Clinical Trial Protocol

	Document Number:	**c23040609-03**
BI Trial No.	1371-0003	
BI Investigational Medicinal Product(s)	BI 894416	
Title	Safety, tolerability and pharmacokinetics of single rising oral doses of BI 894416 versus placebo in healthy male Japanese subjects (single-blind, randomized, placebo-controlled within dose group)	
Lay Title	A study in healthy Japanese men to test how different doses of BI 894416 are tolerated	
Clinical Phase	I	
Clinical Trial Leader	[redacted] Telephone: [redacted], Fax: [redacted]	
Principal Investigator	[redacted] Telephone: [redacted], Fax: [redacted]	
Status	Final Protocol (Revised Protocol (based on global amendment 2))	
Version and Date	Version: 3.0	Date: 17 Aug 2020

CLINICAL TRIAL PROTOCOL SYNOPSIS

Company name	Boehringer Ingelheim (BI)
Protocol date	5 Jun 2020
Revision date	17 Aug 2020
BI trial number	1371-0003
Title of trial	Safety, tolerability and pharmacokinetics of single rising oral doses of BI 894416 versus placebo in healthy male Japanese subjects (single-blind, randomized, placebo-controlled within dose group)
Principal Investigator	[redacted]
Trial site	[redacted]
Clinical phase	I
Trial rationale	The objective of this trial is to investigate the safety, tolerability and pharmacokinetics of BI 894416 in healthy Japanese male subjects. The chosen population of healthy male subjects receiving single rising oral doses is considered adequate to provide the basis for the clinical development program of BI 894416 in Japan.
Trial objectives	To investigate safety, tolerability and pharmacokinetics following single rising doses of BI 894416
Trial endpoints	Primary endpoint The percentage (%) of subjects with drug related adverse events Secondary endpoints: C_{max}, $AUC_{0-\infty}$ of BI 894416
Trial design	single-blind, randomised, placebo-controlled within dose groups
Number of subjects **total entered** **each treatment**	 24 8 per dose group (6 on BI 894416 and 2 on placebo)
Diagnosis	Not applicable
Main criteria for inclusion	Healthy male subjects, age of 20 to 45 years (inclusive), body mass index (BMI) of 18.5 to 25.0 kg/m^2 (inclusive)

Test product(s)	BI 894416 as tablet formulation
dose	25 mg, 50 mg, 70 mg
mode of admin.	Oral with 240 mL of water
Comparator product(s)	Matching placebo(s)
dose	Not applicable
mode of admin.	Oral with 240 mL of water
Duration of treatment	Single dose 1day
Statistical methods	Descriptive statistics will be calculated for all endpoints.

FLOW CHART

Visit	Day	Planned time (relative to BI 894416 or placebo administration [h:min])	Approximate clock time of actual day [h:min]	Event and comment	Safety laboratory[6]	PK $_{blood}$[8,10]	PK $_{urine}$[11]	Medical Examination[9]	Neurological examination[9]	Vital signs (BP, PR)[9]	12-lead ECG[9,10]	Continuous ECG monitoring	Questioning for AEs and concomitant therapy[15]
1	-28 to -1			Screening (SCR)[1]	A[7]			x	x	x	x		
2	-1	-24:00	09:00	Ambulatory visit[2]	B[2]				x		x[12]		x
		-12:00	21:00	Admission to trial site									
	1	-1:00	08:00	Allocation to treatment	C[7]	x	x	x	x	x	x[13]	x[14]	x
		0:00	**09:00**	**BI 894416 or placebo administration[3]**			▲ |					▲ |	
		0:15	09:15			x	|					|	
		0:30	09:30			x	|			x	x[13]	|	x
		0:45	09:45			x	|			x		|	x
		1:00	10:00			x	|			x	x[13]	|	x
		1:30	10:30			x	|			x	x[13]	|	x
		2:00	11:00	240 mL fluid intake		x	|			x	x[13]	|	x
		2:30	11:30			x	|			x	x[13]	|	x
		3:00	12:00			x	|			x	x[13]	|	x
		4:00	13:00	240 mL fluid intake, thereafter lunch[4]	B	x	┼		x	x	x[13]	▼	x
		5:00	14:00			x	|						
		6:00	15:00			x	|			x	x[13]		x
		8:00	17:00	Snack(voluntary)[4]		x	┼			x	x[13]		x
		10:00	19:00			x	|						
		11:00	20:00	Dinner			|						
		12:00	21:00			x	┼			x	x[13]		x
	2	24:00	09:00	Breakfast[4]	C	x	┼		x	x	x[13]		x
		28:00	13:00	Lunch[4]			|						x
		32:00	17:00	Snack(voluntary)			|						
		34:00	18:00			x	|			x	x		x
		35:00	19:00	Dinner			|						
	3	48:00	09:00	Discharge from trial site	B	x	▼		x	x	x		x
	4	72:00	09:00	Ambulatory visit		x				x	x		x
	5	96:00	09:00	Ambulatory visit									x
	8	168:00	09:00	Ambulatory visit	C			x					x
3	15 to 17			End of trial (EOT) examination[5]	C			x	x	x	x		x

PK: pharmacokinetics, ECG: electrocardiogram, BP: blood pressure, PR: pulse rate, AE: adverse event

1. Subject must be informed and written informed consent obtained prior to starting any screening procedures. Screening procedures include medical examination, neurological examination, check of vital signs, ECG (12-lead ECG and rhythm strip over at least 15 min), safety laboratory (including drug screening), demographics (including determination of body height and weight, smoking and alcohol history), relevant medical history, concomitant therapy and review of inclusion/exclusion criteria.

2. Safety laboratory to be taken and to be medically evaluated on Day -1 prior to administration of BI 894416; this ambulatory visit including safety laboratory, neurological exam, ECG and adverse event questioning can be omitted if the screening examination is performed on Day -3 or -2.
3. Oral with 240 mL of water after an overnight fast of at least 10 h; (please also refer to Section 4.2.2.2)
4. If several actions are indicated at the same time point, the intake of meals will be the last action.
5. EOT includes medical examination, neurological examination, vital signs, ECG, safety laboratory, recording of AEs and concomitant therapies.
6. Letters A, B and C describe different sets of safety laboratory examinations (see Section 5.2.3).
7. Drug screening will be performed at screening and prior to dosing at Day 1 of visit 2. A breath alcohol test and cotinine test will be performed during screening and prior to BI 894416 or placebo administration at Visit 2, and may be repeated at any time during the trial at the discretion of an investigator or designee.
8. PK samples for determination of plasma level of BI 894416 as detailed in Section 5.3.2 Sampling times and periods may be adapted based on information obtained during the trial (e.g. preliminary PK data) including addition of samples and visits as long as the total blood volume taken does not exceed approximately 500 mL per subject.
9. For allowed deviation from the scheduled time please refer to Section 6.1.
10. PK samplings and ECGs should be done in direct sequence to allow for a time-matched pair of ECG recordings and plasma concentration of BI 894416.
11. PK urine samples for determination of BI 894416 amount eliminated in urine are to be taken at following time intervals: a blank urine sample is to be obtained within 3 h prior to administration of trial medication; other urine samples are to be collected over the stated post-dose intervals 0-4, 4-8, 8-12, 12-24 and 24-48 h (see Section 5.3.2.2).
12. Three triplicate ECGs are recorded within approximately 1 h. The recordings of each triplicates should be separated by at least 15 min (refer to the Section 5.2.4.1).
13. Triplicate ECG (refer to the Section 5.2.4.1).
14. Continuous ECG monitoring to be done starting at least 15 min before BI 894416, or placebo, administration and for at least 4 h following BI 894416, or placebo (3-lead ECG recording).
15. AEs and concomitant therapies will be recorded throughout the trial, but will be specifically asked for at the time points indicated in the Flow Chart.

TABLE OF CONTENTS

ABBREVIATIONS

ADME	Absorption, distribution, metabolism, and excretion
AE	Adverse event
AESI	Adverse events of special interest
Ae_{t1-t2}	Amount of analyte eliminated in urine over the time interval t_1 to t_2
ALCOA	attributable, legible, contemporaneous, original, accurate (dimension of integrity)
ALT	Alanine transaminase
AP	Alkaline phosphatase
aPTT	Activated partial thromboplastin time
AST	Aspartate transaminase
AUC	Area under the Curve
AUC_{0-24}	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to 24 hour after administration
AUC_{0-8}	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to 8 hour after administration
$AUC_{0-\infty}$	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity
AUC_{0-tz}	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 to the last quantifiable data point
AUC_{ss}	Area under the concentration-time curve of the analyte in plasma at steady state
AUC_{t1-t2}	Area under the concentration-time curve of the analyte in plasma over the time interval t_1 to t_2
AUC_{τ}	Area under the concentration-time curve of the analyte in plasma during a dosage interval
$\%AUC_{tz-\infty}$	Percentage of $AUC_{tz-\infty}$ obtained by extrapolation
BI	Boehringer Ingelheim
BMI	Body mass index (weight divided by height squared)
BP	Blood pressure
CA	Competent authority
CI	Confidence interval
CK	Creatine kinase
CK-MB	Creatine kinase-MB isozyme

CL/F	Apparent clearance of the analyte in plasma after extravascular administration
$CL_{R, t1-t2}$	Renal clearance of the analyte in plasma from the time point t_1 to t_2
C_{max}	Maximum measured concentration of the analyte in plasma
$C_{max, ss}$	Maximum measured concentration of the analyte in plasma at steady state
CRA	Clinical Research Associate
CRF	Case Report Form, paper or electronic (sometimes referred to as 'eCRF')
CRO	Clinical research organization
CTL	Clinical Trial Leader
CTM	Clinical Trial Manager
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
CV	Arithmetic coefficient of variation
DILI	Drug Induced Liver Injury
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
eDC	electronic Data Capture
EOT	End of Trial
ESR	Erythrocyte Sedimentation Rate
EU	European Union
FDA	Food and Drug Administration
fe_{t1-t2}	Fraction of administered drug excreted unchanged in urine over the time interval from t1 to t2
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
gMean	Geometric mean
GMP	Good Manufacturing Practice
GOT	Glutamic Oxaloacetic Transaminase
GPT	Glutamic Pyruvic Transaminase
IB	Investigator's Brochure
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee

INR	International Normalized Ratio
IPD	Important protocol deviation
IQRMP	Integrated Quality and Risk Management Plan
IRB	Institutional Review Board
ISF	Investigator Site File
K_2EDTA	Dipotassium ethylenediaminetetraacetic acid
LC-MS/MS	Liquid chromatography with tandem mass spectrometry
MDA	Methylenedioxyamphetamine
MDMA	Methylenedioxymethamphetamine
MedDRA	Medical Dictionary for Regulatory Activities
MRD	multiple-rising dose
MRT_{po}	Mean residence time of the analyte in the body after oral administration
[redacted]	[redacted]
NK	Natural killer
NOAEL	No observable adverse effect level
OCT2	Organic cation transporter 2
P-gp	P-glycoprotein
PK	Pharmacokinetic(s)
PKS	Pharmacokinetic set
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)
RBC	Red blood cell
relative bioavailability	rel BA
REP	Residual Effect Period
SAE	Serious Adverse Event
SCR	Screening
SOP	Standard Operating Procedure
SRD	Single-rising dose
SYK	Spleen Tyrosine Kinase

$t_{1/2}$	Terminal half-life of the analyte in plasma
T2	T type 2 inflammation
tid	three times a day
t_{max}	Time from (last) dosing to the maximum measured concentration of the analyte in plasma
TMF	Trial Master File
TS	Treated set
TSAP	Trial Statistical Analysis Plan
TSH	Thyroid Stimulating Hormone
t_z	Time of last measurable concentration of the analyte in plasma
ULN	Upper limit of normal
V_z/F	Apparent volume of distribution during the terminal phase after extravascular administration
WBC	White blood cell
WHO	World Health Organization
WOCBP	Woman of childbearing potential
XTC	Ecstasy
ZAP70	Zeta-chain-associated protein kinase of 70 kDa
β	Slope parameter of linear regression line
λz	Terminal rate constant in plasma

1. INTRODUCTION

BI 894416 is a selective inhibitor of the non-receptor protein tyrosine kinase SYK (spleen tyrosine kinase) and is under clinical development to be orally administered for the indication of uncontrolled severe persistent asthma.

This trial will be performed to investigate the safety, tolerability, and pharmacokinetics of single rising oral doses of BI 894416 versus placebo in healthy Japanese male subjects.

1.1 MEDICAL BACKGROUND

Asthma is a heterogeneous disease characterized by a chronic inflammatory process of the airways and is 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, natural killer (NK) cells, mast cells, basophils, and neutrophils [R15-5470]. SYK is a key component of the signal transduction associated with the T2-high and T2-low, and non-T2 asthma pathways that is activated through interaction with allergens and a number of innate and adaptive immune receptors including Fc receptors on basophils, mast, B-cells, and T-cells. SYK is essential for the FcεR1-mediated activation and degranulation of mast cells and basophils. SYK is also important in the signal propagation of the dectin family of innate receptors, which are present on macrophages, dendritic cells, and neutrophils. Furthermore, SYK has important roles in B-cell and T-cell development, having partially redundant functions with Zeta-chain-associated protein kinase of 70 kDa (ZAP70) [R15-5470, R16-5298].

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

1.2 DRUG PROFILE

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

1.2.1 Clinical Experience in Humans

1.2.1.1 Summary of clinical trials

So far, BI 894416 was investigated in 4 phase I clinical trials in healthy male subjects and in one phase I clinical trial in mild asthma patients. Trial 1371-0001 was a first-in-man trial, trial 1371-0004 was a trial to investigate drug-drug interaction, trial 1371-0021 investigated the effect of a high-fat, high-calorie breakfast on BI 894416 absorption and trial 1371-0005

investigated the drug-drug interaction of rifampicin on BI 894416 metabolism. Trial 1371-0008 is an ongoing single-rising dose (SRD)/ multiple-rising dose (MRD) trial in mild asthma patients.

Trial 1371-0001 consisted of two parts. SRD part and a relative bioavailability (rel BA) part. Single-dose treatment up to 70 mg BI 894416, as an oral solution in the SRD part, as well as in the relative BA part, was safe and well tolerated. For details on safety and tolerability, as well as on pharmacokinetics and biomarker data of trial 1371-0001, refer to the IB [c03536505].

Trial 1371-0004 investigated the effect of strong inhibition of CYP3A, as well as the inhibition of P glycoprotein, on the pharmacokinetics of oral single dose of BI 894416. In this trial, 3 mg of BI 894416 was given in period 1. Period 2 consisted of a 3-day pre-treatment with 200 mg itraconazole being administered once a day, of a fourth dose of itraconazole being administered 1 h before BI 894416 administration, and of a fifth dose of itraconazole being administered 23 h after BI 894416 administration. Preliminary pharmacokinetic (PK) data (based on planned time points) indicated that administration of itraconazole increased the geometric mean (gMean) of C_{max}, AUC (area under the curve) $_{0\text{-}tz}$, and $AUC_{0\text{-}\infty}$ of BI 894416 in plasma by 1.13, 1.42, and 1.43 fold respectively. BI 894416, alone or together with itraconazole, was assessed as safe and well-tolerated in trial 1371-0004. For more details refer to the IB [c03536505].

Trial 1371-0021 investigated the relative bioavailability of BI 894416 as tablet formulation following a high-fat, high calorie breakfast compared with administration in the fasting state. When 30 mg BI 894416 was administered as immediate release tablets after high-fat high calorie meal, Cmax was reduced by approximately 30% with a 2 h delay of t_{max}. $AUC_{0\text{-}tz}$ and $AUC_{0\text{-}\infty}$ were not changed by food intake. BI 894416 immediate release tablets can therefore be taken under fasting and fed conditions. For more details refer to the IB [c03536505].

Drug interaction of BI 894416 at a dose of 50 mg with strong CYP3A4- and P-gp-inducer Rifampicin has been investigated in trial 1371-0005. Relative bioavailability of BI 894416 after 600 mg once daily Rifampicin administration decreased to 10.48% for $AUC_{0\text{-}\infty}$ and 30.03% for C_{max}.

Trial 1371-0008 is a combined SRD and MRD trial conducted in mild asthma patients in Germany. As of May 2020, preliminary PK data are available for single doses up to 170 mg from the SRD part, and up to 50 mg tid. dosing in the MRD part. In the MRD part a single dose was administered on Day 1, followed by 7 d tid. dosing and a single dose on day 9. PK profiles were taken on Day 1 and on Day 9.

1.2.1.2 Clinical pharmacokinetics

In the 1371-0008 trial after each dose group, samples were analysed for BI 894416. A calculation of preliminary PK parameters was done based on planned sampling times; therefore PK parameters in the final Clinical Trial Report (CTR) might deviate. Preliminary PK parameters were assessed prior to each dose escalation to ensure that predicted gMean of

C_{max} of patients did not exceed 5,233 nM, predicted gMean values for AUC_{0-24} did not exceed the maximum acceptable human exposure of 36,150 nM•h and that the upper limit of the 95% prediction interval for AUC_{0-24} of individual patients in the next dose group did not exceed 63,000 nM•h. Preliminary PK data from SRD part are shown in Table 1.2.1.2: 1 and from MRD part in Table 1.2.1.2: 2.
SRD part: AUC_{0-24} and C_{max} increased dose proportionally with increasing doses. At 170 mg the gMean exposure limit for C_{max} was met.
MRD part: trough values (data not shown) indicate that steady state was achieved after 4 days. After 7 days of tid. dosing, $C_{max,ss}$ as well as $AUC_{\tau,ss}$ increased with increasing dose and were well below the exposure limits described above.

Table 1.2.1.2: 1 Preliminary PK data from SRD part in 1371-0008

Dose group	N	AUC_{0-24} [nM•h/L]	C_{max} [nM]
75 mg qd	7	15200 (38.2)	2340 (29.7)
125 mg qd	7	25700 (29.9)	4128 (26.1)
170 mg qd	8	31700 (20.6)	5280 (24.3)

gMean (gCV%)

Table 1.2.1.2: 2 Preliminary PK data from MRD part in 1371-0008

Dose group	N	$AUC_{\tau,ss}$ [nM•h/L]	$AUC_{0-24,ss}$* [nM•h/L]	C_{max} [nM]
10 mg tid.	7	1470 (48.6)	4410	299 (42.7)
25 mg tid.	8	4800 (19.8)	14400	985 (19.4)
50 mg tid.	7	5400 (33.5)	16200	1290 (52.1)

gMean (gCV%)

*$AUC_{0-24,ss}$ is calculated with $AUC_{\tau,ss}$ to get the daily exposure for tid. dosing under steady state conditions.

1.2.1.3 Safety

A total of 186 subjects and patients have completed treatment with BI 894416 as part of the Phase I trials. In the completed trials in healthy volunteers, the doses studied ranged from 3 mg to 70 mg BI 894416 given as single doses. In the patient trial 1371-0008, doses ranged from 75 mg to 170 mg BI 894416 administered as single doses and from 10 mg tid to 50 mg tid BI 894416 administered as multiple doses for 7 days.

Phase I trials in healthy volunteers (1371-0001, 1371-0004, 1371-0005, 1371-0021)
No deaths, serious adverse event (SAE)s, AEs leading to discontinuation, protocol-specified AESIs, or other significant AEs (according to ICH E3) were reported in the Phase I trials. No dose dependent increase in frequency of AEs or drug-related AEs was observed with increasing doses of BI 894416 across the range of 3 mg to 70 mg. For more details on AEs by individual dose group, please consult the IB [c03536505].

In the ongoing SRD/MRD trial in asthma patients, 46 of the planned 64 patients were exposed to BI 894416 and 12 of the planned 16 patients received placebo. A total of 7 patients received 75 mg BI 894416, 8 patients received 125 mg BI 894416 and 8 patients received 170 mg BI 894416 in the single rising dose part of the trial (Table 1.2.1.3: 1). In addition, 7 patients received 10 mg tid BI 894416 while 8 patients in each arm of the 25 mg tid and 50 mg tid BI in the MRD part received BI 894416. None of the patients in this trial had SAEs, AESIs (i.e. hepatic injury).

One patient had a severe AE of back pain in the 25 mg tid group. This event was not deemed related to trial medication. One patient in the 50 mg tid dose group had an event of panic attack which was moderate in intensity and led to discontinuation of trial medication but was not deemed related to BI 894416.

Taking into account the number of currently included patients, more patients on BI 894416 were reported with AEs compared with placebo. The AE, which was most frequently reported after intake of BI 894416, was headache (overall 14 of 29 patients in the SRD portion (48.3%) and 6 of 29 patients in the MRD portion (20.7%). Two patients on placebo in the MRD reported headache while the other reported events of headache were taking BI 894416 in SRD and MRD parts.

Nausea was reported in 2 of 29 patients in the SRD part (6.9%). Both events were reported in the 170 mg dose arm. Nausea was also reported in the MRD part for 1 of 29 patients (3.4%) in the 10 mg tid arm. Flatulence was reported for 4 of 29 patients (13.8%) in the 25 mg tid. One patient reporting flatulence was taking placebo while the remaining three were taking BI 894416.

Two patients of 29 (6.9%) in the 25 mg tid dose group reported oropharyngeal pain and both patients were on active treatment. Bronchospasm was reported in 1 patient in the 25 mg tid dose group and in 1 patient in the 50 mg tid dose group. Lower respiratory tract infection was reported in 1 patient in the 10 mg tid and in 1 patient in the 25 mg tid dose group. All other AEs were documented for at most 1 patient overall.

Likewise, headache was mostly classified as drug related by the investigator in 7 of 29 patients in the SRD part (24.1%) and in 4 of 29 patients (13.8%) in the MRD part. The three events of nausea observed in the trial were reported as related to trial medication. Other drug-related AEs were reported by at most 1 patient per preferred term and included tension headache, soft faeces and diarrhoea.

The events of flatulence reported in the 25 mg tid dose arm were reported as related to trial procedure as the patients received meals with higher fiber content than their normal diets. The safety information displayed for the 1371-0008 trial in patients is preliminary data taken from the ongoing trial. As such, the information reported in this protocol may differ slightly from the reported AEs in the clinical trial report.

Table 1.2.1.3: 1 Overall summary of AEs in ongoing trial 1371-0008 – Treated set

	SRD Part				MRD Part			
Category of AE	Placebo N (%)	75 mg BI 894416 N(%)	125 mg BI 894416 N(%)	170 mg BI 894416 N(%)	Placebo N(%)	10 mg BI 894416 N(%)	25 mg BI 894416 N(%)	50 mg BI 894416 N (%)
Treated Patients	6 (100.0)	7 (100.0)	8 (100.0)	8 (100.0)	6 (100.0)	7 (100.0)	8 (100.0)	8 (100.0)
Any AE	1 (16.7)	5 (71.4)	5 (62.5)	7 (87.5)	4 (66.7)	5 (71.4)	5 (62.5)	5 (62.5)
Severe AEs[1]	0	0	0	0	0	0	1 (12.5)	0
Investigator defined drug−related AEs	0	2 (28.6)	3 (37.5)	4 (50.0)	1 (16.7)	2 (28.6)	0	2 (25.0)
AEs leading to discontinuation of trial medication	0	0	0	0	0	0	0	1 (12.5)
AEs of special interest	0	0	0	0	0	0	0	0
Serious AEs	0	0	0	0	0	0	0	0
Other significant AEs (ICH E3)	0	0	0	0	0	0	0	0

[1] Worst intensity recorded
(c32087967)

1.2.2 Residual Effect Period

The Residual Effect Period (REP, i.e., the period after the last dose with measurable drug levels and/or with pharmacodynamic effects likely to be present) of BI 894416 has not been defined yet. However, the elimination half-life of BI 894416 is short (gMean terminal half-life between 2.96 and 5.31 h in the SRD part of trial 1371-0001) and its mode of action is reversible. This suggests that the occurrence of any potential adverse effects would likely be limited to a short time period (i.e., few days).

Conservatively, a minimum period of 14 d after last administration of BI 894416, or placebo, has been selected as the REP. Therefore, the individual subject's end of trial will be 14 d following last dosing with BI 894416, or placebo, at the earliest.

All adverse events (AE) reported between administration of trial medication and the individual subject's end of trial will be counted as on-treatment AEs.

1.2.3 Drug product

Please refer to Section 4.1. For a more detailed description of the BI 894416 profile, please refer to the current IB [c03536505].

1.3 RATIONALE FOR PERFORMING THE TRIAL

BI 894416 is an SYK inhibitor that is being developed to be administered orally to treat patients with severe asthma.
The first single rising dose trial was conducted in healthy volunteers (1371-0001). In trial 1371-0001 doses of BI 894416 up to 70 mg were given and assessed as safe and well-tolerated.

The objective of this trial is to investigate the safety, tolerability, and pharmacokinetics of BI 894416 in healthy Japanese male subjects. The chosen population of healthy male subjects receiving single rising oral doses is considered adequate to provide the basis for the clinical development program of BI 894416 in Japan.

In this trial it is intended to investigate the safety and tolerability of 25 mg, 50 mg, and 70 mg single dose.

The dose range selected for this trial is expected to cover the potential therapeutic dose range in the further clinical development program of BI 894416.

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 trial procedures and risks related to the exposure to the trial medication.

1.4.1 Procedure-related risks

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

ECG electrodes may cause local and typically transient skin reactions.

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

To ensure patient safety, all such events or symptoms reported will be managed according to the judgement of the Investigator.

1.4.2 Drug -related risks and safety measures

Potential effects on immune cells

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

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

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

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

Tumour biology and carcinogenicity

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

Risk mitigation and monitoring: Only male subjects are included in this trial and, in view that carcinogenesis is a process that develops over a long time span, single doses of BI 894416 are not considered a relevant carcinogenic risk to the male subjects participating in this trial. Accordingly, no further risk mitigation is required in this trial.

Platelet aggregation and bleeding risk

A role of SYK in platelet function has been demonstrated in literature [R15-5470]. Several platelet functions rely on SYK signalling (e.g. collagen receptor Glycoprotein VI), but others are independent of SYK [R16-5240]. *In vitro* trials 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 adenosine diphosphate-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. However, platelet function, as measured by bleeding time, is not affected by a drug unless all the platelet pathways are inhibited, due to redundancy within the system. Therefore, no risk for bleeding exists with regard to platelet inhibition, unless a subject is also on another antiplatelet drug that blocks these other pathways. In line with this conclusion, data of previous trial 1371-0001 do not indicate any signs of an increased risk of bleeding.

Risk mitigation and monitoring: Use of any other concomitant drug that could reasonably inhibit platelet aggregation, or coagulation, such as acetylsalicylic acid, clopidogrel and warfarin, will be prohibited (see 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, see the IB [c03536505]. In this trial, each subject is treated with single doses of BI 894416. Due to the slow turnover of bone tissue, no relevant effect on bone density is expected due to single-dose administrations with BI 894416 in this trial, and no specific monitoring of bone density is necessary in this trial.

Mortality/morbidity in preclinical trials

Mortality/sacrifice due to morbidity occurred in CByB6F1 non-transgenic mice and in Wistar Han rats. Clinical signs preceding morbidity were similar in both rodent species and included respiratory changes (rapid, shallow, and/or labored breathing), decreased motor activity, ruffled fur, hunched or prostrate posture, eye changes (squinting, discharge) and/or hypothermia. One humane sacrifice due to overt neurotoxicity was done in one dog of the 3-day escalation trial. For details see the current version of the IB [c03536505].

Risk mitigation and monitoring: Data of previous trial 1371-0001 indicate good safety and tolerability of BI 894416 at all investigated doses (single oral doses up to 70 mg). The dose of BI 894416 given in this trial is equivalent to or lower than doses given previously to healthy subjects. That means, BI 894416 plasma exposures that are expected in this trial are in the range measured previously in trial 1371-0001 and that were associated with good safety and tolerability. Moreover, subjects will be in-house at the trial site, under close medical observation for 48 h after administration of BI 894416. Vital signs and ECGs will be measured during the trial, and subjects will be instructed to report AEs spontaneously and will be asked, at time points defined in the Flow Chart for AEs. In case of AEs in need of treatment, the investigator can authorize symptomatic therapy. In those cases, subjects will be treated as necessary and, if required, kept under supervision at the trial site, or transferred to another hospital, until all medical evaluation results have returned to an acceptable level.

Neurotoxicity

In dog toxicology trials, acute adverse neurological effects, such as tremor and movement disorder assessed as dyskinesia (paresis/rigidity), were observed at high exposures (see IB [c03536505]). One dog was euthanized due to overt neurotoxicity in 3-day escalation trial at 90 mg/kg/day. In dose escalation trial in dogs with assessment of neurotoxicity [n00245394], all clinical signs of neurotoxicity were reversible with cessation of dosing. No structural changes were observed in histopathology. Peripheral nerve conduction velocity and electroencephalogram were unchanged. No specific mechanism causing the neurological effects in dogs has been elucidated. Therefore, it has not been determined whether the neurological changes are species specific; however, external expert review considered this is most likely a channelopathy specific to dog and not likely to occur in man (see IB [c03536505]).

Risk mitigation and monitoring: Subjects with neurological disorder or medical history of relevant neurological disorder are excluded from trial participation (see 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 the neurological examination will be excluded from trial participation (see Section 3.3.3). If necessary according to the investigator, 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 indicate that BI 894416 is not mutagenic or clastogenic. In the 2-week repeat dose range finding trial in male rats [n00240179], degeneration of spermatids of the testes was observed at ≥400 mg/kg/day, which is considered a secondary effect, related to overt toxicity and morbidity.

It is unknown whether BI 894416 or its metabolites are distributed into male semen. Therefore, there is a theoretical risk of a sub therapeutic exposure to BI 894416, or its metabolites, for a woman of child bearing potential (WOCBP) via the semen of a trial subject. Developmental and reproductive trials have not yet been conducted. Therefore, the effect of sub therapeutic concentrations of BI 894416, or its metabolites, with regards to embryofetal development has not been explored so far.

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

Phototoxicity

Phototoxicity potential of BI 894416 was measured in the open-lid Neutral Red Uptake test. There was no indication of phototoxicity by BI 894416. Subjects will be advised to avoid direct exposure to sun and UV light during the entire trial (see Section 4.2.2.2). Further protective measures would not be necessary given the low phototoxic potential of BI 894416 (see IB [c03536505]).

Potential effects on QT interval

Preclinical trials suggested no proarrhythmic potential or cardiovascular liability with BI 894416. However, statistical results of first-in-man trial 1371-0001 suggested a dose- and concentration-dependent increase of QTcF interval. At gMean C_{max} of the 70 mg dose group, placebo- and baseline-corrected predicted mean QTcF increase was 5.9 ms (upper limit of the 90% confidence interval (CI) was 10.5 ms).

Risk mitigation: Subjects with cardiovascular disorders (Section 3.3.3, exclusion criterion 5), subjects who used drugs that cause QT/QTc prolongation (Section 3.3.3, exclusion criterion 11), subjects that show a marked baseline prolongation of QT/QTc interval or any other relevant ECG finding at screening (Section 3.3.3, exclusion criterion 20), and subjects with a history of additional risk factors for Torsade de Pointes arrhythmia (Section 3.3.3, exclusion criterion 21) are excluded from trial participation. Moreover, subjects will be in-house under close observation for 48 h following drug administration, and ECGs are done pre- and post-dose at the time points given in the Flow Chart. Considering these risk-mitigating measures, the risks to subjects participating at trial 1371-0003 due to potential effects on QT interval are considered minimal.

Liver toxicity

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

1.4.3 Overall assessment

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

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

BI 894416 plasma exposures in the current trial are expected to be within plasma exposure values that were observed in previous first-in-man trial 1371-0001 and SRD and MRD trial in mild asthma patients 1371-0008 and that were associated with good safety and tolerability.

Considering the medical need for treatment of uncontrolled severe persistent asthma and the potential advantage of a highly specific SYK, the sponsor considers that the benefit of this trial outweighs the potential risks.

2. TRIAL OBJECTIVES AND ENDPOINTS

2.1 MAIN OBJECTIVES, PRIMARY AND SECONDARY ENDPOINTS

2.1.1 Main objectives

The main objectives of this trial are to investigate safety and tolerability of BI 894416 in healthy male subjects following oral administration of single rising doses.
Secondary objective is the exploration of PK of BI 894416.

2.1.2 Primary endpoint

The primary endpoint for assessment of safety and tolerability of BI 894416 is the percentage [%] of subjects with drug related adverse events.

2.1.3 Secondary endpoint

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

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

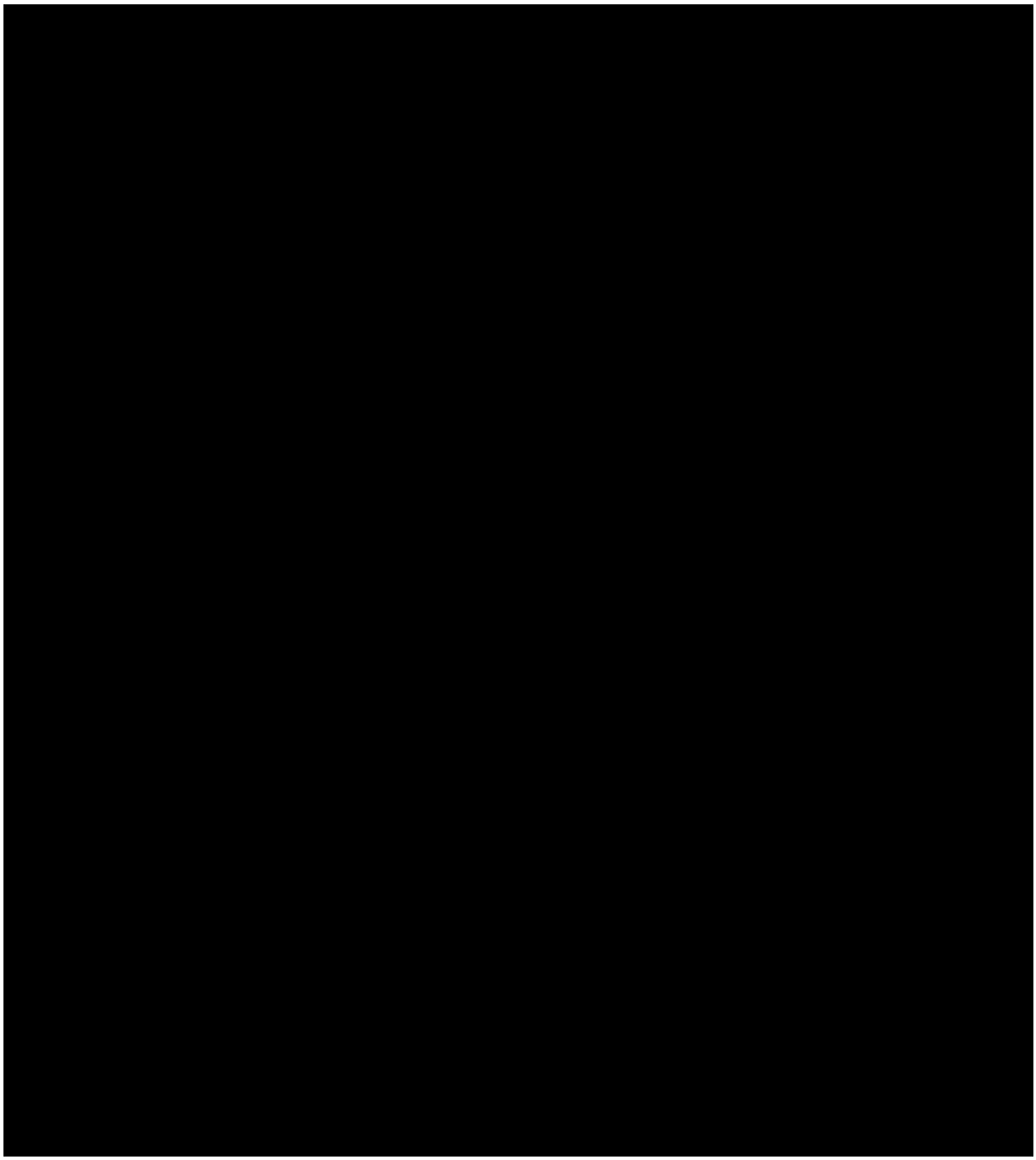
- C_{max} (maximum measured concentration of the analyte in plasma)

[redacted]

2.2.2.1 Safety and tolerability

Safety and tolerability of BI 894416 will be assessed based on:
- Adverse events (including clinically relevant findings from the medical examination, neurological examination and continuous ECG monitoring)
- Safety laboratory tests
- 12-lead ECG
- Vital signs (blood pressure, pulse rate)

[redacted]



3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

This single rising dose trial is designed as single-blind, randomised, and placebo-controlled within dose groups.

It is planned to include a total of 24 healthy male subjects in the trial. The subjects will be assigned to 3 groups consisting of 8 subjects per group; the groups will be dosed sequentially (see Table 3.1: 1).

The trial schedule and design is depicted in Figure 3.1: 1 and 3.1:2

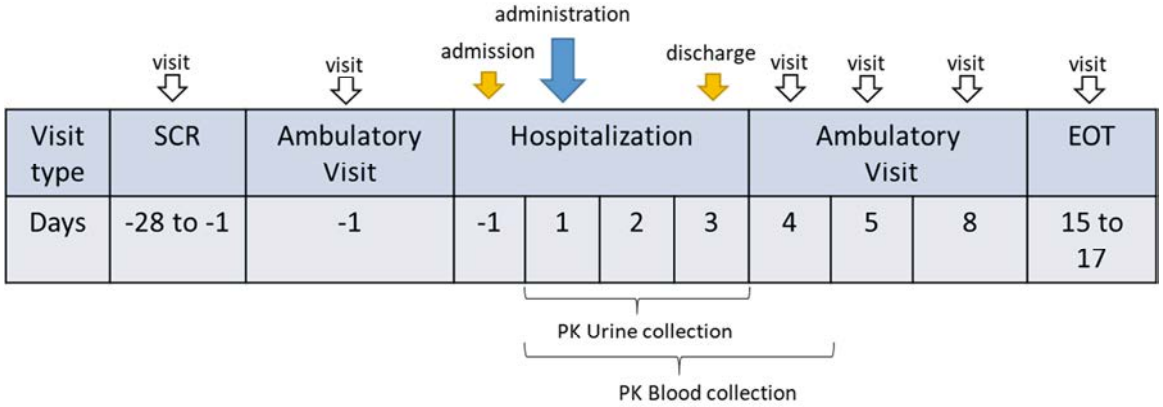


Figure 3.1: 1 Overview of trial schedule

Figure 3.1: 2 Trial design

Within each dose group, 6 subjects will receive BI 894416 and 2 will receive placebo. Only one dose is tested within each dose group.

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

Table 3.1: 1 Dose groups

Dose Group	1	2	3
Dose (mg)	25	50	70
Number of subjects	8	8	8
Subjects receiving placebo	2	2	2
Subjects receiving active drug	6	6	6

The groups will be dosed consecutively in ascending order of the doses, and a time interval of at least 7 d will be maintained between the last drug administration to subjects in the previous dose group (dose group N) and the first drug administration to subjects in the subsequent dose group (dose group N+1). The decision to treat the next dose group will be based upon safety and tolerability of all the preceding dose groups. The next dose group will only be treated if, in the opinion of the investigator (or authorised deputy, Sub Investigator), and Clinical trial leader (CTL), no safety concerns have arisen in the preceding dose groups, i.e. no dose-limiting events occurred, and if none of the pre-specified trial-specific stopping criteria have been met (refer to Section 3.3.4).

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

Although no formal Safety Review meeting will take place within a given dose group, safety will be continuously monitored during this trial, and an individual will only be dosed in the absence of any safety concern, i.e. no dose-limiting events occurred, and if none of the pre-specified trial-specific stopping criteria have been met (refer to Section 3.3.4).

At minimum, data from 4 subjects on active drug need to be available for escalation to a higher dose. The minimum data set for review consists of the following:

- AEs in the current and preceding dose groups up to at least 7 d post dosing including clinically relevant findings from ancillary safety testing listed below (Note: AEs may be ongoing at the time of Safety Reviews and AE information may be subject to change prior to Database Lock)
- Results from 12-lead ECG in the current and preceding dose groups up to at least 3 d post dosing
- Vital signs in the current and preceding dose groups up to at least 3 d post dosing.
- Clinical laboratory tests in the current and preceding dose groups up to at least 7 d post dosing
- Review of criteria for stopping subject treatment as per Section 3.3.4.1

The decision to escalate the dose will be made jointly by the Principal Investigator, or an authorised deputy, Sub Investigator, and the CTL after in-depth analysis of all available safety data, especially SAEs, AEs, and out-of-range laboratory results that are considered clinically significant by the investigator. Dose escalation will only be permitted if no safety concerns exist neither in the opinion of the Principal Investigator (or an authorised deputy, Sub Investigator) and the CTL.

Safety Reviews can be conducted face-to-face or by video/telephone conference. The CTL is responsible for the organisation and minutes of the reviews. Minutes will be signed off by the Principal Investigator (or an authorised deputy, Sub Investigator) and CTL, and will be filed in the investigator site file (ISF) and trial master file (TMF).

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

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

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

Single-blind conditions regarding the subject's treatment (active or placebo) are maintained within each dose group. However, subjects and investigators will be aware of the dose of the drug administered. The disadvantage of this trial design is a possible observer bias with regard to the dose-dependent effects; in addition, the sequential dosing of groups could potentially result in time-related effects. However, as such effects are expected to be small relative to the differences between the doses in the broad range investigated, unbiased comparisons between treatments can still be expected.

It is standard in single rising dose trials involving healthy subjects to include a placebo group to control for safety and tolerability of the trial medication. Each dose group consists of 8 subjects, with 6 on active treatment, and 2 on placebo. For data analysis purposes, the placebo control group will include all subjects that were treated with placebo, regardless of the groups they were treated. Six subjects per active treatment group are generally considered to be sufficient for the exploratory evaluation of pharmacokinetics.

For this trial, 25 mg has been selected as the minimum dose, which may be required to achieve therapeutic systemic exposure to BI 894416. However, higher doses might still be well tolerated while providing a larger magnitude of therapeutic effects. Finally, even if the therapeutic dose is determined to be as low as 25 mg, higher than therapeutic doses are typically explored in Phase I trials to provide a safety margin for following trials e.g., drug-drug-interaction trials, trials with patients with impaired excretion function, etc., where substantial increases in exposure may be seen.

Also, 70 mg has been selected as the maximum dose, a dose that is expected to be high enough to obtain exposure in the therapeutic range. The human exposure cap was a C_{max} gMean value of 5,233 nmol/L, AUC_{0-24} gMean value of 36,150 nmol·h/L, AUC_{0-24} the upper limit of 95% prediction interval of 63,000 nmol·h/L. The exposure cap of AUC_{0-24} gMean corresponded to 3-fold below exposure at the dog NOAEL and 7-fold below the lowest

exposure in dogs where neurologic effects were observed (for more details, please see the current version of the Investigator's Brochure (IB) [c3536505]). C_{max} gMean, AUC gMean and the upper limit of 95% prediction interval value are predicted to be below the exposure cap (Table 3.2: 1); therefore, single administration of 70 mg are considered safe.

Table 3.2: 1 Predicted PK parameters

Dose	AUC_{0-24} [nmol·h/L] gMean	Exposure multiple[1]	AUC_{0-24} [nmol·h/L] 95%ile	Exposure multiple[2]	C_{max} [nmol/L] gMean	Exposure multiple[3]
70 mg single	13973	2.59	26232	2.4	2177	2.4

Note: A population with a mean body weight of 65 kg (17% arithmetic coefficient of variation [CV]) was used in the simulations to predict the between subject variability.

1 in relation to AUC gMean exposure limit (36,150 nmol·h/L)

2 in relation to 95th percentile exposure limit (63,000 nmol·h/L)

3 in relation to C_{max} gMean exposure limit (5,233 nmol/L)

3.3 SELECTION OF TRIAL POPULATION

It is planned that 24 healthy male subjects will enter the trial. These subjects will be recruited from the volunteers' pool of the trial site.

Only male subjects will be included in the trial because no data on reproductive toxicology are available at this time.

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

Not applicable, as the trial 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 medical examination, vital signs (BP, PR), 12-lead ECG, and clinical laboratory tests
2. Japanese ethnicity, according to the following criteria:
   - born in Japan, have lived outside of Japan <10 years, and have parents and grandparents who are Japanese
3. Age of 20 to 45 years (inclusive) at screening
4. BMI of 18.5 to 25.0 kg/m^2 (inclusive) at screening
5. Signed and dated written informed consent prior to admission to the trial, in accordance with Good Clinical Practice (GCP) and local legislation

6. Subjects who agree to minimize the risk of making their partner pregnant by fulfilling any of the following criteria starting from the first administration of trial medication until 90 days after last administration of trial medication
    - Use of adequate contraception, any of the following methods plus condom: intrauterine device, combined oral contraceptives that started at least 2 months prior to the first drug administration.
    - Vasectomized (vasectomy at least 1 year prior to enrolment)
    - Surgical sterilization (including bilateral tubal occlusion, hysterectomy or bilateral oophorectomy) of the subject's female partner

3.3.3 Exclusion criteria

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

1. Any finding in the medical examination (including BP, PR or ECG) deviating from normal and assessed as clinically relevant by the investigator
2. Repeated measurement of systolic blood pressure outside the range of 90 to 140 mmHg, diastolic blood pressure outside the range of 50 to 90 mmHg, or pulse rate outside the range of 50 to 90 bpm
3. Any laboratory value outside the reference range that the investigator considers to be of clinical relevance
4. Any evidence of a concomitant disease 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 (Subjects who were positives to Hepatitis B surface antigen, Hepatitis B surface antibody, Hepatitis B core antibody, Hepatitis C antibodies, HIV-1 and HIV-2 antigen and/or antibody, T-SPOT and Syphilis test)
10. History of relevant allergy or hypersensitivity, including allergy to the trial medication or its excipients
11. Use of drugs within 30 d of planned administration of trial medication that might reasonably influence the results of the trial, including drugs that cause QT/QTc interval prolongation
12. Intake of an investigational drug in another clinical trial within 60 d of planned administration of investigational drug in the current trial, or concurrent participation in another clinical trial in which investigational drug is administered
13. Smoker, unless the subject quit smoking for at least 12 months prior to first planned administration of trial medication
14. Inability to refrain from smoking during trial
15. Alcohol abuse, i.e. consumption of more than 30 g per day
16. Drug abuse or positive drug screening

17. Blood donation of more than 400 mL within 12 weeks, or 200 mL within 30 d, or plasma donation within 2 weeks prior to administration, or intended blood donation during the trial
18. Intention to perform excessive physical activities within one week prior to the administration of trial medication or during the trial
19. Inability to comply with the dietary regimen of the trial site
20. A marked baseline prolongation of QT/QTc interval, such as QTc intervals that are repeatedly greater than 450 ms, or any other relevant ECG finding at screening
21. A history of additional risk factors for *Torsade de Pointes*, such as heart failure, hypokalaemia, or family history of Long QT Syndrome
22. Subject is assessed by the investigator as unsuitable for inclusion, because, for instance, the subject is not considered able to understand and comply with trial requirements, or has a condition that would not allow safe participation in the trial
23. History of disease that affects the present situation

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

24. History of relevant neurological disorder affecting the peripheral or central nervous system, including, but not limited to, stroke, epilepsy, inflammatory or atrophic diseases affecting the nervous system, cluster headache or any cancer of the nervous system*
25. 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
26. History of cancer, except successfully treated basal cell carcinoma
27. Use of any drug that could reasonably inhibit platelet aggregation or coagulation, e.g. acetylsalicylic acid, within 10 d prior to administration of trial medication, or planned use during the trial or within 7 d after last dose of trial medication

* Febrile seizures in childhood or adolescence, recovered carpal tunnel syndrome, recovered uncomplicated meningitis, recovered herpes zoster, tension headache, occasional benign tics, e.g. due to stress, or minor par- or dysesthesia, e.g. as a side effect of prior blood withdrawal, do not constitute a history of relevant neurological disorder.

For trial restrictions, refer to Section 4.2.2.

3.3.4 Withdrawal of subjects from treatment or assessments

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

If a subject is removed from, or withdraws from, the trial prior to the first administration of trial medication, the data of this subject will not be entered in the case report form (CRF) and will not be reported in the clinical trial report (CTR). If a subject is removed from, or withdraws from, the trial after the first administration of trial medication, this will be documented and the reason for discontinuation must be recorded in the CRF; in addition, the data will be included in the CRF and will be reported in the CTR.

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

before the end of the REP (see Section 1.2.2), the discontinued subject should, if possible, be questioned for AEs and concomitant therapies at, or after, the end of the REP in order to ensure collection of AEs and concomitant therapies throughout the REP, if not contrary to any consent withdrawal of the subject.

3.3.4.1 Discontinuation of trial treatment

An individual subject will be removed from the trial if:

1. The subject wants to discontinue trial treatment or trial participation , without the need to justify the decision
2. The subject needs to take concomitant medication that interferes with the investigational medicinal product or other trial treatment
3. The subject can no longer able to participate trial for other medical reasons, such as surgery, adverse events (AE)s, or diseases
4. The subject has an elevation of AST and/or ALT ≥3-fold upper limit of normal (ULN) and an elevation of total bilirubin ≥2-fold ULN, as measured in the same blood sample, and/or needs to be followed up according to the DILI checklist provided in the ISF

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

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

3.3.4.2 Withdrawal of consent to trial participation

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

3.3.4.3 Discontinuation of the trial by the sponsor

Boehringer Ingelheim reserves the right to discontinue the trial at any time for any of the following reasons:

1. Failure to meet expected enrolment goals overall or at a particular trial site
2. New toxicological findings, serious adverse events, or any safety information invalidating the earlier positive benefit-risk assessment. Dose escalation will be terminated if more than 50% of the subjects at one dose level show clinically relevant drug-related adverse events of moderate or severe intensity, or if at least one drug-related serious adverse event is reported
3. Deviation from the clinical trial protocol (CTP), violation of GCP, or violation of the contract with BI, impairing the appropriate conduct of the trial
4. The sponsor decides to discontinue the further development of the investigational product

Addition to this, dose escalation will be stopped if at least 2 subjects on active treatment at one dose level have relevant individual QT prolongations, i.e. a QTc increase greater than 60 ms from baseline in connection with an absolute QT or QTc greater than 500 ms, as confirmed by a repeat ECG recording.

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

3.3.5 Replacement of subjects

If some subjects do not complete the trial, the CTL, together with the Trial Pharmacokineticist and the Trial Statistician, are to decide if and how many subjects will be replaced. A replacement subject will be assigned a unique trial subject number, and will be assigned to the same treatment as the subject he replaces.

4. TREATMENTS

4.1 INVESTIGATIONAL TREATMENTS

The investigational product BI 894416 as tablet formulation has been manufactured by BI Pharma GmbH & Co. KG.

4.1.1 Identity of the Investigational Medicinal Products

The characteristics of the test product are given below:

Substance:	BI 894416
Pharmaceutical formulation:	Tablet
Source:	BI Pharma GmbH & Co. KG, Germany
Unit strength:	10 mg and 25 mg,
Posology:	single dose
Route of administration:	oral
Duration of use:	Single dose

The characteristics of the reference product (placebo) are given below:

Substance:	Placebo
Pharmaceutical formulation:	Tablet
Source:	BI Pharma GmbH & Co. KG, Germany
Unit strength:	Not applicable
Posology:	single dose
Route of administration:	oral
Duration of use:	Single dose

4.1.2 Selection of doses in the trial and dose modification

The dose range of BI 894416 for this trial was selected on the basis of the data obtained in the first-in-man SRD trials 1371-0001 and 1371-0008. So far, single doses up to 70 mg in healthy subjects and single doses up to 170 mg in asthma patients in fasting status was well tolerated.

4.1.3 Method of assigning subjects to treatment groups

Prior to the screening visit, subjects will be contacted in writing and informed about the planned visit dates. The subjects willing to participate will be recruited to dose groups according to their temporal availability. As soon as enough subjects are allocated to 1 of the 3 dose groups, the following subjects will be allocated to one of the other dose groups and so

on until the dose groups are completed. Therefore, the allocation of subjects to dose groups is not influenced by trial personnel, but only by the subjects' temporal availability. Because the trial is conducted on healthy subjects from a homogenous population, relevant imbalances between the dose groups are not expected.

Subjects will be assigned to treatments (active treatment or placebo) prior to the first administration of trial medication. For this purpose, the randomisation list will be provided to the trial site in advance. Numbers of the randomization list will be allocated to subjects by the method 'first come first served'. Subjects are then assigned to treatment according to the randomisation list. Once a subject number has been assigned, it cannot be reassigned to any other subject.

The randomisation procedure is described in Section 7.6.

4.1.4 Drug assignment and administration of doses for each subject

The treatments to be evaluated are outlined in Table 4.1.4: 1 below. The number of tablets for placebo corresponds to the number of tablets in the corresponding dose level.

Table 4.1.4: 1 BI 894416 and placebo* treatments, tablets

Dose group	Substance	Pharmaceutical form	BI 894416 10 mg	BI 894416 25 mg	Total dose of BI 894416
1	BI 894416	Tablet	0	1	25 mg
2	BI 894416	Tablet	0	2	50 mg
3	BI 894416	Tablet	2	2	70 mg
1-3	Placebo*	Tablet	identical to active treatment		--

* Subjects receiving placebo are equally distributed across dose groups

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

During the first 4 h after drug administration, the subjects are not allowed to lie down, i.e. no declination of the upper body of more than 45 degrees from upright posture except for medical examination, or to sleep.

Subjects will be kept under close medical surveillance until 48 h after dosing.

For restrictions with regard to diet, see Section 4.2.2.2.

4.1.5 Blinding and procedures for unblinding

4.1.5.1 Blinding

The trial is designed single-blind. The treatments administered (active or placebo) will be blinded to subjects, but will be known to the investigators (outcome assessors). Only the current dose level will be known to the subjects due to the rising dose design.

A single–blind design is considered acceptable, because the potential bias in this type of trial seems to be low and, according to trial procedures, it is assured that the investigator's knowledge of the next treatment does not influence the decision to enter a subject.

All trial data will be handled open label. This means that trial functions of the sponsor are unblinded, including clinical monitor, data manager, statistician, bioanalyst, pharmacokineticist, pharmacometrician, drug metabolism scientist, as well as dedicated personnel of the trial site.

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

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

Access to the randomisation schedule will be controlled and documented.

4.1.5.2 Unblinding and breaking the code

As this trial will be conducted single blind, subjects' treatment assignments will be known to investigators. Therefore, no emergency envelopes will be provided.

4.1.6 Packaging, labelling, and re-supply

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

For details on packaging and for the description of the label, refer to the ISF.

The telephone number of the sponsor, as well as the name, address, and telephone number of the trial site are provided in the subject information form. Examples of the labels will be available in the ISF.

No re-supply is planned.

4.1.7 Storage conditions

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

Clinical Trial Manager (CTM), as provided in the list of contacts, is to be contacted immediately.

4.1.8 Drug accountability

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

- Approval of the clinical trial protocol by the Institutional Review Board (IRB)
- Availability of a signed and dated clinical trial contract between the sponsor and the investigational site
- Approval/notification from the regulatory authority, e.g. competent authority (CA)
- 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 adequately documenting that the subjects were provided the doses specified by the CTP and will 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 investigational medicinal product remains in the investigator's possession.

All unused trial medication will be disposed locally by the trial site upon written authorisation of the CTM. 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 employ symptomatic therapy. In those cases, subjects will be treated as necessary and, if required, kept under supervision at the trial site, or transferred to another 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 trial 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 trial. If necessary, acetaminophen may be given occasionally, if required to treat an adverse event require.

Drugs that may increase exposure of BI 894416 should be avoided during the entire trial. Based on in vitro data, CYP3A is involved in the metabolism of BI 894416. In addition, BI 894416 is substrate of P-glycoprotein *in vitro*. Data from the drug-drug interaction trial 1371-0004 (see Section 1.2.1) indicate that inhibition of CYP3A and P-glycoprotein may cause mild increases of BI 894416 plasma concentrations. Therefore administration of CYP3A and P-glycoprotein inhibitors should be avoided during the entire trial.

BI 894416 is also a substrate of organic cation transporter 2 (OCT2). It is not excluded that inhibition of OCT2 could increase BI 894416 plasma exposure. Therefore administration of inhibitors of OCT2 should be avoided during the entire trial.

4.2.2.2 Restrictions on diet and life style

While admitted to the trial site, the subjects will be instructed not to consume any foods or drinks other than those provided by the staff. Standardised meals will be served at the times indicated in the Flow Chart. No food is allowed for at least 10 h before and 4 h after trial medication intake

One h before drug intake until 4 h after trial medication intake, fluid intake is restricted to the water administered with the trial medication, and an additional 240 mL of water served at 2 h and 4 h post-dose (mandatory for all subjects). From 4 h after drug intake on Day 1 until 24 h post-dose, fluid intake is restricted to 3 L.

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

Poppy seed containing products should not be consumed starting 4 d before first investigational medicinal product administration until last PK sampling of the trial.

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

Smoking is not allowed during the trial.

Excessive physical activity, such as competitive sport, should be avoided from 7 d 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 trial.

4.3 TREATMENT COMPLIANCE

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

Subjects who are non-compliant, for instance, who do not appear for scheduled visits or violate trial restrictions, may be removed from the trial and the CRF will be completed accordingly. For further procedures, please see Section 3.3.4.

5. ASSESSMENTS

5.1 ASSESSMENT OF EFFICACY

Not applicable. No efficacy endpoints will be evaluated in this trial.

5.2 ASSESSMENT OF SAFETY

5.2.1 Medical examination

At screening, the medical examination will include demographics, height and body weight, smoking and alcohol history, relevant medical history and concomitant therapy, review of inclusion and exclusion criteria, review of vital signs (BP, PR), 12-lead ECG, laboratory tests, medical examination, and neurological examination. At the end of trial examination, it will include review of vital signs, 12-lead ECG, laboratory tests, a medical examination and a neurological examination.

5.2.2 Vital signs

Systolic and diastolic blood pressures (BP), as well as pulse rate (PR), will be measured by a blood pressure monitor, 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 and on the same arm, if possible.

5.2.3 Safety laboratory parameters

For the assessment of laboratory parameters, blood and urine samples will be collected by the trial site at the times indicated in the Flow Chart after the subjects have fasted for at least 10 h, except 4 h post dosing on Day 1. 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.

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, and if clinically relevant in the opinion of the investigator, or if the investigator finds an abnormality in the urinalysis.

Table 5.2.3: 1 Routine laboratory tests

Functional lab group	Test name (comment/abbreviation)	A[1]	B[1]	C[1]
Haematology	Haematocrit	X	X	X
	Haemoglobin	X	X	X
	Red Blood Cell Count (RBC)	X	X	X
	Reticulocytes (relative and absolute)	X	X	X
	White Blood Cells (WBC)	X	X	X
	Platelet Count/Thrombocytes (quant)	X	X	X
	Erythrocyte Sedimentation Rate (ESR)	X	X	X
Automatic WBC differential, (relative)	Neutrophil; eosinophils; basophils; monocytes; lymphocytes	X	X	X
Manual differential WBC (if automatic differential WBC is abnormal)	Polymorphnuclear neutrophils (segs), band neutrophils (stabs), eosinophils, basophils, monocytes, lymphocytes			
Immunoglobulins in serum	IgA	X	--	X
	IgE	X	--	X
	IgG	X	--	X
	IgM	X	--	X
Lymphocyte differentiation (relative)	T cells (CD3+), T helper cells (CD3+CD4+), cytotoxic T cells (CD3+CD8+), B cells (CD19+), natural killer cells (CD16+CD56+CD3-), CD4:CD8 ratio	X	--	X
Coagulation	Activated partial thromboplastin time (aPTT)	X	X	X
	Prothrombin time (Quick's test and INR)	X	X	X
	Fibrinogen	X	X	X
Enzymes	AST (Aspartate transaminase)/GOT	X	X	X
	ALT (Alanine transaminase)/GPT	X	X	X
	Alkaline phosphatase (AP)	X	X	X
	Gamma-glutamyl transferase (GGT)	X	X	X
	Creatine kinase (CK); CK-MB only if CK is elevated	X	--	X
	Lactate dehydrogenase	X	--	X
	Lipase	X	--	X
	Amylase	X	--	X
Hormones	Thyroid Stimulating Hormone (TSH)	X	--	--
Substrates	Plasma glucose	X	X	X
	Creatinine	X	X	X
	Total bilirubin	X	X	X
	Direct bilirubin	X	X	X
	Total protein	X	--	X
	C-Reactive Protein	X	X	X
	Uric acid	X	--	X
	Total cholesterol	X	--	X
	Triglycerides	X	--	X
Electrolytes	Sodium	X	X	X
	Potassium	X	X	X
	Calcium	X	X	X
	Inorganic phosphate	X	--	X

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

Table 5.2.3: 1 Routine laboratory tests (cont.)

Functional lab group	BI test name (comment/abbreviation)	A[1]	B[1]	C[1]
Urinalysis (Stix)	Urine nitrite	X	--	X
	Urine protein	X	--	X
	Urine glucose	X	--	X
	Urine ketone	X	--	X
	Urobilinogen	X	--	X
	Urine bilirubin	X	--	X
	Urine erythrocytes	X	--	X
	Urine leucocytes	X	--	X
	Urine pH	X	--	X
Urine sediment[1] (microscopic examination if erythrocytes, leukocytes nitrite or protein are abnormal in urine)	Only positive findings will be reported (for instance, the presence of sediment bacteria, casts in sediment, squamous epithelial cells, erythrocytes, leukocytes)			

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

The tests listed in Table 5.2.3: 2 are exclusionary laboratory tests that may be repeated as required. The results will not be entered in the CRF/database and will not be reported in the CTR. Infectious serology is planned at screening only. Drug screening will be performed at screening and after admission to the trial site prior to dosing on Day 1 of visit 2.

Table 5.2.3: 2 Exclusionary laboratory tests

Functional lab group	Test name
Drug screening (urine)	Amphetamine/ Methylenedioxyamphetamine (MDA) Barbiturates Benzodiazepine Cannabis Cocaine Methamphetamines/ Methylenedioxymethamphetamine (MDMA)/XTC Opiates Phencyclidine Tricyclic antidepressants
Infectious serology (blood)	Hepatitis B surface antigen (qualitative) Hepatitis B surface antibody (qualitative) Hepatitis B core antibody (qualitative) Hepatitis C antibodies (qualitative) HIV-1 and HIV-2 antigen and/or antibody (qualitative) T-SPOT Syphilis test (RPR, TP antibody method)
Imaging test	Chest x-ray (For checking onset or history of tuberculosis)

To encourage compliance with alcohol and smoking restrictions, a breath alcohol test and cotinine test will be performed during Screening Visit and before drug administration, and

may be repeated at any time during the trial at the discretion of an investigator or designee. The results will not be included in the CTR.

The laboratory tests listed in Tables 5.2.3: 1 and 5.2.3: 2 will be performed at the local laboratory of the trial site or/and at a CRO designated by the sponsor. Laboratory data will be transmitted electronically from the site to BI.

5.2.4 Electrocardiogram

5.2.4.1 12-lead resting ECG

Recording
Twelve-lead resting ECGs (I, II, III, aVR, aVL, aVF, V1 - V6) will be recorded using a computerised electrocardiograph at the time points given in the Flow Chart. Precise electrode placement will be performed according to the method of [redacted] and [redacted], modified by [redacted] and [redacted], i.e. 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 trial.

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 10 s after subjects have rested for at least 5 min in a supine position. ECG recording will always precede all other trial procedures scheduled for the same time, except for blood drawing from an intravenous cannula that is already in place, to avoid compromising ECG quality.

ECGs will be recorded as single ECGs or as triplicate ECGs, i.e. three single ECGs recorded within 180 s, as indicated in the Flow Chart.

ECGs may be repeated for quality reasons due to, for instance, alternating current artefacts, muscle movements, or electrode dislocation. For repetition within triplicate ECGs, the time window of 180 s applies as well. The repeat ECGs are assigned to the respective scheduled time point.

Additional (unscheduled) ECGs may be collected by the investigator for safety reasons. These ECGs are assigned to the prior scheduled time point in the Sponsor's database.

Storage
All ECGs will be stored electronically in the System provided by [redacted].

Data transfer
All triplicate ECGs will be transferred electronically to the central ECG laboratory [redacted] for evaluation.

In case of ECGs repeated due to quality reasons, only the repeated ECG recordings will be transferred to the central ECG lab, whereas the initially recorded ECGs will be discarded. Unscheduled ECGs, i.e. those taken for safety reasons, will be transferred to the central ECG lab, but will not be included into the statistical analysis of interval lengths.

Data transfer from the central ECG lab to the sponsor is described in a document that is filed in the TMF.

Evaluation

a) Central ECG lab
Central ECG lab evaluation will be performed (during the trial and/or after the trial) for first ECG of triplicate ECGs at every time point. For baseline, all three ECGs of the triplicate ECG at Day 1 pre-dose will be evaluated. This will include the determination of cardiac QRS-axis, as assessed by the ECG machine's algorithm, as well as the intervals RR, PR, QRS, and QT measured semi-automatically. Heart rate (HR) and the QT interval corrected for HR, i.e. QTcF and QTcB, will be determined by the sponsor (see trial statistical analysis plan［TSAP］for details).

All semi-automatic interval measurements in one subject will be performed on the same lead. The intervals will be measured from four cardiac cycles (beats) in lead II. If lead II shows a flat T wave, or is not measurable for any reason, lead V5 will be used. If lead V5 is not measurable, then lead I will be used. The lead actually used will be reported in the CTR. For automatic interval measurements no lead will be provided

For blinding arrangements see Section 4.1.5.1. No more than two blinded readers will evaluate all ECGs of the trial. ECGs from a particular subject should be evaluated by a single reader. For quality assurance and control of the measurements, all ECGs of a subject will be subsequently reviewed by the ECG technician's supervisor, or his/her designee, to assess the overall variance of the measured intervals, to detect accidental switching of leads and/or false subject assignments of the ECGs. After quality control, the fiducial point markings will be reviewed by the cardiologist assigned to the trial.

Evaluation of ECGs will comply with the ICH E14 guidance document and supplements [R07-4722, R16-0366] as well as the FDA requirements for annotated digital ECGs [R09-4830].

b) Trial site
All local ECGs will be evaluated by the investigator or a designee.

For the inclusion, or exclusion, (see Section 3.3) of a subject and for the assessment of cardiac safety during the trial, the QT and QTcB values generated by the computerised ECG system, or their manual corrections by the investigators, will be used. In doubtful cases, ECGs may be sent upfront, i.e. prior to the regular data transfer, for cardiologic assessment by the central lab. In this case, these centrally measured results would overrule any other results obtained.

Abnormal findings, irrespective of whether they originate from central or local evaluation, will be reported as AEs (during the trial) or baseline conditions (at screening) if judged clinically relevant by the investigator.

Any ECG abnormalities will be monitored carefully and, if necessary, the subject will be removed from the trial and will receive the appropriate medical treatment.

5.2.4.2 Continuous ECG monitoring

Cardiac rhythm, including heart rate, will be monitored by means of continuous 3-lead ECG recording for at least 15 min before drug administration, for baseline assessment, and for 4 h following drug administration. This continuous ECG monitoring supports the early detection of adverse events, such as clinically relevant bradycardia, tachycardia, or arrhythmia, at the trial site. Beyond this clinical evaluation at the trial site, no further data collection or analyses are performed based on continuous ECG monitoring.

ECG data from continuous ECG recording will not be transferred to the clinical trial database and will be evaluated by the investigator or a designee. Abnormal findings during continuous ECG recording will be recorded as AEs, if judged clinically relevant by the Investigator.

5.2.5 Other safety parameters

5.2.5.1 Neurological examination

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

The neurological examination will include the following assessments:

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

Documentation, Assessment, and Reporting

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

5.2.6 Assessment of adverse events

5.2.6.1 Definitions of adverse events

5.2.6.1.1 Adverse event

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

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

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

- Worsening of the underlying disease or of other pre-existing conditions
- Changes in vital signs, ECG, medical 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. Adverse events deemed serious for any other reason are important medical events that, based upon appropriate medical judgment, jeopardise the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation or development of dependency or abuse

An AE that possibly leads to disability will be ‘deemed serious for any other reason’ and reported as an SAE.

5.2.6.1.3 AEs considered 'Always Serious'

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

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

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

5.2.6.1.4 Adverse events of special interest

The term adverse events of special interest (AESI) relates to any specific AE that has been identified at the project level as being of particular concern for prospective safety monitoring and safety assessment within this trial, e.g. the potential for AEs based on knowledge from other compounds in the same class. AESIs need to be reported to the sponsor's Pharmacovigilance Department within the same timeframe that applies to SAEs, please see section 5.2.6.2.2.

The following are considered as AESIs:

- Hepatic injury
  A hepatic injury is defined by the following alterations of hepatic laboratory parameters:
  - o 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
  - o Aminotransferase (ALT, and/or AST) elevations ≥10 fold ULN

  These lab findings constitute a hepatic injury alert and the subjects showing these lab abnormalities need to be followed up according to the 'DILI checklist' provided in the ISF. In case of clinical symptoms of hepatic injury, e.g. 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 investigational medicinal product treatment continues or remains unchanged

5.2.6.2 Adverse event collection and reporting

5.2.6.2.1 AE collection

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

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

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

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

- From signing the informed consent onwards until an individual subject's end of trial:
    - All AEs (serious and non-serious) and all AESIs
    - The only exception to this rule are AEs (serious and non-serious) and AESIs in Phase I trials in healthy subjects, 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 new 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 that are relevant for the reported SAE or AESI, on the BI SAE form via fax within 24 h to the sponsor's unique entry point; the contact details will be provided in the ISF. The same timeline applies if follow-up information becomes available. In specific occasions the Investigator could inform the sponsor upfront via telephone. This does not replace the requirement to complete and fax the BI SAE form.

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

5.2.6.2.3 Information required

All AEs and SAEs, including those persisting after the individual subject's end of trial, must be followed up until they have resolved, have been assessed as 'chronic' or 'stable', or no further information can be obtained.

5.2.6.2.4 Pregnancy

Once a male subject has been enrolled in the clinical trial and has taken trial medication, and if a partner of the male subject becomes pregnant, the investigator must report any drug exposure during pregnancy in this partner 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

Date and clock times of drug administration and pharmacokinetic sampling will be recorded in Source data and in the CRFs.

Exact times of plasma sampling will be documented in the eCRFs by the medical personnel. The actual sampling times will be used for determination of pharmacokinetic parameters.

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

5.3.2 Methods of sample collection

5.3.2.1 Blood sampling for pharmacokinetic analysis

For quantification of BI 894416 concentrations in plasma, 3.0 mL of blood will be drawn from an antecubital or forearm vein into an K_2EDTA (dipotassium ethylenediaminetetraacetic acid)-anticoagulant blood drawing tube at the times indicated in the Flow Chart. Blood will be withdrawn by means of either an indwelling venous catheter or by venepuncture with a metal needle.

Two plasma aliquots each having at least 0.5 mL will be obtained and stored in an upright position at approximately -20°C or below at the trial site until shipment on dry ice to the

analytical laboratory. Details on sample handling, processing and shipments are described in the lab manual.
At a minimum, the sample tube labels should list BI trial number, subject number, visit, and planned sampling time. Further information such as matrix and analyte may also be provided.

After completion of the trial, the plasma samples 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 trial samples will be discarded after completion of the additional investigations, but not later than 5 years after the CTR is archived.

5.3.2.2 Urine sampling for pharmacokinetic analysis

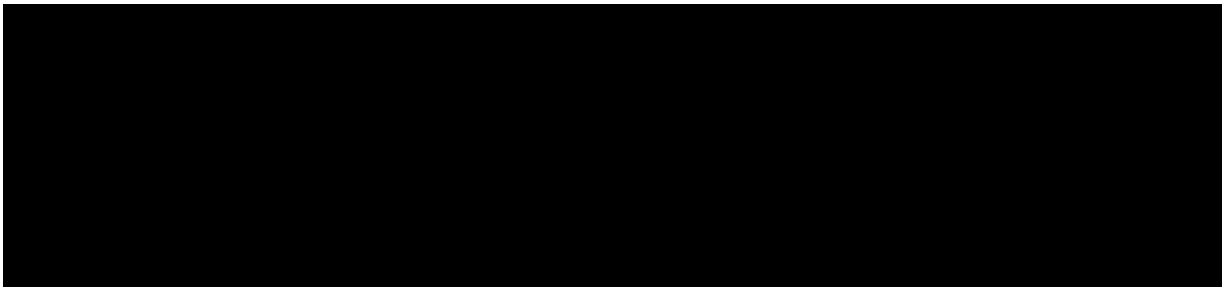
A blank urine sample will be collected before administration of trial medication (within 3 h before drug dosing) and two 0.5 mL aliquots will be retained to check for analytical interference by concomitant or rescue medication.

All urine voided during the sampling intervals indicated in the Flow Chart will be collected in urine containers and stored at room temperature. Subjects are told to empty their bladders at the end of each sampling interval. Details on sample handling, processing and shipments are described in the lab manual.

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

Two urine aliquots each having at least 0.5 mL will be obtained and stored in an upright position at approximately -20°C or below at the trial site until shipment on dry ice to the analytical laboratory. Details on sample handling, processing and shipments are described in the lab manual.
The second aliquot will be transferred after the bioanalyst has acknowledged safe arrival of the first aliquot. At the analytical laboratory, the urine samples will be stored at approximately -20°C or below until analysis.

After completion of the trial, the urine samples 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) will be generated by these additional investigations. The trial samples will be discarded after completion of the additional investigations but not later than 5 years after the CTR has been archived.



[redacted]

5.4 ASSESSMENT OF BIOMARKER(S)

Not applicable.

5.5 BIOBANKING

Not applicable.

5.6 OTHER ASSESSMENTS

5.6.1 Pharmacogenomic evaluation

Pharmacogenomic investigations explore the role of genetic variation in determining an individual's response to drugs. For this purpose, a sample of at most 10 mL of blood will be obtained from each subject at Day -1.

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

5.7 APPROPRIATENESS OF MEASUREMENTS

All measurements performed during this trial are standard measurements and will be performed in order to monitor subjects' safety and to determine pharmacokinetic parameters in an appropriate way. The scheduled measurements will allow monitoring of changes in vital signs, standard laboratory values, and ECG parameters that might occur as a result of administration of trial medication. The safety assessments are standard, are accepted for evaluation of safety and tolerability of an orally administered drug, and are widely used in clinical trials. The pharmacokinetic parameters and measurements outlined in Sections 2.1.3, 2.2.2.2, and 5.3 are generally used assessments of drug exposure.

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

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

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

Trial measurements and assessments scheduled to occur 'before' trial medication administration at Day 1 are to be performed and completed within a 2 h-period prior to the investigational medicinal product administration (including blank values for PK). A blank urine sample for PK will be collected within 3 h before drug administration.

The acceptable deviation from the scheduled time for vital signs and ECG will be ± 10 min for the first 4 h after investigational medicinal product administration and ± 30 min thereafter. For laboratory test, the acceptable deviation is ± 30 min.

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

The acceptable deviation from the scheduled time for neurological tests is ± 45 min on Day 1 and ± 90 min for other days.

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

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

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

6.2.1 Screening period

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

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

Genotyping will be performed (for details, see Section 5.6.1).

6.2.2 Treatment period

Each subject will receive one dose of trial medication (BI 894416 or placebo) at Visit 2.

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

Trial participants will be admitted to the trial site in the evening of Day -1 and kept under close medical surveillance for at least 48 h following drug administration. The subjects will then be allowed to leave the trial site, after formal assessment and confirmation of their fitness by the investigator or [redacted] designee. On all other trial days, subjects will be treated in an ambulatory fashion.

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

The safety measurements performed during the treatment period are specified in Section 5.2 of this protocol and in the Flow Chart. For details on times of all other trial procedures, refer to the Flow Chart. AEs and concomitant therapy will be assessed continuously from screening until the end of trial examination.

6.2.3 Follow-up period and trial completion

For AE assessment, laboratory tests, recording of ECG and vital signs, medical examination, and neurological examination during the follow-up period, see Sections 5.2.1 to 5.2.6.

Subjects who discontinue treatment before the end of the planned treatment period should undergo the End of Trial 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 End of Trial Visit must be followed until they have resolved, have been sufficiently characterised, or no further information can be obtained.

If a subject discontinues from the trial, the subject will be followed until the investigator, or sub-investigator, is convinced of the subject's safety. If follow-up is not possible or comes to an end, follow-up should be formally completed after discussion with the sponsor. If a subject stops attending trial assessments, the investigator should assess the subject's status as comprehensively as possible and the well-being of the subject should be monitored. However, if the subject withdraws from the trial, it is the subject's choice whether or not to participate in further assessments; he cannot be compelled.

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 STATISTICAL DESIGN – MODEL

The primary objectives of this trial is to investigate the safety and tolerability of BI 894416 by using descriptive statistics for all endpoints comparing active dose groups to placebo. The primary endpoint is defined in Section 2.1.2. Inferential statistics is not planned (as explained in section 7.2)

Secondary objectives are the exploration of PK of BI 894416 endpoints as specified in section 2.1.3 by descriptive statistics.

7.2 NULL AND ALTERNATIVE HYPOTHESES

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

Any confidence intervals computed are to be interpreted in the perspective of the exploratory character of the trial; i.e., confidence intervals are considered as interval estimates for effects.

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 investigational medicinal product. The treatment assignment will be determined based on the first treatment the subjects received. The treated set will be used for safety analyses.
- Pharmacokinetic parameter analysis set (PKS): This set includes all subjects in the treated set (TS) who provide at least one PK endpoint that was not excluded due to a protocol violation relevant to the evaluation of PK or due to PK non-evaluability (as specified in the following subsection ‘Pharmacokinetics’). Thus, a subject will be included in the PKS, even if he contributes only one PK parameter value for one period to the statistical assessment. Descriptive and model based analyses of PK parameters will be based on the PKS.

Adherence to the protocol will be assessed by the trial team. Important protocol deviation (IPD) categories will be specified in the TSAP, 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 will be calculated according to BI internal standard operating procedure (SOP). Noncompartmental pharmacokinetic parameters will be calculated based on actual sampling times using a validated pharmacokinetic software (e.g., Phoenix® WinNonlin®).

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

Relevant protocol violations may be

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

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

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

Plasma/urine concentration data and parameters of a subject which is flagged for exclusion will be reported with its individual values but will not be included in the statistical analyses.

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 as in the bioanalytical report (that is to the same number of decimal places provided in the bioanalytical report).

7.3.1 Primary endpoint analyses

The primary endpoint as specified in Section 2.1.2 will be derived according to BI standards. The analysis will be based on the treated set (TS) and will be descriptive in nature.

7.3.2 Secondary endpoint analyses

Primary analyses

The secondary endpoints (refer to Section 2.1.3) will be analysed descriptively. Analyses will be performed for the parent drug.

Further exploratory analyses

Dose proportionality will be explored via graphical checks and if applicable via the power model stated below. The analysis will be performed for the pharmacokinetic endpoints $AUC_{0-\infty}/C_{max}$ specified in Section 2.1.3.

The power model describes the functional relationship between the dose level and PK endpoint on the log scale via

$$y_{km} = \log(x_{km}) = \mu + \beta \cdot \log(D_k) + e_{km},$$

where

y_{km}	logarithm of response (PK parameter) measured on subject m receiving dose k,
x_{km}	response (PK parameter) measured on subject m receiving dose k,
μ	the overall mean,
β	slope parameter of linear regression line,
D_k	level of dose k, k=1,…,3,
e_{km}	the random error associated with the m^{th} subject who was administered dose k ($e_{km} \sim N(0, \sigma^2)$ iid).

The slope parameter β together with its two-sided 90% confidence interval will be estimated. Additionally, the r-fold change $r^{\beta-1}$ together with its 90% CI will be derived.

As some small doses at the beginning and/or some doses at the upper end might not contribute to the linear relationship between dose and PK, dose proportionality over the entire dose range investigated might not be shown. In that case an attempt will be made to identify a subrange of at least 3 consecutive doses where dose proportionality can be concluded.

[redacted]

7.3.4 Safety analyses

Safety will be assessed as defined by the endpoints listed in Section 2.1.2 and 2.2.2 based on the treated set (TS). Safety analyses will be descriptive in nature and will be based on BI standards.

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. The placebo group in the safety evaluation will consist of all subjects treated with placebo, regardless of the dose group in which they were treated. The test treatment groups will be compared to the placebo group in a descriptive

way. Tabulations of frequencies/proportions will be used for the evaluation of categorical (qualitative) data, and tabulations of descriptive statistics will be used to analyse continuous (quantitative) data.

Measurements (such as ECGs, vital signs, or laboratory parameters) or AEs will be assigned to treatments (see Section 4.1) based on the actual treatment at the planned time of the measurement or on the recorded time of AE onset (concept of treatment-emergent AEs).

Therefore, measurements planned or AEs recorded prior to intake of trial medication will be assigned to the screening period, those between the trial medication intake and the individual subject's end of REP (see Section 1.2.1) will be assigned to the treatment period.

Events occurring after the REP but prior to trial termination date will be assigned to 'follow-up'. These assignments including the corresponding time intervals will be defined in detail in the TSAP. Note that AEs occurring after the last per protocol contact but entered before database lock will be reported to Pharmacovigilance only and will not be captured in the trial database.

Additionally, further treatment intervals (called analysing treatments) may be defined in the TSAP in order to provide summary statistics for other than above periods, such as combined treatments, on-treatment totals, or periods without treatment effects (such as screening and post-trial intervals).

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Frequency, severity, and causal relationship of AEs will be tabulated by treatment, system organ class and preferred term. SAEs, AESIs (see Section 5.2.6.1) and other significant AEs (according to ICH E3) will be listed separately.

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

Laboratory data will be compared to their reference ranges. Values outside the reference range as well as possibly clinically significant values 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.

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

7.3.5 Pharmacokinetic - pharmacodynamic analysis

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

7.4 INTERIM ANALYSES

No interim analysis is planned.

7.5 HANDLING OF MISSING DATA

7.5.1 Safety

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

7.5.2 Pharmacokinetics

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

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

7.6 RANDOMISATION

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

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

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

7.7 DETERMINATION OF SAMPLE SIZE

It is planned to include a total of 24 subjects in this trial. The planned sample size is not based on a power calculation. The size of 8 subjects per dose group (6 on active treatment, and 2 on placebo) is commonly used in single-rising dose trials of the present type and is in general considered as sufficient for the exploratory evaluation of single dose safety and pharmacokinetics [R95-0013].

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, the Japanese GCP regulations (Ministry of Health and Welfare Ordinance No. 28, March 27, 1997) 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 the investigator and the subjects, and are stored in the ISF.

8.1 TRIAL APPROVAL, SUBJECT INFORMATION, INFORMED CONSENT

This trial will be initiated only after all required legal documentation has been reviewed and approved by the responsible 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 investigator or delegate must give a full explanation to trial subjects based on the subject information form. A language understandable to the subject should be chosen and technical terms and expressions avoided, if possible.

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 trial conduct including monitoring approaches, vendor management and other processes focusing on areas of greatest risk.

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

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

8.3 RECORDS

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

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

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

8.4 EXPEDITED REPORTING OF ADVERSE EVENTS

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

8.5 STATEMENT OF CONFIDENTIALITY AND 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 World Health Organization (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 storage facility are qualified for the storage of biological samples collected in clinical trials.
- An appropriate sample and data management system, incl. audit trail for clinical data and samples to identify and destroy such samples according to ICF is in place
- A fit for the purpose documentation (biomarker proposal, analysis plan and report) ensures compliant usage
- A fit for purpose approach will be used for assay/equipment validation depending on the intended use of the biomarker data

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

8.6 TRIAL MILESTONES

The **start of the trial** is defined as the date when the first subject in the whole trial signs informed consent.

The **end of the trial** is defined as the 'date of the last visit of the last subject in 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.

When the trial is completed, the investigator should inform the head of the trial site in writing of the completion of the trial, and the head of the trial site should promptly inform the IRB and sponsor in writing of the completion.

8.7 ADMINISTRATIVE STRUCTURE OF THE TRIAL

The trial is sponsored by [redacted]

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 CTL, 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 CTM
- Clinical Research Associates, and investigators of participating trial sites

The trial medication will be provided by the [redacted]

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

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

The digitally recorded 12-lead ECGs will be sent to a specialised contract research organisation [redacted] for evaluation during the trial or post trial.

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 CRO appointed by BI according to BI SOPs.

Tasks and functions assigned in order to organise, manage, and evaluate the trial are defined according to BI SOPs. A list of responsible persons and relevant local information can be found in the ISF.

9. REFERENCES

9.1 PUBLISHED REFERENCES

P08-01263 Expert panel report 3: guidelines for the diagnosis and management of asthma: full report 2007 (NIH publication no. 07-4051, revised August 2007). http://.nhlbi.nih.gov; Bethesda: U.S. Department of Health and Human Services, National Institutes of Health, National Heart, Lung and Blood Institute (2007).

R07-4722 Guidance for industry: E14 clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs. Rockville: U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER) (2005).

R09-4830 Brown BD, Badilini F. HL7 aECG implementation guide (March 21, 2005).

R14-4230 Wenzel SE. Asthma phenotypes: the evolution from clinical to molecular approaches. Nature Med. 2012. 18(5): 716-725.

R15-4770 Blancato J, Graves A, Rashidi B, Moroni M, Tchobe L, Ozdemirli M, et.al. SYK Allelic Loss and the Role of Syk-Regulated Genes in Breast Cancer Survival. PloS ONE. 2014. 9(2): e87610.

R15-5470 Mocsai A, Ruland J, Tybulewicz VLJ. The SYK tyrosine kinase: a crucial player in diverse biological functions. Nat Rev Immunol. 2010. 10(6): 387-402.

R15-5888 Pelaia G, Vatrella A, Busceti MT, Gallelli L, Calabrese C, Terracciano R, Maselli R. Cellular mechanisms underlying eosinophilic and neutrophilic airway inflammation in asthma. Mediators Inflamm. 2015. 2015: 879783.

R16-0366 E14 Implementation Working Group
ICH E14 guideline: the clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs: questions & answers (R3) (current version dated 10 December 2015). http://.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E1 4/E14_Q_As_R3__Step4.pdf (access date: 29 January 2016) ; Geneva: International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (2015).

R16-0945 Fahy JV. Type 2 inflammation in asthma - present in most, absent in many. Nat Rev Immunol. 2015. 15: 57-65.

R16-4459 Krisenko MO, Geahlen RL. Calling in SYK: SYK's dual role as a tumor promoter and tumor suppressor in cancer. Biochim Biophys Acta Mol Cell Res. 2015. 1853(1): 254-263.

R16-5240 Boylan B, Gao C, Rathore V, Gill JC, Newman DK, Newman PJ. Identification of FcγRIIa as the ITAM-bearing receptor mediating αIIbβ3 outside-in integrin signaling in human platelets. 2008. 112(7): 2780-2786.

R16-5298 Alsadeq A, Hobeika E, Medgyesi D, Klaesener K, Reth M. The role of the Syk/Shp-1 kinase-phosphatase equilibrium in B cell development and signaling. J Immunol. 2014. 193: 268-276.

R95-0013 Broom C. Design of first-administration studies in healthy man. Early Phase Drug Evaluation in Man. O'Grady J, Linet OI (Eds.), Macmillan Press: London, 1990, 206 213.

9.2 UNPUBLISHED REFERENCES

c03536505 [redacted] Investigator Brochure: BI 894416 Asthma. Current version.

c32087967 [redacted] Safety monitoring committee meeting clinical output of 1371-0003. 1 Apr 2020.

n00240179 [redacted] BI 894416: Exploratory 15 day oral (gavage) toxicity study in male rats. Nonclinical Report. 13B105. 29 June 2015.

n00243171 [redacted] Assessment of pro-proliferative effects of the SYK inhibitor BI 1002494 on human breast cancer cell lines and in silico genetic evaluation of SYK for tumour suppressor characteristics using data from breast cancer patient databases. Nonclinical Report. 2016-i-r-resp3-report1. 11 July 2016.

n00245394 [redacted] BI 894416: Dose Escalation in Dogs with Assessment of Electroencephalography and Nerve Conduction Velocity. Nonclinical Report. 15R160. 21 February 2017.

10. APPENDICES

Not applicable.

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

11.1 GLOBAL AMENDMENT 1

Date of amendment		6 Jul 2020
BI Trial number		1371-0003
BI Investigational Medicinal Product(s)		BI 894416
Title of protocol		Safety, tolerability and pharmacokinetics of single rising oral doses of BI 894416 versus placebo in healthy male Japanese subjects (single-blind, randomized, placebo-controlled within dose group)
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		Section 5.2.3
Description of change		Safety Laboratory updated
Rationale for change		IgD cannot be measured at site. T-SPOT test added to make sure subject safety.

11.2 GLOBAL AMENDMENT 2

Date of amendment		17 Aug 2020
BI Trial number		1371-0003
BI Investigational Medicinal Product(s)		BI 894416
Title of protocol		Safety, tolerability and pharmacokinetics of single rising oral doses of BI 894416 versus placebo in healthy male Japanese subjects (single-blind, randomized, placebo-controlled within dose group)
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		3.1
Description of change		Description adjustment about deputy of Principle investigator and CTL.

Rationale for change		Based on comments from authority.
Section to be changed		3.3.2
Description of change		More detailed information about contraception methods were added.
Rationale for change		Based on comments from authority.
Section to be changed		3.3.3, Fig 5.2.3: 2 and Flowchart
Description of change		Chest region x-ray and HBsAg test added. Detailed condition about infection was added.
Rationale for change		Based on comments from authority to make sure subject safety.
Section to be changed		NA
Description of change		Administrative description corrections
Rationale for change		Based on comments from authority.

APPROVAL / SIGNATURE PAGE

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Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Author-Clinical Trial Leader	[redacted]	18 Aug 2020 02:53 CEST
Author-Trial Statistician		18 Aug 2020 09:02 CEST
Author-Trial Clinical Pharmacokineticist		18 Aug 2020 10:57 CEST
Approval-Therapeutic Area [redacted]		19 Aug 2020 11:36 CEST
Approval-Team Member Medicine		22 Aug 2020 06:00 CEST
Verification-Paper Signature Completion		24 Aug 2020 04:59 CEST

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