***
Substance:	BI 894416
Pharmaceutical formulation:	Capsule
Source:	[redacted]
Unit strength:	62.5 mg
Posology:	1-0-0
Route of administration:	Oral with 240 mL of water after an overnight fast of at least 10 h or Oral with 240 mL of water following a high-fat high-calorie breakfast
Duration of use:	One day (single dose) for each treatment

The characteristics of the reference product are given below:

Name:	***R1-Reference Formulation 1 (IR tablet)***
Substance:	BI 894416
Pharmaceutical formulation:	Tablet
Source:	[redacted]
Unit strength:	10 mg
Posology:	6-0-0
Route of administration:	Oral with 240 mL of water after an overnight fast of at least 10 h
Duration of use:	One day (single dose) for each treatment

Trial part 2 (optional)

Name:	***T7 & T8/ Prototype Formulation G or I(optimized ER tablet or ER capsule formulation)***
Substance:	BI 894416
Pharmaceutical formulation:	Tablet (Formulation G) or Capsule (Formulation I)
Source:	[redacted]
Unit strength:	50 to 75 mg
Posology:	1-0-0
Route of administration:	Oral with 240 mL of water after an overnight fast of at least 10 h or (T7) Oral with 240 mL of water following a high-fat high-calorie breakfast (T8)
Duration of use:	One day (single dose) for each treatment

Name:	***T9 & T10/ Prototype Formulation H or K(optimized ER tablet or ER capsule formulation***
Substance:	BI 894416
Pharmaceutical formulation:	Tablet (Formulation H) or Capsule (Formulation K)
Source:	[redacted]
Unit strength:	50 to 75 mg
Posology:	1-0-0
Route of administration:	Oral with 240 mL of water after an overnight fast of at least 10 h or (T9) Oral with 240 mL of water following a high-fat high-calorie breakfast (T10)
Duration of use:	One day (single dose) for each treatment

The characteristics of the reference product are given below:

Name:	***R2- Reference Formulation 2 (IR tablet)***
Substance:	BI 894416
Pharmaceutical formulation:	Tablet
Source:	[redacted]

Unit strength:	10 mg
Posology:	6-0-0
Route of administration:	Oral with 240 mL of water after an overnight fast of at least 10 h
Duration of use:	One day (single dose) for each treatment

4.1.2 Selection of doses in the trial and dose modifications

The doses selected for the ER tablet or ER capsule are expected to result in clinically relevant BI 894416 exposures. Dose modification within a defined range would become necessary, if the extent of absorption from a ER formulation differed from that of the IR formulation.

4.1.3 Method of assigning subjects to treatment groups

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

According to the planned sample size of trial part 1(n=24), 2 cohorts (12 subjects each) are planned. Each subject will be allocated to one of 10 treatment sequences (R1, T1 to T4 and T5, or R1, T1 to T4 and T6). For details, refer to Section 7.6.

According to the planned sample size of trial part 2 (n=18), each subject will be allocated to one of five treatment sequence (R2, T7 to T10). For details, refer to Section 7.6.
Prior to the start of the study, subjects willing to participate will be recruited to cohorts according to their temporal availability. In the morning of Day 1 (Visit 2), subjects will be allocated to treatment sequences prior to the first administration of trial medication. For this purpose, numbers of the randomisation list will be allocated to the subjects sequentially just prior to first dosing by using the method 'first come, first served'. Subjects are then assigned to a treatment sequence according to the randomisation list. Hence, no bias is introduced when providing the randomization list in advance to the site. Reference and test treatments will be administered in the sequence specified in the Flow Chart.

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

The randomisation procedure is described in Section 7.6.

4.1.4 Drug assignment and administration of doses for each subject

This trial is an open-label, randomised, single-dose study in two parts.

All 24 subjects of trial part 1 will receive six treatments in randomised order as a five-period crossover design with an additional sixth period as a fixed sequence.

All 18 subjects of trial part 2 will receive in randomised order first three treatments in a three-period crossover design, followed by two treatments in a two-period crossover design (if appropriate).

Trial part 1

The treatments to be evaluated in trial part 1 are outlined in Table 4.1.4: 1 below.

Table 4.1.4: 1 Dosage and treatment schedule – trial part 1

Treatment	Substance	Formulation	Unit strength	Dosage	Total dose
Trial part 1					
T1 (Test 1)	BI 894416	Tablet/ **Formulation A2**, fasted (n=24)	62.5 mg	1 Tablet SD	62.5 mg
T2 (Test 2)	BI 894416	Tablet/ **Formulation C2**, fasted (n=24)	62.5 mg	1 Tablet SD	62.5 mg
T3 (Test 3)	BI 894416	Capsule/ **Formulation D2**, fasted (n=24)	62.5 mg	1 Capsule SD	62.5 mg
T4 (Test 4)	BI 894416	Capsule/ **Formulation F2**, fasted (n=24)	62.5 mg	1 Capsule SD	62.5 mg
T5 (Test 5)	BI 894416	Tablet/ **Formulation C2**, ***fed*** (n≥10)	62.5 mg	1 Tablet SD	62.5 mg
T6 (Test 6)	BI 894416	Capsule/ **Formulation F2**, ***fed*** (n≥10)	62.5 mg	1 Capsule SD	62.5 mg
R1 (Reference 1)	BI 894416	Tablet/ **Reference Formulation 1**, fasted (n=24)	10 mg	6 Tablets SD	60 mg

In trial part 1, in the first five periods, administration of trial medication will be performed after all 24 subjects have fasted overnight. Fasting is to start no later than 10 h before the scheduled dosing. In the sixth period (T5 and T6), administration of trial medication will be performed under fed condition. A high-fat, high-calorie meal (for details, refer to Table 4.1.4: 3) will be served 30 min before drug administration. At least 10 subjects (n≥10) will receive treatment 5, at least 10 of the other subjects (n≥10) will receive treatment 6.

The investigator (or authorised designee) will administer the trial medication as an oral dose together with about 240 mL of water to subjects in a standing position. For drug administration, the so-called four-eye principle (two-person rule) should be applied. For this, one authorised employee of the trial site should witness the administration of trial medication, and – if applicable – its preparation (e.g. reconstitution), if correct dosage cannot be ensured otherwise.

Trial part 2 (optional)

The treatments to be evaluated are outlined in Table 4.1.4: 2 below.

Table 4.1.4: 2 Dosage and treatment schedule – trial part 2 A & B (optional)

Treatment	Substance	Formulation	Unit strength	Dosage	Total dose
Trial part 2A					
T7 (Test 7)	BI 894416	Tablet or Capsule/ **Formulation G or I**, fasted (n=18)	50 to 75 mg	1 Tablet SD	50 to 75 mg
T8 (Test 8)	BI 894416	Tablet or Capsule/ **Formulation G or I**, fed (n=18)	50 to 75 mg	1 Tablet SD	50 to 75 mg
R2 (Reference 2)	BI 894416	Tablet/ **Reference Formulation 2**, fasted (n=18)	10 mg	6 Tablets SD	60 mg
Trial part 2B					
T9 (Test 9)	BI 894416	Tablet or Capsule/ **Formulation H or K**, fasted (n=18)	50 to 75 mg	1 Tablet SD	50 to 75 mg
T10 (Test 10)	BI 894416	Tablet or Capsule/ **Formulation H or K**, fed (n=18)	50 to 75 mg	1 Tablet SD	50 to 75 mg

In trial part 2A, administration of trial medication will be performed under fasted and fed conditions. Fasting is to start no later than 10 h before the scheduled dosing. Fed condition are defined as having completely consumed a high-fat, high-calorie meal (for details, refer to Table 4.1.4: 3 which will be served 30 min before drug administration. The administration of the reference formulation medication will be performed only under fasted conditions.

The investigator (or authorised designee) will administer the trial medication as an oral dose together with about 240 mL of water to subjects in a standing position. For drug administration, the so-called four-eye principle (two-person rule) should be applied. For this, one authorised employee of the trial site should witness the administration of trial medication, and – if applicable – its preparation (e.g. reconstitution), if correct dosage cannot be ensured otherwise.

In trial part 2B, administration of trial medication will be performed under fasted and fed conditions. Fasting is to start no later than 10 h before the scheduled dosing. Fed condition are defined as having completely consumed a high-fat, high-calorie meal (for details, refer to Table 4.1.4: 3) which will be served 30 min before drug administration.

The investigator (or authorised designee) will administer the trial medication as an oral dose together with about 240 mL of water to subjects in a standing position. For drug administration, the so-called four-eye principle (two-person rule) should be applied. For this, one authorised employee of the trial site should witness the administration of trial medication,

and – if applicable – its preparation (e.g. reconstitution), if correct dosage cannot be ensured otherwise.

Trial part 1 and 2

In certain treatment periods, as stipulated above, 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: 3; this meal is in compliance with the FDA guidance 'Food-Effect Bioavailability and Fed Bioequivalence Studies' [R03-2269]. For restrictions with regard to diet, refer to Section 4.2.2.2.

Table 4.1.4: 3 Composition of the high-fat, high-calorie meal

Ingredients
1 chicken eggs (whole content) for fried eggs
10 g butter for frying eggs
2 slices grilled bacon
2 toasted slices of white bread
20 g butter for buttering toast slices
1 hash brown
240 mL whole milk (3.5% fat)
Sum[1]: 910 kcal

[1] The total caloric content was supplied approximately as following: 144 kcal as protein, 280 kcal as carbohydrate, and 486 kcal as fat.

Subjects will be kept under close medical surveillance until 72 h after drug administration. During the first 2 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, except medical examination and assessments).

The treatments will be separated by a wash-out phase of at least 4 days.

4.1.5 Blinding and procedures for unblinding

This 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 is known to investigators and subjects.

4.1.6 Packaging, labelling, and re-supply

The investigational medicinal products will be provided either by BI or by [redacted], as described in Section 4.1.1. 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 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 local clinical monitor (for BI manufactured products) or the Qualified Person (for [redacted] manufactured products 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 or [redacted] team, if the following requirements are fulfilled:

- Approval of the clinical trial protocol by the IRB/ ethics committee
- Availability of a signed and dated clinical trial contract between the sponsor and the investigational site
- Approval/ notification of the regulatory authority, e.g. competent authority
- Availability of the *curriculum vitae* of the Principal Investigator
- Availability of a signed and dated clinical trial protocol

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 trial clinical monitor. 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 should be avoided during the entire study.

If needed, ibuprofen or paracetamol may be given to treat adverse events, e.g. headache.

4.2.2.2 Restrictions on diet and life style

Poppy-seeds containing foods should not be consumed starting 3 days before screening and the first drug administration in the first treatment period until after the last pharmacokinetic sample in the last 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 10 h before and 4 h after drug intake.

On Day 1 of each treatment period, from 1 h before drug intake until lunch, fluid intake is restricted to the milk served with breakfast (refer to Table 4.1.4: 3), 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 not restricted.

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 pharmacokinetic sample in the last treatment period is collected.

Alcoholic beverages are not permitted from 2 days before screening and the first administration of trial medication in the first period until discharge from the unit at each study period (where applicable).

Smoking is not allowed 3 months prior to screening and during the trial.

Barbecued meat and broccoli should be avoided during the trial.

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 BI 894416.

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.

Mouth and hand checks will be conducted after dosing to ensure the tablet(s)/ capsule has been swallowed.

The date and time that each subject is dosed will be recorded in the subject's source data. Any violation of compliance will require evaluation by the investigator and sponsor to determine if the subject can continue in the study.

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, refer to Section 3.3.4.1).

5. ASSESSMENTS

5.1 ASSESSMENT OF EFFICACY

Not applicable.

5.2 ASSESSMENT OF SAFETY

5.2.1 Physical examination

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

5.2.2 Vital signs

Systolic and diastolic blood pressures (BP) as well as pulse rate (PR) or heart rate (heart rate is considered to be equal to pulse rate) will be measured by a blood pressure monitor (DASH 4000) 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. For all safety laboratory sets A and B, subjects should be 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**	**B**
Haematology	Haematocrit	X	X
	Haemoglobin	X	X
	Red Blood Cell Count/ Erythrocytes	X	X
	White Blood Cells/ Leucocytes	X	X
	Platelet Count/ Thrombocytes (quant)	X	X
Automatic WBC differential, relative	Neutrophils; Eosinophils; Basophils; Monocytes; Lymphocytes	X	X
Automatic WBC differential, absolute	Neutrophil, absol.; Eosinophils, absol.; Basophils, absol.; Monocytes, absol.; Lymphocytes, absol.	X	X
Manual differential WBC (if automatic differential WBC is abnormal and clinically relevant in the opinion of the investigator)	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 – INR (International Normalization Ratio)	X	X
Enzymes	AST [Aspartate transaminase]/ GOT, SGOT	X	X
	ALT [Alanine transaminase]/ GPT, SGPT	X	X
	Alkaline Phosphatase	X	X
	Gamma-Glutamyl Transferase	X	X
Hormones	Thyroid Stimulating Hormone	X	--
Substrates	Glucose (Plasma)	X	X
	Creatinine	X	X
	Bilirubin, Total	X	X
	Bilirubin, Direct (only if bilirubin above upper limit normal)	X	X
	Protein, Total	X	X
	C-Reactive Protein (Quant)	X	X
Electrolytes	Sodium	X	X
	Potassium	X	X
	Calcium	X	X
	Chloride	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)	X	X

A and B, are different sets of laboratory examinations. Flow Chart detail at which time point the respective set is performed

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
	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 ([redacted] Alcolmeter S-D2) 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 urine cotinine test is only performed at screening.

The laboratory tests listed in Tables 5.2.3: 1 and 5.2.3: 2 will be performed at "[redacted], with the exception of drug screening and urine cotinine test. These tests will be performed at the trial site using an [redacted] Drug Screen Test Cup or comparable test systems.

5.2.4 Electrocardiogram

Twelve-lead ECGs (I, II, III, aVR, aVL, aVF, V1 - V6) will be recorded using a computerised electrocardiograph ([redacted] ELI 250) 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 as paper copies. 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). Precise electrode placement will be marked with an indelible mark on the skin to allow reproducible placement throughout the study.

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 and at EoT examination, 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 jeopardize 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 hospitalization 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 Section 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, refer to 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 or eDC system, as applicable. 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, i.e. signature of the informed consent form, 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 immediately (within 24 hours) to the sponsor's unique entry point (country specific reporting process 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 send the BI SAE form.

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

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.

5.2.6.2.4 Pregnancy

Once the male subject has been enrolled in the clinical trial and has taken trial medication, and if a partner of the male trial participant becomes pregnant, the investigator must report any drug exposure during pregnancy in a partner of the male trial participant immediately (within 24 hours) by means of Part A of the Pregnancy Monitoring Form to the sponsor's unique entry point, after a written consent of the pregnant partner. The outcome of the pregnancy associated with the drug exposure during pregnancy must be followed up and reported to the sponsor's unique entry point on the Pregnancy Monitoring Form for Clinical Trials (Part B).

The ISF will contain the Pregnancy Monitoring Form for Clinical Trials (Part A and Part B) as well as non-trial specific information and consent for the pregnant partner. As pregnancy itself is not to be reported as an AE, in the absence of an accompanying SAE and/ or AESI, only the Pregnancy Monitoring Form for Clinical Trials and not the SAE form is to be

completed. If there is an SAE and/or AESI associated with the pregnancy, an SAE form must be completed in addition.

5.3 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

5.3.1 Assessment of pharmacokinetics

For the assessment of pharmacokinetics, 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

BI 894416

For quantification of BI 894416 concentrations in plasma, approximately 2.0 mL of blood will be drawn from an antecubital or forearm vein into a [redacted] 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.

[redacted]

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.

Further use of samples

After the completion of BI 894416-quantification in plasma aliquots, the left-over and/ or back-up aliquots 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.

Results of any further investigations are not planned to be part of the CTR but can be included into 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 Section 5.3, 2.1.2, 2.1.3, and 2.2.2.1 are generally used assessments of drug exposure.

Due to reversible neurologic effects observed in dog studies at high exposures, 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 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 safety laboratory tests will be ± 30 min within 4 hours after administration and ±60 min thereafter.

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 ± 60 min will be allowed for PK samples.

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- and neurological examination, refer to Sections 5.2.1 to 5.2.5.

This study permits the re-screening of a subject who has discontinued the study as a pre-treatment failure (i.e., subject has not been randomised/ has not been treated); the reason for failure must be temporary and expected to resolve. If re-screened, the subject must be re-consented.

The identity of the subjects will be confirmed at admission and pre-dose. The subjects will be admitted to the clinical unit on the evening before dosing (Day -1). The admission and pre-dose procedures are presented in Flow Chart. In addition, the ongoing eligibility of subjects will be re-assessed at admission/ pre-dose, as described in Flow Chart.

6.2.2 Treatment periods

Samples for genotyping will be taken from all subjects prior to first drug administration in period 1 (for details, refer to Section 5.5.1).

Trial part 1

Each subject is expected to participate in 6 treatment periods. At least 4 days will separate drug administrations between treatment periods.

On Day -1 of the first treatment period, study participants will be admitted to the trial site and kept under close medical surveillance for at least 72 h following the last drug administration. Subjects will then be allowed to leave the trial site after formal assessment and confirmation of their fitness.

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

The safety measurements performed during the treatment period are specified in Section 5.2, their sampling time points are in 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.

Decision making and procedures after trial part 1

After completion of trial part 1, a preliminary pharmacokinetic analysis will be performed (for details, refer to Section 7.4). On the basis of these data and supported by pharmacokinetic simulations, the sponsor will decide on whether (i) at least one formulation will meet the requirements for use in future clinical studies, or (ii) no formulation will meet the requirements and an improvement is not possible, or (iii) a formulation principle can be improved and needs to be further optimized. In case of (i) and (ii) the trial will be stopped. In case of (iii) the trial will be continued with trial part 2A. For details on decision rules, refer to Section 3.1. Should the study be continued, a batch of modified study medication will be produced and provided by [redacted] This medication will then be used in trial part 2A.

A formal and documented formulation selection review will take place after trial part 1.

The review can be conducted face-to-face or by video/ telephone conference. The Clinical Trial Leader is responsible for the organisation and minutes of the reviews. Minutes will be signed off by the Principal Investigator (or an authorised deputy) and Clinical Trial Leader (or an authorised deputy), and will be filed in the ISF and TMF.

In addition and depending on the findings, suitable experts from the sponsor or external institutions may be consulted on an as needed basis. In these cases expert recommendations will be documented in the minutes of the review and considered for the decision making. Continuation to trial part 2A will only be permitted, if no safety concerns exist neither in the opinion of the Principal Investigator (or an authorised deputy) nor the Clinical Trial Leader (or an authorised deputy).

The data set will consist of the following:

- BI 894416 plasma concentrations of up to at least 58 h after dosing

- Preliminary pharmacokinetic parameter estimates (for details, refer to Section 7.4)
- Safety data of up to at least 72h after dosing, e.g. adverse events, 12-lead ECG, vital signs and clinical laboratory tests

Trial part 2A (optional)

Each subject is expected to participate in 3 treatment periods (Day 1 in each period), if applicable. At least 4 days will separate drug administrations between 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 72 h following drug administration. Subjects will then be allowed to leave the trial site after formal assessment and confirmation of their fitness.

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

The safety measurements performed during the treatment period are specified in Section 5.3 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.

Decision making and procedures after trial part 2A

After completion of trial part 2A, a preliminary pharmacokinetic analysis will be performed (for details, refer to Section 7.4). On the basis of these data and supported by pharmacokinetic simulations, the sponsor will decide on whether (i) the formulation will meet the requirements for use in future clinical studies, or (ii) the formulation will not meet the requirements and an improvement is not possible, or (iii) a formulation can be improved and needs to be further optimized. In case of (i) and (ii) the trial will be stopped. In case of (iii) the trial will be continued with trial part 2B. For details on decision rules, refer to Section 3.1. Should the study be continued, a batch of modified study medication will be produced and provided by [redacted] This medication will then be used in trial part 2B.

A formal and documented formulation review will take place after trial part 2B.

The review can be conducted face-to-face or by video/ telephone conference. The Clinical Trial Leader is responsible for the organisation and minutes of the reviews. Minutes will be signed off by the Principal Investigator (or an authorised deputy) and Clinical Trial Leader (or an authorised deputy), and will be filed in the ISF and TMF.

In addition and depending on the findings, suitable experts from the sponsor or external institutions may be consulted on an as needed basis. In these cases expert recommendations will be documented in the minutes of the review and considered for the decision making. Continuation to trial 2B will only be permitted if no safety concerns exist neither in the opinion of the Principal Investigator (or an authorised deputy) nor the Clinical Trial Leader (or an authorised deputy).

The data set will consist of the following:

- BI 894416 plasma concentrations of up to at least 58 h after dosing
- Preliminary pharmacokinetic parameter estimates (for details, refer to Section 7.4)
- Safety data of up to at least 72h after dosing, e.g. adverse events, 12-lead ECG, vital signs and clinical laboratory tests

In the event the result of any particular part of the study is inconclusive, additional subjects may be recruited and enrolled to permit a scheduled group to be repeated once. For the repeat group, formulation may be adjusted within the design space of the IMPD to establish conditions that optimize the bioavailability of the oral formulation.

Trial part 2B (optional)

Each subject of trial part 2A is expected to participate in 2 further treatment periods (Day 1 in each period), if applicable. At least 4 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 72 h following drug administration. The subjects will then be allowed to leave the trial site after formal assessment and confirmation of their fitness.

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

The safety measurements performed during the treatment period are specified in Section 5.3 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.

Each subject will receive a card stating the telephone number of the investigator and subjects will be kept under close medical surveillance until 72 h after drug administration. A physician will be responsible for the clinical aspects of the study and will be available at all times during the study.

6.2.3 Follow-up period and trial completion

For AE assessment, laboratory tests, recording of ECG and vital signs, and physical- and neurological examination during the follow-up period, refer to Sections 5.2.1 to 5.2.5. Subjects who discontinue treatment before the end of the planned treatment period should undergo the EoT 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 EoT 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 relative bioavailability of extended release formulations compared with the immediate release formulation, following oral administration under fasted and fed conditions on the basis of the primary and secondary pharmacokinetic endpoints, as listed in Sections 2.1.2 and 2.1.3.

In addition relative bioavailability between selected extended release formulations will be investigated. The trial is designed to allow intra-subject comparisons and will be evaluated statistically by use of a linear model for logarithmically transformed pharmacokinetic endpoints.

A further objective is to evaluate and compare further pharmacokinetic parameters between the treatments.

In addition the assessment of safety will be evaluated for the parameters specified in Section 2.2.2.2.

All parameters will be assessed descriptively.

7.2 NULL AND ALTERNATIVE HYPOTHESES

The relative bioavailability of the reference formulation will be compared with the test formulations, the ratios of the geometric means (test/ reference), and their corresponding 2-sided 90% confidence intervals (CIs) will be provided. In addition, relative bioavailability between selected extended release formulations will be investigated in the same way as between test and reference. 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 randomized and 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 pharmacokinetic endpoint that was defined as primary or secondary and was not excluded due to a protocol violation relevant to the evaluation of pharmacokinetics or due to pharmacokinetic non-evaluability (as specified in the following subsection ‘Pharmacokinetics’). Descriptive and model based analyses of pharmacokinetic parameters will be based on the PKS.

Adherence to the protocol will be assessed by the trial team. Important protocol deviations (IPD) categories will be described in the 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 BI SOP 'Standards and processes for analyses performed within Clinical Pharmacokinetics/ Pharmacodynamics' [001-MCS-36-472].

Plasma concentration data and parameters of a subject will be included in the statistical pharmacokinetic analyses if they are not flagged for exclusion due to a protocol violation relevant to the evaluation of pharmacokinetics (to be decided no later than in the Report Planning Meeting) or due to pharmacokinetic 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 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 pharmacokinetic disposition curve

Plasma concentration data and parameters of a subject which is flagged for exclusion will be listed with its individual values but will not be included in the statistical analyses. Descriptive statistics of pharmacokinetic 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

Primary analyses

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

The pairwise comparisons of R1 with T1, T2, T3 and T4 will be analyzed in a five-way crossover model. This model will include effects accounting for the following sources of variation: sequence, subjects nested 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 treatmentk in period j,
μ = the overall mean,

ζ_i = the i^{th} sequence effect

s_{im} = the effect associated with the m^{th} subject in the i^{th} sequence

π_j = the j^{th} period effect

τ_k = the k^{th} treatment effect

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.

The fasted vs fed comparisons (T2 - T5 and T4 - T6) will be analyzed as a two period fixed sequence cross-over model. The model used will include effects accounting for the following sources of variation: subjects and treatment. The effect 'subjects' will be considered as random, whereas the effect 'treatment' will be considered as fixed. The model is described by the following equation:

$y_{km} = \mu + s_m + \tau_k + e_{km}$, where

y_{km} = logarithm of response measured on subject m receiving treatment k,
μ = the overall mean,

s_m = the effect associated with subject m

τ_k = the k^{th} treatment effect

e_{km} = the random error associated with subject m receiving treatment k.

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

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

The difference between the expected means for log(T)-log(R) will be estimated by the difference in the corresponding adjusted means (Least Squares Means). Additionally, their two-sided 90% confidence intervals will be calculated (which corresponds to the two one-sided t-test procedure, each at a 5% significance level) based on the residual error from the ANOVA and will be back-transformed to the original scale to provide the point estimate and 90% CIs for the ratio T/R.

Further exploratory analyses

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

In addition to the model based approach all parameters will be calculated and analysed descriptively.

If an analysis model fails to converge or is not suitable, the model will be simplified.

7.3.2 Secondary endpoint analyses

The secondary endpoint (refer to Section 2.1.3) will be analysed in the same way as the primary endpoint.

7.3.3 Further endpoint analyses

7.3.3.1 Pharmacokinetic analyses

Further endpoints (refer to Section 2.2.2) will be analysed in the same way as the primary endpoint.

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 statistical comparison between treatment groups for safety data is planned, unless otherwise specified within the relevant section.

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

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

Measurements (such as ECG, vital signs, or laboratory parameters) or AEs will be assigned to treatments (refer to 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, those between first trial medication intake and end of REP (refer to Section 1.2.3) will be assigned to the treatment period. Events occurring after the REP but prior to next intake or end of trial termination date will be assigned to 'follow-up'. 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 (refer to 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.

7.4 INTERIM ANALYSES

No inferential statistical interim analysis is planned.

After trial part 1, a preliminary analysis of pharmacokinetic parameters e.g. $AUC_{0-\infty}$ or AUC_{0-tz}, [redacted] of BI 894416, provided as individual values and geometric means, will be performed for all tested formulations and modes of administration (fasted or fed). Pharmacokinetic simulations will be used as basis for prediction of steady state exposures. Further details will be described in a separate analysis plan. Similar analyses will be performed after trial part 2A, if appropriate.

In contrast to the final pharmacokinetic 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. Therefore, minor deviations may occur between preliminary and final results. The preliminary results will be distributed to the investigator and the trial

team. The pharmacokinetic parameters will be calculated according to the BI SOP 'Standards and processes for analyses performed within Clinical Pharmacokinetics/ Pharmacodynamics' (001- MCS-36-472). A quality check of the preliminary data will be performed.

Depending on the results of available preliminary pharmacokinetic analyses, additional analyses may be performed, if requested by the Clinical Trial Leader, the Principal Investigator, or Trial Clinical Pharmacokineticist. Preliminary pharmacokinetic results will not be reported in the CTR.

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 pharmacokinetic data will be performed according to the relevant Corporate Procedure [001-MCS-36-472].

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

7.6 RANDOMISATION

Trial part 1

The patients are randomized to one of the following 10 treatment sequences, in a ratio of 1:1:1:1:1:1:1:1:1:1:

- T3-R1-T1-T4-T2-T5
  T3-R1-T1-T4-T2-T6

- T2-T1-T3-R1-T4-T5
  T2-T1-T3-R1-T4-T6

- T4-T3-R1-T2-T1-T5
  T4-T3-R1-T2-T1-T6

- T1-T4-T2-T3-R1-T5
  T1-T4-T2-T3-R1-T6

- R1-T2-T4-T1-T3-T5
  R1-T2-T4-T1-T3-T6

The block size will be documented in the CTR.

Trial part 2A (optional)

Subjects will be randomised to one of the 3 treatment sequences (T7-T8-R2, R2-T7-T8 and T8-R2-T7) in a 1:1:1 ratio. The block size will be documented in the CTR.

Trial part 2B (optional)

Subjects will be randomised to one of the 2 treatment sequences (T9-T10 and T10-T9) in a 1:1 ratio. The block size will be documented in the CTR.

Randomization scheme, packaging and labelling

The sponsor will arrange for the randomisation which will be provided to [redacted] to allow them to conduct the manufacturing, 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 sponsor will provide the randomisation scheme to [redacted] according to which [redacted] will dispense the study medication.

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 24 subjects in trial part 1 and 18 subjects in trial part 2. The sample size determination is not based on a power calculation but is considered sufficient to achieve the aims of this exploratory trial.

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. The rights of the investigator and of the sponsor with regard to publication of the results of this trial are described in the investigator contract. As a 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 investigator and 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 [redacted] delegate must sign (or place a seal on) and date the informed consent form. If a trial collaborator has given a supplementary explanation, the trial collaborator also signs (or places a seal on) and dates the informed consent.

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

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

8.2 DATA QUALITY ASSURANCE

A risk-based approach is used for trial quality management. It is initiated by the assessment of critical data and processes for trial subject protection and reliability of the results as well as identification and assessment of associated risks. An Integrated Quality and Risk Management Plan documents the rationale and strategies for risk management during the 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 the trial conduct, the 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.

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

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 must retain the source and essential documents (including ISF) according to contract or the local requirements valid at the time of the end of the trial (whatever is longer).

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

8.4 EXPEDITED REPORTING OF ADVERSE EVENTS

BI is responsible to fulfil their legal and regulatory reporting obligation, including SUSAR reporting, in accordance with regulatory requirements in participating countries and regions.

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 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 the 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 [redacted], under the supervision of the Principal Investigator. Relevant documentation on the participating (Principal) Investigators (e.g. their curricula vitae) will be filed in the ISF.

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

- Manage the trial in accordance with applicable regulations and internal SOPs
- Direct the clinical trial team in the preparation, conduct, and reporting of the trial
- Ensure appropriate training and information of local clinical trial managers (CTM), Clinical Research Associates, and investigators of participating trial sites

The trial medication will be provided by the [redacted] (IR) and [redacted] (ER).

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

Analyses of BI 894416 concentrations in plasma will be performed at [redacted]

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

Data management and statistical evaluation will be done by 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.

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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		22 July 2020
EudraCT number **EU number**		2019-003424-21
BI Trial number		1371-0022
BI Investigational Medicinal Product(s)		BI 894416
Title of protocol		Formulation selection and subsequent optimization of two different oral formulations of BI 894416 in healthy male subjects (open-label, randomised, single-dose study in two parts; trial part 1: five-period crossover design with an additional sixth period in a fixed sequence; trial part 2: three-period crossover followed by a two-period crossover design)
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		Synopsis, Section 3.1, Section 4.1.4 Section 7.3.1 Throughout the document
Description of change		Adaptation of the wording to the statistical scenarios Minor editorial and formatting changes throughout the document
Rationale for change		Since block- and sample size do not match, an imbalances between treatment 5 and treatment 6 is anticipated. Therefore, the wording was adapted in the Synopsis, as well as in Sections 3.1 and 4.1.4 to rectify the wording and the statistical model was adapted in the Synopsis and Section 7.3.1. Non-substantial', because no major changes to the primary and secondary objectives were made Minor editorial and formatting changes for consistency reasons

11.2 GLOBAL AMENDMENT 2

Date of amendment		
EudraCT number **EU number**		
BI Trial number		
BI Investigational Medicinal Product(s)		
Title of protocol		
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		
Description of change		
Rationale for change		

APPROVAL / SIGNATURE PAGE

Document Number: c28590127 **Technical Version Number:4.0**

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

Title: Formulation selection and subsequent optimization of two different oral formulations of BI 894416 in healthy male subjects (open-label, randomised, single-dose study in two parts; trial part 1: five-period crossover design with an additional sixth period in a fixed sequence; trial part 2: three-period crossover followed by a two-period crossover design)

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Author-Trial Statistician	[redacted]	22 Jul 2020 13:04 CEST
Approval-Therapeutic Area Head		22 Jul 2020 14:01 CEST
Author-Clinical Trial Leader		22 Jul 2020 17:09 CEST
Author-Trial Clinical Pharmacokineticist		22 Jul 2020 17:48 CEST
Verification-Paper Signature Completion		23 Jul 2020 12:47 CEST
Approval-Team Member Medicine		23 Jul 2020 15:07 CEST

(Continued) Signatures (obtained electronically)

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