Clinical Trial Protocol

	Document Number: c13141675-05
EudraCT No.:	2017-000324-98
BI Trial No.:	1408-0001
BI Investigational Product(s):	BI 705564
Title:	Safety, tolerability, pharmacokinetics and pharmacodynamics of single rising oral doses of BI 705564 (single-blind, partially randomised, placebo-controlled parallel group design) and food effect on a tablet formulation of BI 705564 (open-label, randomised, single-dose, two-period, two-sequence crossover design) in healthy male subjects
Clinical Phase:	I
Trial Clinical Monitor:	Phone: Fax:
Principal Investigator:	Phone: Fax:
Status:	Final Protocol (Revised Protocol (based on global amendment 4))
Version and Date:	Version: 5.0 Date: 11 SEPTEMBER 2017

CLINICAL TRIAL PROTOCOL SYNOPSIS

Name of company: Boehringer Ingelheim		**Tabulated Trial Protocol**	
Name of finished product: Not applicable			
Name of active ingredient: BI 705564			
Protocol date: 15 FEB 2017	**Trial number:** 1408-0001		**Revision date:** 11 SEP 2017
Title of trial:	Safety, tolerability, pharmacokinetics and pharmacodynamics of single rising oral doses of BI 705564 (single-blind, partially randomised, placebo-controlled parallel group design) and food effect on a tablet formulation of BI 705564 (open-label, randomised, single-dose, two-period, two-sequence crossover design) in healthy male subjects		
Principal Investigator:			
Trial site:			
Clinical phase:	I		
Objectives:	(1) Single rising dose part under *fasting* conditions: To investigate safety, tolerability, pharmacokinetics and pharmacodynamics following single rising oral doses of BI 705564 (2) Food effect part: To investigate the relative bioavailability of BI 705564 as tablet formulation under fed and fasting conditions following oral administration (3) Single rising dose part under *fed* conditions: To investigate safety, tolerability, pharmacokinetics and pharmacodynamics following single rising oral doses of BI 705564 under fed conditions		
Methodology:	(1) Single rising dose part under *fasting* conditions: Single-blind, partially randomised within dose groups, placebo-controlled, parallel group design (2) Food effect part: Open-label, randomised, single-dose, two-period, two-sequence crossover design (3) Single rising dose part under *fed* conditions: Single-blind, partially randomised within dose groups, placebo-controlled, parallel group design under fed conditions		

Name of company: Boehringer Ingelheim		**Tabulated Trial Protocol**	
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No. of subjects planned:	
total entered:	92*
each treatment:	(1) Single rising dose part under *fasting* conditions: 48 8 per dose group (6 on active drug and 2 on placebo) (2) Food effect part: 12 (all on active drug) (3) Single rising dose part under *fed* conditions: 32* 8 per dose group (6 on active drug and 2 on placebo) * Additional subjects may be entered to allow testing of additional doses on the basis of experience gained during the trial conduct (e.g. preliminary PK data), provided the planned and approved highest dose will not be exceeded. Thus, the actual total number of subjects entered in the study may exceed 92 (32 in single rising dose part under fed conditions), but will not exceed 108 (48 in single rising dose part under fed conditions) subjects entered.
Diagnosis:	Not applicable
Main criteria for inclusion:	Healthy male subjects, age of 18 to 50 years (inclusive), body mass index (BMI) of 18.5 to 29.9 kg/m^2 (inclusive)
(1) Single rising dose part under *fasting* conditions	
Test products:	BI 705564 as solution (powder for oral solution [PfOS], 0.25 mg/mL) and film-coated tablet (10 mg)
dose:	Solution (PfOS): 1 mg, 3 mg q.d. Tablet: 10 mg, 20 mg, 40 mg, 80 mg q.d.
mode of admin.:	Oral with 240 mL of water after an overnight fast of at least 10 h
Comparator products:	Matching placebo as solution (i.e. solvent) and film-coated tablet formulation
dose:	Not applicable
mode of admin.:	Oral with 240 mL of water after an overnight fast of at least 10 h
(2) Food effect part	
Test product:	Fed: BI 705564 as film-coated tablet formulation (10 mg tablets)
dose:	Tablet: 10 mg q.d.
mode of admin.:	Oral with 240 mL of water after a high-fat, high-calorie meal

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Comparator products:	Matching placebo as film-coated tablet formulation
dose:	Not applicable
mode of admin.:	Oral with 240 mL of water after a high-fat, high-calorie breakfast
Duration of treatment:	(1) Single rising dose part under *fasting* conditions: One single dose (2) Food effect part: Single dose for each treatment (2 single doses in total), separated by a washout period of at least 10 days (3) Single rising dose part under *fed* conditions: One single dose
Criteria for pharmacokinetics:	(1) Single rising dose part under *fasting* conditions Secondary endpoints: $AUC_{0-\infty}$ and C_{max} Further PK parameters of interest will be calculated as appropriate (2) Food effect part Primary endpoints: AUC_{0-tz} and C_{max} Secondary endpoint: $AUC_{0-\infty}$ Further PK parameters of interest will be calculated as appropriate (3) Single rising dose part under *fed* conditions Secondary endpoints: $AUC_{0-\infty}$ and C_{max} Further PK parameters of interest will be calculated as appropriate

Name of company: Boehringer Ingelheim		**Tabulated Trial Protocol**	
Name of finished product: Not applicable			
Name of active ingredient: BI 705564			
Protocol date: 15 FEB 2017	**Trial number:** 1408-0001		**Revision date:** 11 SEP 2017
Criteria for safety:	(1) Single rising dose part under *fasting* conditions Primary endpoint to assess safety and tolerability of BI 705564 is the number [N (%)] of subjects with drug-related adverse events. Further criteria of interest: Adverse events (AEs) including clinically relevant findings from the physical examination, safety laboratory tests, 12-lead electrocardiogram (ECG), continuous ECG monitoring, vital signs (blood pressure [BP], pulse rate [PR]). (2) Food effect part Further criteria of interest: AEs including clinically relevant findings from the physical examination, safety laboratory tests, 12-lead electrocardiogram (ECG), vital signs (blood pressure [BP], pulse rate [PR]). (3) Single rising dose part under *fed* conditions Primary endpoint to assess safety and tolerability of BI 705564 is the number [N (%)] of subjects with drug-related adverse events. Further criteria of interest: Adverse events (AEs) including clinically relevant findings from the physical examination, safety laboratory tests, 12-lead electrocardiogram (ECG), continuous ECG monitoring, vital signs (blood pressure [BP], pulse rate [PR]).		
Statistical methods:	(1) Single rising dose part under *fasting* conditions Descriptive statistics will be calculated for all endpoints. Dose proportionality of BI 705564 will be explored using a regression model. A 95% confidence interval (CI) for the slope will be computed. (2) Food effect part Relative bioavailability will be estimated by the ratios (tablet fed/tablet fasting) of the geometric means for the primary and secondary endpoints. Additionally, their two-sided 90% confidence intervals (CIs) will be provided. This method corresponds to the two one-sided t-tests procedure, each at the 5% significance level. Since the main focus is on estimation and not testing, an acceptance range was not specified. The statistical model will be an ANOVA on the logarithmic scale including effects for 'sequence', 'subjects nested within sequences', 'period' and 'treatment'. CIs will be calculated based on the residual error from ANOVA. Descriptive statistics will be calculated for all endpoints. (3) Single rising dose part under *fed* conditions Descriptive statistics will be calculated for all endpoints. Dose proportionality of BI 705564 will be explored using a regression model. A 95% confidence interval (CI) for the slope will be computed.		

FLOW CHART

(1) Single rising dose part under *fasting* conditions

Visit	Day	Planned time (relative to drug administration) [h:min]	Approximate clock time of actual day [h:min]	Event and comment	Safety laboratory	PK $_{blood}$ [10, 11]	PK $_{urine}$ [10, 12]			12-lead ECG	Continuous ECG monitoring	Vital signs (BP, PR)	Questioning for AEs and concomitant therapy [6]
1	-21 to -1			Screening (SCR)[1]	x					x		x	
2	-3 to -1	-72:00[7]	08:00	Ambulatory visit	x								x
	1	-2:00	06:00	Admission to trial site[2], allocation to treatment[2]	x[5,2]	x[2]	x[2]			x[2,9]	x[2]	x[2]	x[2]
		0:00	**08:00**	**Drug administration**			▲				▲		
		0:30	08:30			x				x[9]		x	x
		1:00	09:00			x				x[9]		x	x
		1:30	09:30			x[8]				x[9]		x	
		2:00	10:00	240 mL fluid intake		x				x[9]		x	x
		3:00	11:00			x				x[9]		x	x
		4:00	12:00	240 mL fluid intake, thereafter lunch[3]	x	x				x[9]	▼	x	x
		6:00	14:00			x				x[9]		x	x
		8:00	16:00	Snack (voluntary)[3]		x				x[9]		x	x
		10:00	18:00			x							
		11:00	19:00	Dinner									
		12:00	20:00			x				x[9]		x	x
	2	24:00	08:00	Discharge from trial site, breakfast[3] (voluntary)	x	x	▼			x[9]		x	x
		34:00	18:00	Ambulatory visit		x						x	x
	3	48:00	08:00	Ambulatory visit	x	x				x[9]		x	x
	4	72:00	08:00	Ambulatory visit		x				x[9]		x	x
	6	120:00	08:00	Ambulatory visit									x[15]
	8	168:00	08:00	Ambulatory visit	x								x
	10	216:00	08:00	Ambulatory visit									x
4	11 to 15			End of trial (EOT) examination[4]	x					x		x	x

1. Subject must be informed and written informed consent obtained prior to starting any screening procedures. Screening procedures include physical examination, check of vital signs, ECG (including rhythm strip of at least 15 minutes), safety laboratory (including drug screening), demographics (including determination of body height and weight, smoking status and alcohol history), relevant medical history, concomitant therapy and review of inclusion/exclusion criteria. Pharmacogenetic samples will be collected, if needed.
2. The time is approximate. The respective procedure is to be performed and completed within 3 h prior to drug administration. Allocation to treatment may be performed at any time following enrolment but must be completed prior to drug administration.
3. If several actions are indicated at the same time point, the intake of meals will be the last action.
4. End of trial examination includes physical examination, vital signs, ECG, safety laboratory, recording of AEs and concomitant therapies.
5. Only urine drug screening and alcohol breath test will be done at this time point.
6. 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.

7. Safety laboratory to be taken and to be medically evaluated within 3 days prior to administration of study drug. This ambulatory visit, including safety laboratory, can be omitted, if the screening examination is performed on Days -3, -2 or -1.
8. One blood sample for stability testing will be taken at this time point in Dose Group 10 mg (tablet) (see Section 5.5.2.4).
9. The ECG recording has to be performed as triple.
10. Sampling times and periods may be adapted based on information obtained during the trial (e.g. preliminary PK/PD data) including addition of samples and visits as long as the total blood volume taken does not exceed 500 mL per subject.
11. Including blood sample for metabolite identification in dose group 40 mg tablet (see Section 5.5.2.2).
12. A blank urine sample (x) is to be obtained 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, and 12-24 h.
13. 2 x 8 mL blood at pre-dose (2nd vial as back-up).

15. May be done up to 26 h earlier. AE questioning to be done at this occasion.

(2) Food effect part

Visit	Day	Planned time (relative to drug administration) [h:min]	Approximate clock time of actual day [h:min]	Event and comment	Safety laboratory	PK_{blood} [8]	12-lead ECG	Vital signs (BP, PR)	Questioning for AEs and concomitant therapy [6]
1	-21 to -1			Screening (SCR)[1]	x		x[7]	x	
2/	-3 to -1	-72:00[9]	08:00	Ambulatory visit	x				x
3*	1	-2:00	06:00	Admission to trial site[2], allocation to treatment[2] (Visit 2 only)	x[2,5]	x[2]	x[2,7]	x[2]	x[2]
		-0:30	07:30	High fat, high calorie breakfast (only in treatment 'fed')					
		0:00	**08:00**	**Drug administration**					
		0:30	08:30			x			
		1:00	09:00			x	x[7]	x	x
		1:30	09:30			x			
		2:00	10:00	240 mL fluid intake		x	x[7]	x	x
		3:00	11:00			x			
		4:00	12:00	240 mL fluid intake, thereafter lunch[3]		x	x[7]	x	x
		6:00	14:00			x			x
		8:00	16:00	Snack (voluntary)[3]		x	x[7]	x	x
		10:00	18:00			x			
		11:00	19:00	Dinner					
		12:00	20:00			x			x
	2	24:00	08:00	Discharge from trial site, breakfast[3] (voluntary)	x	x	x[7]	x	x
		34:00	18:00	Ambulatory visit		x			x
	3	48:00	08:00	Ambulatory visit		x			x
	4	72:00	08:00	Ambulatory visit		x			x
4	11 to 15			End of trial (EOT) examination[4]	x		x[7]	x	x

* Two identical visits, separated by a wash-out interval of at least 10 days between drug administrations

1. Subject must be informed and written informed consent obtained prior to starting any screening procedures. Screening procedures include physical examination, check of vital signs, ECG, safety laboratory (including drug screening), demographics (including determination of body height and weight, smoking status and alcohol history), relevant medical history, concomitant therapy and review of inclusion/exclusion criteria. Pharmacogenetic samples will be collected, if needed.
2. The time is approximate. The respective procedure is to be performed and completed within 3 h prior to drug administration. Allocation to treatment may be performed at any time following enrolment but must be completed prior to the first drug administration.
3. If several actions are indicated at the same time point, the intake of meals will be the last action.
4. End of trial examination includes physical examination, vital signs, ECG, safety laboratory, recording of AEs and concomitant therapies.
5. Only urine drug screening and alcohol breath test
6. 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.
7. The ECG will be recorded as single ECG. However, the number of ECGs per time point may be increased to three ECGs based on the preliminary ECG results obtained during the single rising dose part.
8. Sampling times 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 500 mL per subject.
9. Safety laboratory to be taken and medically evaluated within 3 days prior to administration of study drug. This ambulatory visit, including safety laboratory, can be omitted in visit 2, if the screening examination is performed on Days -3, -2 or -1.

(3) Single rising dose part under *fed* conditions

Visit	Day	Planned time (relative to drug administration) [h:min]	Approximate clock time of actual day [h:min]	Event and comment	Safety laboratory	PK $_{blood}$ [9]	PK $_{urine}$ [9, 10]			12-lead ECG	Continuous ECG monitoring	Vital signs (BP, PR)	Questioning for AEs and concomitant therapy [6]
1	-21 to -1			Screening (SCR)[1]	x					x		x	
2	-3 to -1	-72:00[7]	08:00	Ambulatory visit	x								x
	1	-2:00	06:00	Admission to trial site[2], allocation to treatment[2]	x[5,2]	x[2]	x[2]			x[2,8]	x[2]	x[2]	x[2]
		-0:30	07:30	High fat, high calorie breakfast									
		0:00	**08:00**	**Drug administration**			▲				▲		
		0:30	08:30			x				x[8]		x	x
		1:00	09:00			x				x[8]		x	x
		1:30	09:30			x				x[8]		x	
		2:00	10:00	240 mL fluid intake		x				x[8]		x	x
		3:00	11:00			x				x[8]		x	x
		4:00	12:00	240 mL fluid intake, thereafter lunch[3]	x	x				x[8]	▼	x	x
		6:00	14:00			x				x[8]		x	x
		8:00	16:00	Snack (voluntary)[3]		x				x[8]		x	x
		10:00	18:00			x							
		11:00	19:00	Dinner									
		12:00	20:00			x				x[8]		x	x
	2	24:00	08:00	Discharge from trial site, breakfast[3] (voluntary)	x	x	▼			x[8]		x	x
		34:00	18:00	Ambulatory visit		x						x	x
	3	48:00	08:00	Ambulatory visit	x	x				x[8]		x	x
	4	72:00	08:00	Ambulatory visit		x				x[8]		x	x
	6	120:00	08:00	Ambulatory visit									x[13]
	8	168:00	08:00	Ambulatory visit	x								x
	10	216:00	08:00	Ambulatory visit									x
4	11 to 15			End of trial (EOT) examination[4]	x					x		x	x

1. Subject must be informed and written informed consent obtained prior to starting any screening procedures. Screening procedures include physical examination, check of vital signs, ECG (including rhythm strip of at least 15 minutes), safety laboratory (including drug screening), demographics (including determination of body height and weight, smoking status and alcohol history), relevant medical history, concomitant therapy and review of inclusion/exclusion criteria. Pharmacogenetic samples will be collected, if needed.
2. The time is approximate. The respective procedure is to be performed and completed within 3 h prior to drug administration. Allocation to treatment may be performed at any time following enrolment but must be completed prior to drug administration.
3. If several actions are indicated at the same time point, the intake of meals will be the last action.
4. End of trial examination includes physical examination, vital signs, ECG, safety laboratory, recording of AEs and concomitant therapies.
5. Only urine drug screening and alcohol breath test will be done at this time point.
6. 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.

7. Safety laboratory to be taken and to be medically evaluated within 3 days prior to administration of study drug. This ambulatory visit, including safety laboratory, can be omitted, if the screening examination is performed on Days -3, -2 or -1.
8. The ECG recording has to be performed as triple.
9. Sampling times and periods may be adapted based on information obtained during the trial (e.g. preliminary PK/PD data) including addition of samples and visits as long as the total blood volume taken does not exceed 500 mL per subject.
10. A blank urine sample (x) is to be obtained 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, and 12-24 h.
11. 2 x 8 mL blood at pre-dose (2nd vial as back-up).

13. May be done up to 26 h earlier. AE questioning to be done at this occasion.

TABLE OF CONTENTS

ABBREVIATIONS

ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
AESI	Adverse events of special interest
AMG	Arzneimittelgesetz (German drug law)
ANA	Anti-nuclear antibodies
ANOVA	Analysis of variance
AUC	Area under the concentration-time curve of the analyte in plasma
$AUC_{0-\infty}$	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity
B	Slope parameter associated with the power model used to evaluate dose proportionality
BA	Bioavailability
BCR	B cell receptor
BI	Boehringer Ingelheim
BLQ	Below limit of quantification
BMI	Body mass index (weight divided by height squared)
BP	Blood pressure
Bpm	Beats per minute
BTK	Bruton's tyrosine kinase
CA	Competent authority
CD	Cluster of differentiation
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
C_{max}	Maximum measured concentration of the analyte in plasma

CML	Clinical monitor local
CNS	Central nervous system
CRA	Clinical research associate
CRF	Case report form
CTP	Clinical trial protocol
CTR	Clinical trial report
CTSU	Clinical Trial Supplies Unit
CV	Arithmetic coefficient of variation
CYC	Cyclophosphamide
CYP	Cytochrome P450
DG	Dose Group
DILI	Drug induced liver injury
ECG	Electrocardiogram
EDTA	Ethylenediaminetetraacetic acid
EMA	European Medicines Agency
EOT	End of trial
ESRD	End stage renal disease
F	Absolute bioavailability factor
FcR	Fc receptor
GC	Glucocorticoid
gCV	Geometric coefficient of variation
GI	Gastro-intestinal
GLP	Good laboratory practice
gMean	Geometric mean
HED	Human equivalence dose
HP-β-CD	Hydroxypropyl-ß-cyclodextrin
HR	Heart rate
IB	Investigator’s brochure
IC	Informed consent
ICH	International Conference on Harmonisation

IEC	Independent Ethics Committee
IL	Interleukin
IPV	Important protocol violation
IRB	Institutional Review Board
ISF	Investigator site file
ISN	International Society of Nephrology
KI	Inhibition constant
KO	Knock-out
MedDRA	Medical Dictionary for Regulatory Activities
MIST	Metabolites in safety testing
MMF	Mycophenolate
MRSD	Maximum recommended safe starting dose
NOA	Not analysed
NOAEL	No observed adverse effect level
NOEL	No observed effect level
NOP	No peak detectable
NOR	No valid result
NOS	No sample available
PAD	Pharmacologically active dose
PD	Pharmacodynamic(s)
PE	Polyethylene
PfOS	Powder for reconstitution of an oral solution
PK	Pharmacokinetic(s)
PKS	Pharmacokinetic set
PP	Polypropylene
PR	Pulse rate
q.d.	*Quaque die*, once daily
QT	Time between start of the Q-wave and the end of the T-wave in an electrocardiogram
QTc	QT interval corrected for heart rate using the method of Fridericia (QTcF) or Bazett (QTcB)

R	Reference treatment
RDC	Remote data capture
REP	Residual effect period
RPS	Renal Pathology Society
SAE	Serious adverse event
SCR	Screening
SOP	Standard Operation Procedure
SRD	Single-rising dose
Ss	(at) steady state
SUSAR	Suspected Unexpected Serious Adverse Reaction
T	Test product or treatment
TDMAP	Trial Data Management and Analysis Plan
TEC	tec protein tyrosine kinase
TLR	toll-like receptors
TMF	Trial master file
TS	Treated set
TSAP	Trial statistical analysis plan
ULN	Upper limit of normal
WOCBP	Women of childbearing potential
XLA	X-linked agammaglobulinemia

2. RATIONALE, OBJECTIVES, AND BENEFIT - RISK ASSESSMENT

2.1 RATIONALE FOR PERFORMING THE TRIAL

Healthy male subjects will be recruited for this study. They provide a relatively stable physiological, biochemical and hormonal basis for studying drug effects, they show no disease-related variation and they are not taking regular concomitant medications.

In the single rising dose parts, within each dose group, all actively treated individuals will receive the same BI 705564 dose. The next higher dose will only be administered to the next group, if the treatment in the preceding dose group was safe and showed acceptable tolerability.

In the food effect part, BI 705564 will be administered to subjects in a randomized two-way-crossover fashion to understand the effect of food on relative bioavailability and to support upcoming clinical studies in respect to better trial designs.

2.1.1 Starting Dose

An estimation was made on the basis of the US FDA Guidance for Industry 'Estimating the Maximum Recommended Safe Starting Dose in Initial Clinical Trials for Therapeutics in Healthy Volunteers' [R06-1037]:

It is stated in the FDA Guidance that 'a species might be considered an inappropriate toxicity model for a given drug, if the dose-limiting toxicity in that species was concluded to be of limited value for human risk assessment, based on historical comparisons of toxicities in the animal species to those in humans across a therapeutic class (i.e., the dose-limiting toxicity is species-specific). In this case, data from that species should not be used to derive the HED.'

2.1.2 Maximum Dose and Dose Range

Therefore: (1) Systemic exposure of BI 705564 (C_{max}, AUC_{0-24}) will be closely monitored throughout the study and used to guide dose escalation. (2) A maximum allowable exposure is prospectively defined.

In conclusion, the maximum dose in this first-in-man/ single rising dose study will be limited by an exposure threshold (group gMean values) of
whichever is reached first. With the exception of escalation from Dose Group 1 to Dose Group 2, the decision for dose escalation at each dose level will be guided by the results of PK interim analysis at each dose level and, if necessary, model based estimations. For dose escalation from Dose Group 1 to Dose Group 2, availability of interim pharmacokinetic data is not required.

2.1.3 Dose Escalation

Dose escalation in the SRD part under fasting conditions

2.1.4 Food effect part

Since a of BI 705564 at higher doses might be improved by the application of food, the effect of food on the relative bioavailability of BI 705564, as tablet formulation will be investigated. The food effect may be dose dependent.

2.1.5 Conclusion

The safe starting dose in this study is determined This dose is not expected to trigger any relevant or unacceptable biological activities.

In the single rising dose part under fasting conditions, the following dose escalation scheme is planned:

Each dose escalation step in the single rising dose part under fasting conditions will be guided by interim PK measurements and projected exposure levels.

With global amendment No 4, a single rising dose part under fed conditions is added.

Each dose escalation step in the single rising dose part under fed conditions will be guided by interim PK measurements and projected exposure levels.

2.2 TRIAL OBJECTIVES

The primary objective of the single rising dose parts under fasting and under fed conditions is to investigate safety and tolerability of BI 705564 in healthy male subjects following oral administration of single rising doses. Secondary objectives are the exploration of

pharmacokinetics (PK) including dose proportionality, and pharmacodynamics (PD) of BI 705564 after single rising doses.

The objective of the food effect part is to explore the relative bioavailability of BI 705564 tablets under fed and fasting conditions following the oral administration of single doses.

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

2.3 BENEFIT - RISK ASSESSMENT

Participation in this study is without any (therapeutic) benefit for healthy subjects. Their participation in the study, however, is of major importance to the development of this compound which is expected to be superior over other BTK inhibitors being developed in non-oncological indications due to its higher selectivity. Subjects participating in this trial are exposed to the risks of study procedures and those, related to the exposure of trial medication.

2.3.1 Procedure-related risks

The use of an indwelling venous catheter for the purpose of blood sampling may be accompanied by mild bruising and also, in rare cases, by transient inflammation of the wall of the vein. In addition, in rare cases, a nerve might be injured while inserting the venous catheter, potentially resulting in paresthesia, reduced sensibility, and/or pain for an indefinite period. Same risks apply to venipuncture for blood sampling.

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

2.3.2 Drug-related risks and safety measures

Factors of risk may derive from particular knowledge or the lack thereof, regarding (1) the mode of action, (2) the nature of the target, (3) the relevance of animal models and/or (4) findings in non-clinical safety studies.

2.3.2.1 Mode of action

BTK is a well characterized target with known functions in the immune signalling pathways of B cells and myeloid cell lineages (see Section 1.1). First clinical experience with the approved BTK inhibitor ibrutinib is available (see Sections 1.1 and 1.2.5). In addition, a ‘human model’ with loss of function mutations of the BTK gene is known as syndrome XLA. The immunodeficiency of XLA patients seems to be limited to the decreased levels of circulating antibodies. The resulting (predominant) bacterial infections should be well controlled by the application of antibiotics and gammaglobulin substitution, if necessary [R17-0404].

Ibrutinib treatment in patients with hematologic malignancies is associated with adverse events including hypertension, thrombocytopenia, and GI complaints (abdominal pain,

nausea, diarrhea, and vomiting). As these are not usual features of XLA, they may be related to off-target inhibition by ibrutinib of other enzymes besides BTK. Atrial fibrillation has been reported in patients receiving ibrutinib. The causal relationship of this finding to ibrutinib is not clear. The majority of affected patients had pre-existing cardiovascular disease, and most cases resolved quickly [R17-0124]. Other investigational BTK inhibitors (GDC-0853 and CC-292) were generally well tolerated in Phase 1 and Phase 2 clinical trials in healthy volunteers and in patients with rheumatoid arthritis. Serious infections, hypertension, thrombocytopenia, and atrial fibrillation were not reported [R17-0165, R17-0166]. All these conditions can be well monitored and are accessible to established therapies.

BI 705564 (see Section 1.2.1).

will be the minimum time between treatments in the food effect part (wash-out period) and from last administration of study drug until the end of trial examination in all study parts.

2.3.2.2 Nature of the target

The BTK protein is intra-cellular expressed in myeloid and lymphoid cell lines, predominantly in the immune system (bone marrow, appendix, lymph nodes, tonsils, and spleen), as well as in the lung. [R17-0406] Although on-target effects are unlikely to occur after a single dose of BI 705564, they might resemble those seen in XLA patients: Inhibition of B-cell differentiation which may manifest as a transient decrease of peripheral B-cell numbers, transient decrease of immunglobuline levels and unlikely bacterial infections. Main safety measures performed throughout the study will be therefore: (1) Exclusion of subjects with a repeated decrease of CD19+ B cell count at screening. (2) Monitoring of white blood cell counts and particularly CD19+ B cell counts, as well as immunoglobulin levels for at least 10 days after drug administration. (3) Close monitoring for adverse events including symptoms of infections. (4) In case of infections, appropriate clinical evaluation and, if necessary, adequate treatment thereof.

'Down-stream' effects of BTK inhibition are well characterized (see Section 1.2.1). How these effects may vary in different populations, e.g. healthy subjects versus diseased patients, young versus elderly, different patient populations, etc., is not known. Also, no information on BTK polymorphisms in healthy individuals and their potential influence on pharmacodynamics effects of BI 705564 or other BTK inhibitors are available.

2.3.2.3 Relevance of animal species and models

Animal models and assays, used during the pharmacological (mice) and toxicological (rats, dogs) assessment of BI 705564 were similar, at large, to those used for the development and submission of ibrutinib. As such, their relevance for humans was acknowledged by regulatory authorities [R17-0403]. For further information, see current version of IB [c12104992-02].

2.3.2.4 Findings in non-clinical safety studies

Documents supporting the submission of this first-in-man trial with BI 705564 were compiled according to Good Clinical Practice (GCP) principles. All pivotal, non-clinical safety studies in support of this clinical trial were conducted in compliance with Good Laboratory Practice (GLP). For further information, see current version of IB [c12104992-02].

- Toxicology

  In the 4-week rat toxicity study (see Section 1.2.3.2),
  laboratory monitoring will include this parameter during the conduct of the study (see Flow Charts and Section 5.2.3).

  In the same study, dose independent,

  (see Flow Charts and Section 5.2.3).

  In the 4-week dog toxicity study (see Section 1.2.3.2),

2.3.2.5 Risks resulting from trial medication auxiliaries

Hydroxypropyl-ß(HP-ß)-cyclodextrin is a standard excipient in pharmaceutical preparations and is used also in marketed products. The toxicological profile of HP-ß-cyclodextrin has been thoroughly investigated [R01-0682]. Orally administered cyclodextrin is practically non-toxic due to lack of absorption from the GI tract. Chronic administration of 16-24 g HP-

ß-cyclodextrin to healthy volunteers for 14 days led to an increased incidence of soft stool and diarrhoea.

In the current trial, HP-ß-cyclodextrin is the main ingredient of the solvent for oral solution.

2.3.2.6 Drug induced liver injury

Although rare, a potential for drug-induced liver injury (DILI) is under constant surveillance by sponsors and regulators. Therefore, this trial requires timely detection, evaluation, and follow-up of laboratory alterations in selected liver laboratory parameters to ensure subjects´ safety. See also Section 5.2.2.1.

2.3.2.7 Risk minimization (safety precautions and stopping rules)

The following precautionary measures will be taken in this study in order to minimize the risk for healthy volunteers:

- Careful starting dose selection, as described in Section 2.1.1.
- In the single rising dose part under fasting conditions, decreasing escalation factors with increasing doses, as described in Section 2.1.3 were chosen. In the single rising dose part under fed conditions, escalation factors of 2 were chosen, based on experience gained during the trial.
- In the single rising dose parts, for safety reasons, each dose group of 8 subjects (6 on active, 2 on placebo) will be divided into two cohorts of 4 subjects each (3 on active, 1 on placebo). The first cohort of each dose group will be dosed in a fixed sequence manner (active - placebo - active - active) and each drug administration will be separated by at least 60 minutes between the first 3 subjects. This design ensures that between first and second active dose of each dose level there is a time interval of at least 2 hours. For orally administered drugs, this is usually a sufficient time frame to observe acute effects and to obtain a significant proportion of the systemic exposure. If BI 705564 is safe and shows acceptable tolerability during these initial administrations, the remaining subjects of this dose group can be dosed as close as 10 minutes apart.
- For each dose group, the 2 cohorts will be separated by at least 46 hours (between the 1st subject of each cohort) which is expected to cover the period of highest risk/ peak effect.
- Interim measurements of BI 705564 plasma levels will be performed. The expected gMean systemic exposure (C_{max}, AUC) in the next higher dose group will be estimated based on current and preceding doses using a dose proportionality approach

or model-based estimations, as applicable. The next higher dose level will only be administered, if estimated group gMean values of C_{max} and AUC do not exceed the maximum acceptable human exposure
whichever is reached first. This should provide a safety margin to the NOAEL of >20 (see Table 1.2.3.2: 1). In the single rising dose part under fasting conditions, for dose escalation from Dose Group 1 to Dose Group 2, availability of interim PK data is not required.

- If one dose level is safe and shows acceptable tolerability, and if no stopping criterion is met (see Section 3.3.4.2), the next higher dose may be given, keeping a minimum dosing time interval of 10 days between the first subject of the current dose group and the first subject of the following dose group.

- Extensive standard safety laboratory measurements including serum electrolytes, serum amylase and lipase, differential white blood counts, as well as CD19+ B cell and platelet counts will be performed before and after study drug administration (see Flow Charts and Section 5.2.3).

- A thorough ECG and heart rate monitoring will be performed, including continuous ECG measurements over 4 hours post dose to cover the anticipated period of highest drug exposure, and additional repeated single 12-lead ECGs.

- Prior to each dose escalation, a documented safety review will be performed by the Principal Investigator (or an authorized deputy) and the Trial Clinical Monitor (or an authorized deputy). For details, see Section 3.1.

- In the food effect part, the 10 mg dose will be tested first and thereafter the 40 mg dose will be tested*. The 10 mg dose will only be given, if, in the single rising dose part, doses of up to 40 mg are safe and of acceptable tolerability. The 40 mg dose will only be given, if, in the single rising dose part, doses of up to 160 mg are safe and of acceptable tolerability and, if, based on available preliminary PK data, the systemic exposure (group gMean C_{max}, AUC_{0-24}) is not expected to exceed the maximal group gMean values reached in the single rising dose part*.

  * Global Amendment No 4: In the food effect part, the 40 mg dose is not tested.

- Subjects will be confined under close observation for at least 24 hours after drug administration at the trial site and will be discharged only after a formal assessment and confirmation of fitness by an investigator or qualified designee. During in-house confinement subjects will be under medical observation and thoroughly monitored for both, expected and unexpected adverse events.

2.4 OVERALL ASSESSMENT AND CONCLUSION

BI 705564 is an inhibitor of BTK to be developed for the treatment of LN, SLE and rheumatoid arthritis. Clinical experience has been gained with another BTK inhibitor, ibrutinib, which was approved for the treatment of hematologic malignancies (chronic

lymphocytic leukaemia, mantle cell lymphoma, and Waldenström's macroglobulinemia). Treatment with ibrutinib in patients with hematologic malignancies is associated with adverse events including hypertension, thrombocytopenia, and GI complaints which may be related to off-target effects. In contrast, BI 705564 is considered to be a more selective BTK inhibitor and may have a more favourable safety profile.

Considering preclinical data of BI 705564, the well characterised target structure and its physiologic role in B cell differentiation and function, and taking into account the safety measures described above, participation in this single dose regimen does not represent an undue risk to healthy subjects.

Inhibition of BTK in patients with LN and SLE is expected to block the stimulation of autoantibody-producing B cells, and the release of inflammatory cytokines from monocytes and macrophages. By diminishing these harmful effects, BI 705564 may slow or halt disease progression. Considering the medical need for a better LN/ SLE treatment and taking into account the potential advantage of a highly selective BTK inhibitor, the expected benefit of this trial is likely to outweigh the potential risks and justifies exposure of healthy volunteers.

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

Global Amendment No 4 – major changes in Section 3:

Originally, the study was planned to consist of two study parts: (1) SRD part under fasting conditions consisting of 8 dose groups (1 to 160 mg) à 8 volunteers (64 volunteers in total) and (2) food effect part investigating the effect of a high-fat, high-calorie breakfast on doses of 10 mg and 40 mg in 12 volunteers each, i.e. in 24 volunteers total.

Data obtained during the trial indicate that no relevant increase of exposure was to be expected with dose groups 120 mg and 160 mg in the SRD part under fasting conditions. Therefore, the two highest dose groups of the SRD part under fasting conditions (120 mg and 160 mg) are not dosed. Data of the food effect part 10 mg indicate that relative bioavailability of BI 705564 tablet may be increased by food. The food effect part 40 mg is not dosed. Instead, a third study part is added. A SRD part under fed conditions is added to the study and is designed to investigate single rising oral doses of BI 705564 after a high-fat, high-calorie breakfast. It is planned to apply BI 705564 to 4 dose groups à 8 volunteers per group (32 volunteers in total) with the possibility to add up to 2 interim dose groups in the SRD part under fed conditions (see Section 3.1, “Single rising dose part under fed conditions”).

See Appendix 11 for details.

3.1 OVERALL TRIAL DESIGN AND PLAN

A total of 92 healthy male subjects is planned to participate in the trial, thereof 48 in the single rising dose part under fasting conditions, 12 in the food effect part, and 32 in the single rising dose part under fed conditions. Additional subjects may be entered in the single rising dose part under fed conditions (see below). Thus, the actual number of subjects may exceed 92 but not 108 subjects entered.

Single rising dose part under fasting conditions

This part is designed single-blind, partially randomised, and placebo-controlled within parallel dose groups.

A total of 48 healthy male subjects is planned to participate in the single rising dose part under fasting conditions, resulting in 6 sequential groups comprising 8 subjects each.

Within each dose group, 6 subjects will receive the active drug and 2 will receive placebo. Only one dose is tested within each dose group. Dose groups will be treated consecutively in ascending order of doses. Each dose group will consist of 2 cohorts of 4 subjects each (3 on active drug and 1 on placebo).

On the first study day within each dose group, the first cohort will be treated in a single-blind manner in the following order: First subject (active) followed at least 1 hour later by the second subject (placebo) followed at least 1 hour later by the third subject (active) followed at least 10 minutes later by the fourth subject (active).

If BI 705564 treatment is safe and showed acceptable tolerability in the first cohort, subjects in the second cohort will be treated not earlier than 2 days later (at least 46 h between the 1st subject of each cohort) in a single-blind, randomised manner. In the second cohort, a time interval of at least 10 minutes will be maintained between administrations of trial drug to the individual subjects.

A time interval of at least 10 days will be maintained between the first drug administration in the previous dose group and the first drug administration of the subsequent dose group. The dose groups to be evaluated are outlined in Table 3.1: 1 below.

Table 3.1: 1 Dose groups in the single rising dose part under fasting conditions

Dose Group	**1**	**2**	**3**	**4**	**5**	**6**
Dose (mg) q.d.	1	3	10	20	40	80
Formulation	PfOS	PfOS	Tab	Tab	Tab	Tab
Number of subjects	8	8	8	8	8	8
Subjects with placebo	2	2	2	2	2	2
Subjects with active drug	6	6	6	6	6	6

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

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

The minimum data set for review consists of the following data:

- AEs in the current and preceding dose groups up to at least 48 h post dosing, including clinically relevant findings from ancillary safety testing, as 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 and continuous ECG monitoring in the current and preceding dose groups up to at least 48 h post dosing.
- Vital signs in the current and preceding dose groups up to at least 48 h post dosing.
- Clinical laboratory tests in the preceding dose groups and clinical laboratory tests of the first cohort of the current dose group up to at least Visit 2 Day 8.

- Preliminary PK data for selected time points, as per Section 7.3.5. For escalation from Dose Group 1 to Dose Group 2, preliminary PK data are not required.
- Check 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) and the Trial Clinical Monitor (or an authorised deputy) after in-depth analysis of all available safety data, especially SAEs (if occurred), AEs and out-of-range laboratory results (if considered clinically significant). Safety Reviews can be conducted face-to-face or by video/ telephone conference. The trial clinical monitor is responsible for organization and minutes of the reviews. Minutes will be signed off by the Principal Investigator (or an authorised deputy) and filed in the ISF and TMF.

The investigator and/ or the sponsor should stop dose escalation in case the safety evaluation leads to concerns that would not allow higher dosing.

An overview of all relevant trial activities is provided in Flow Chart 1. For visit schedules and details of trial procedures at selected visits, see Sections 6.1 and 6.2, respectively.

Food effect part

This part will be performed as a randomised, open-label, two-way crossover trial part in healthy male subjects in order to compare the test treatment (T) to the reference treatment (R).

A 10 mg dose will be tested in a group of 12 subjects. For decision criteria see Section 2.3.2.7.

The subjects will be randomly allocated to the two treatment sequences (T-R or R-T). The treatments will be one 10 mg tablet of BI 705564 in the fed state (T) and one 10 mg tablet of BI 705564 in the fasting state (R). For details, see Section 4.1.

There will be a washout period of at least 10 days between treatments.

An overview of all relevant trial activities is provided in Flow Chart 2. For visit schedule and details of trial procedures at selected visits, see Sections 6.1 and 6.2, respectively.

Single rising dose part under fed conditions

This part is designed single-blind, partially randomised, and placebo-controlled within parallel dose groups.

A total of 32 healthy male subjects is planned to participate in the single rising dose part under fed conditions, resulting in 4 sequential groups comprising 8 subjects each. However, additional subjects may be entered to allow testing of additional doses on the basis of the experience gained during the conduct of the trial (e.g. preliminary PK data), provided that the planned and approved highest dose will not be exceeded. Thus, the actual number of subjects entered in the single rising dose part may exceed 32, but will not exceed 48 subjects entered. Such changes may be implemented via non-substantial CTP amendments.

Within each dose group, 6 subjects will receive the active drug and 2 will receive placebo. Only one dose is tested within each dose group. Dose groups will be treated consecutively in ascending order of doses. Each dose group will consist of 2 cohorts of 4 subjects each (3 on active drug and 1 on placebo).

On the first study day within each dose group, the first cohort will be treated in a single-blind manner in the following order: First subject (active) followed at least 1 hour later by the second subject (placebo) followed at least 1 hour later by the third subject (active) followed at least 10 minutes later by the fourth subject (active).

If BI 705564 treatment is safe and showed acceptable tolerability in the first cohort, subjects in the second cohort will be treated not earlier than 2 days later (at least 46 h between the 1st subject of each cohort) in a single-blind, randomised manner. In the second cohort, a time interval of at least 10 minutes will be maintained between administrations of trial drug to the individual subjects.

A time interval of at least 10 days will be maintained between the first drug administration in the previous dose group and the first drug administration of the subsequent dose group. The dose groups to be evaluated are outlined in Table 3.1: 2 below.

Table 3.1: 2 Dose groups in the single rising dose part under fed conditions

Dose Group	**7**	**8**	**12***	**13***
Dose (mg) q.d.	20	40	80	160
Formulation	Tab	Tab	Tab	Tab
Number of subjects	8	8	8	8
Subjects with placebo	2	2	2	2
Subjects with active drug	6	6	6	6

* For technical reasons related to drug packaging, numbers 9-11 cannot be attributed to dose groups in the SRD part under fed conditions.

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

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

The minimum data set for review consists of the following data:

- AEs in the current and preceding dose groups up to at least 48 h post dosing, including clinically relevant findings from ancillary safety testing, as 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 and continuous ECG monitoring in the current and preceding dose groups up to at least 48 h post dosing.
- Vital signs in the current and preceding dose groups up to at least 48 h post dosing.
- Clinical laboratory tests in the preceding dose groups and clinical laboratory tests of the first cohort of the current dose group up to at least Visit 2 Day 8.
- Preliminary PK data for selected time points, as per Section 7.3.5.
- Check 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) and the Trial Clinical Monitor (or an authorised deputy) after in-depth analysis of all available safety data, especially SAEs (if occurred), AEs and out-of-range laboratory results (if considered clinically significant). Safety Reviews can be conducted face-to-face or by video/ telephone conference. The trial clinical monitor is responsible for organization and minutes of the reviews. Minutes will be signed off by the Principal Investigator (or an authorised deputy) and filed in the ISF and TMF.

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

An overview of all relevant trial activities is provided in Flow Chart 3. For visit schedules and details of trial procedures at selected visits, see Sections 6.1 and 6.2, respectively.

3.1.1 Administrative structure of the trial

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

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

- Manage the trial in accordance with applicable regulations and internal Standard Operation Procedures (SOPs),
- Direct the clinical trial team in the preparation, conduct, and reporting of the trial,
- Ensure appropriate training and information of local clinical monitors (CML), Clinical Research Associates (CRAs), and participating trial sites.

The trial medication will be provided by the

The trial will be conducted at the , under the supervision of the Principal Investigator.

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

The analyses of BI 705564 concentrations in plasma and urine will be performed at
.

BI 705564 metabolism analyses will be performed at the

The analyses of BI 705564 will be performed at
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The assay and will be performed at the

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

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

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

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

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

Single rising dose parts under fasting and fed conditions

For single-rising dose trials, the design described in Section 3.1 is viewed favourable under the provision not to expose the subjects involved to undue risks since the main study objective is to investigate safety and tolerability of BI 705564.

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

It is standard in trials involving healthy volunteers to include a placebo group as control for the evaluation of safety, tolerability, and pharmacodynamics effects. Each dose group consists of 8 subjects with 6 on active treatment, and 2 on placebo. The placebo control group

includes all subjects of all dose groups treated with placebo. 6 subjects per active treatment group are in general considered as sufficient for the exploratory evaluation of pharmacokinetics.

Food effect part

For relative bioavailability trials, the crossover design is preferred due to its efficiency. Since each subject serves as his own control, the comparison between treatments is based on a comparison within subjects rather than between subjects. This trial design, therefore, removes inter-subject variability from the comparison between treatments [R94-1529].

Blinding is not possible because the treatments are distinguishable.

The open-label treatment is not expected to bias results.

3.3 SELECTION OF TRIAL POPULATION

It is planned that 48 healthy male subjects will enter the single rising dose part under fasting conditions, that 12 healthy male subjects will enter the food effect part of the study, and that 32 healthy male subjects will enter the single rising dose part under fed conditions (i.e., 92 volunteers in total).

The actual number of subjects entered into the trial may exceed the total of 92 (all three trial parts together), if additional, intermediate doses within the approved dose range will be tested in the single rising dose part under fasting conditions (see Section 3.1). Subjects will be recruited from the volunteers' pool of the trial site.

Subjects that were entered and treated in the single rising dose part under fasting conditions may be entered again in the food effect part, provided the time interval between the drug administration in the single rising dose part and the first drug administration in the food effect part is more than 60 days. Subjects that were entered and treated in the single rising dose part under fasting conditions are not allowed to be entered in the single rising dose part under fed conditions.

Only male subjects will be included into the study because hitherto no data on reproductive toxicology are available.

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

3.3.1 Main diagnosis for study entry

The study will be performed in healthy subjects.

3.3.2 Inclusion criteria

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

1. Healthy male subjects according to the assessment of the investigator, based on a complete medical history including a physical examination, vital signs (BP, PR), 12-lead ECG, and clinical laboratory tests
2. Age of 18 to 50 years (incl.)
3. BMI of 18.5 to 29.9 kg/m^2 (incl.)
4. Signed and dated written informed consent prior to admission to the study in accordance with GCP and local legislation

3.3.3 Exclusion criteria

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

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

19. Inability to comply with dietary regimen of 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 Torsades de Pointes (such as heart failure, hypokalemia, or family history of Long QT Syndrome)
22. Subject is assessed as unsuitable for inclusion by the investigator, for instance, because considered not able to understand and comply with study requirements, or has a condition that would not allow safe participation in the study

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

23. Male subjects with WOCBP partner who are unwilling to use male contraception (condom or sexual abstinence) from the first administration of trial medication until 30 days after last administration of trial medication
24. Repeated absolute B cell (CD19+) counts below 40/µL at screening
25. Repeated platelet counts below 100 cells/nL at screening
26. Serum potassium below normal range at screening
27. A history or current clinical signs of acute pancreatitis

For study restrictions, see Section 4.2.2.

3.3.4 Removal of subjects from therapy or assessments

3.3.4.1 Removal of individual subjects

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

1. The subject withdraws consent for trial treatment or trial participation, without the need to justify the decision.
2. The subject needs to take concomitant drugs that interfere with the investigational product or other trial medication.
3. The subject is no longer able to participate for other medical reasons (such as surgery, adverse events (AEs), or diseases).
4. An AE or clinically significant laboratory change or abnormality occurred that the investigator judges to warrant discontinuation of treatment. This may include cases of sustained symptomatic hypotension (BP <90/50 mmHg) or hypertension (BP >180/100 mmHg) or of clinically relevant changes in ECG requiring intervention as well as unexplained liver enzyme elevations at any time during the trial.
5. The subject shows an elevation of AST and/or ALT ≥3-fold ULN combined with an elevation of total bilirubin ≥2-fold ULN (measured in the same blood sample) and/ or needs to be followed up according to the 'DILI checklist' provided in the ISF.

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

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

If a subject is removed from or withdraws from the trial prior to first administration of trial medication, the data of this subject will not be entered in the case report form (CRF) or trial database and will not be reported in the clinical trial report (CTR). If a subject is removed from or withdraws from the trial after first administration of trial medication, this will be documented and the reason for discontinuation must be recorded in the CRF. In this case, the data will be included in the CRF/ trial database and will be reported in the CTR. At the time of discontinuation, a complete end of trial examination will be performed, if possible, and the information will be recorded in the CRF.

3.3.4.2 Discontinuation of the trial by the sponsor

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

1. New toxicological findings or serious adverse events invalidate the earlier positive benefit-risk-assessment. More specifically, the trial will be terminated, if more than 50% of subjects show drug-related and clinically relevant adverse events of moderate or severe intensity or, if at least one drug-related serious adverse event is reported that is considered to be unacceptable.
2. The expected enrolment goals overall or at a particular trial site are not met.
3. Violation of GCP, or the CTP by a trial site or investigator, disturbing the appropriate conduct of the trial.
4. The sponsor decides to discontinue the further development of the investigational product.
5. Dose escalation will be stopped as soon as at least 2 subjects at one dose level on active drug shows relevant individual QT prolongation, i.e. a QTc increase of greater than 60 ms from baseline in connection with absolute QT or QTc greater than 500 ms which has been confirmed by a repeat ECG recording.
6. Dose escalation will be stopped, if the C_{max} or AUC_{0-24} of at least 2 subjects of one dose group increases above the following exposure thresholds or, if the estimated gMean exposure of the next dose group is expected

   Estimation will be done based on preliminary pharmacokinetics results of preceding dose groups (see Section 7.3.5).

3.3.5 Replacement of subjects

In case there are less than 4 subjects on active drug per dose level in the single rising dose parts under fasting or fed conditions or less than 9 subjects per dose level in the food effect part who do not complete the trial, the trial clinical monitor together with the trial pharmacokineticist and the trial statistician are to decide, if and how many subjects will be replaced. A replacement subject will be assigned a unique study subject number, and will be assigned to the same treatment as the subject he replaces.

4. TREATMENTS

Global Amendment No 4 – major changes in Section 4:

With this amendment, 120 mg and 160 mg dose groups in the SRD part under fasting conditions and the 40 mg dose group of the food effect part were deleted. An additional SRD part under fed conditions was added. See Section 3 and Appendix 11 for details.

4.1 TREATMENTS TO BE ADMINISTERED

The investigational product has been manufactured by Boehringer Ingelheim Pharma GmbH & Co. KG and Almac Clinical Services Limited in UK.

4.1.1 Identity of BI investigational product and comparator product

Single rising dose part under fasting conditions

Powder for oral solution

The characteristics of the test product are given below:

Substance:	BI 705564
Pharmaceutical formulation:	Powder for oral solution
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG, Germany
Drug in bottle:	20 mg
Unit strength:	0.25 mg/mL (concentration in prepared solution)
Posology:	4 mL (1 mg)-0-0 (DG 1); 12 mL (3 mg)-0-0 (DG 2)
Route of administration:	p.o.
Duration of use:	Single dose

Component for reconstitution: The oral solution for dosing will be prepared as detailed in the reconstitution instruction given in Appendix 10.1 using a solvent containing hydroxypropyl-beta-cyclodextrin (HP-ß-CD). The solvent will be supplied in separate 100 mL glass vials and will be used as placebo solution (see Appendix 10.1).

Tablets

The characteristics of the test product are given below:

10 mg Tablet

Substance:	BI 705564
Pharmaceutical formulation:	Film-coated tablet
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG, Germany
Unit strength:	

Posology:

Route of administration: p.o.

Duration of use: Single dose

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

Oral solution

Substance: Matching placebo containing hydroxypropyl-beta-cyclodextrin

Pharmaceutical formulation: Oral solution

Source: Boehringer Ingelheim Pharma GmbH & Co. KG, Germany

Unit strength: n.a.

Posology: (4 mL)-0-0 (DG 1); (12 mL)-0-0 (DG 2)

Route of administration: p.o.

Duration of use: Single dose

Tablets

Substance: Placebo matching in size and weight to 10 mg tablet

Pharmaceutical formulation: Film-coated tablet

Source: Boehringer Ingelheim Pharma GmbH & Co. KG, Germany

Unit strength: n.a.

Posology: 1-0-0 (DG 3); 2-0-0 (DG 4); 4-0-0 (DG 5); 8-0-0 (DG 6)

Route of administration: p.o.

Duration of use: Single dose

Food effect part

The characteristics of the test products are given below:

Tablet (fed and fasting)

Substance: BI 705564

Pharmaceutical formulation: Film-coated tablet

Source: Boehringer Ingelheim Pharma GmbH & Co. KG, Germany

Unit strength:

Route of administration: p.o.

Duration of use: Single dose

Single rising dose part under fed conditions

Tablets

The characteristics of the test product are given below:

10 mg Tablet

Substance: BI 705564

Pharmaceutical formulation: Film-coated tablet

Source: Boehringer Ingelheim Pharma GmbH & Co. KG, Germany

Unit strength:

Posology:

Route of administration: p.o.

Duration of use: Single dose

100 mg Tablet

Substance: BI 705564

Pharmaceutical formulation: Film-coated tablet

Source: Boehringer Ingelheim Pharma GmbH & Co. KG, Germany

Unit strength:

Route of administration: p.o.

Duration of use: Single dose

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

Tablets

Substance: Placebo matching in size and weight to 10 mg tablet

Pharmaceutical formulation:	Film-coated tablet
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG, Germany
Unit strength:	n.a.
Posology:	2-0-0 (DG 7); 4-0-0 (DG 8); 8-0-0 (DG 12); 6-0-0 (DG 13)
Route of administration:	p.o.
Duration of use:	Single dose

Substance:	Placebo matching in size and weight to 100 mg tablet
Pharmaceutical formulation:	Film-coated tablet
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG, Germany
Unit strength:	n.a.
Posology:	1-0-0 (DG 13)
Route of administration:	p.o.
Duration of use:	Single dose

4.1.2 Method of assigning subjects to treatment groups

Prior to the screening visit, subjects will be contacted in writing and informed about the planned visit dates. Subjects willing to participate will be recruited to dose groups in the single rising dose- or food effect part according to their temporal availability. As soon as enough subjects have been allocated to 1 of the 12 dose cohorts (2 cohorts per dose group) in the single rising dose part under fasting conditions, the following subjects will be allocated to one of the other dose cohorts in the single rising dose part under fasting conditions. As soon as enough subjects have been allocated to 1 of the 8 dose cohorts (2 cohorts per dose group) in the single rising dose part under fed conditions, the following subjects will be allocated to one of the other dose cohorts in the single rising dose part under fed conditions. In the food effect part, there is only one dose group. Therefore, the allocation of subjects to dose cohorts or groups is not influenced by trial personnel, but only by the subjects' temporal availability. As the study includes healthy subjects from a homogenous population, relevant imbalances between dose groups are not expected.

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

The randomisation procedure is described in Section 7.5.

4.1.3 Selection of doses in the trial

Doses, selected for this trial, are intended to cover the sub-therapeutic as well as the estimated therapeutic and supra-therapeutic range and include a safety margin (see Section 1.2 and 2.1).

4.1.4 Drug assignment and administration of doses for each subject

Single rising dose part under fasting conditions

Treatments to be evaluated are outlined in Table 4.1.4: 1. The number of units/ dose volume for placebo corresponds to the number of units/ dose volume of the respective dose group.

Table 4.1.4: 1 BI 705564 and placebo treatments, oral administration under fasting conditions

Dose group	Substance	Pharmaceutical form	Unit strength	Number of units / dose volume per administration	Total daily dose
1	BI 705564	Oral solution	0.25 mg/mL	4 mL	1 mg
2	BI 705564	Oral solution	0.25 mg/mL	12 mL	3 mg
3	BI 705564	Film-coated tablet	10 mg	1 tablet	10 mg
4	BI 705564	Film-coated tablet	10 mg	2 tablets	20 mg
5	BI 705564	Film-coated tablet	10 mg	4 tablets	40 mg
6	BI 705564	Film-coated tablet	10 mg	8 tablets	80 mg
1-2	Placebo*	Oral solution	--	Identical to active treatment	--
3-6	Placebo*	Film-coated tablet	--	Identical to active treatment	--

* Subjects receiving placebo are equally distributed across dose groups

The oral solutions for dosing (active drug and placebo) will be prepared according to the instruction given in Appendix 10.1 under the responsibility of the investigator.

The trial medication will be administered to the subjects, while in a sitting or standing position, as an oral dose together with about 240 mL of water under supervision of the investigating physician or an authorised designee. The so-called four-eye principle (two-person rule) should be applied for administration of trial medication and – if applicable – its preparation (e.g. reconstitution), if correct dosage cannot be ensured otherwise. Administration will be performed following an overnight fast which is to start no later than 10 hours before the scheduled dosing.

Subjects will be kept under close medical surveillance until at least 24 hours following drug administration. During the first 4 hours after drug administration, they are not allowed to sleep and will be confined to bed with a bed inclination angle of at least 45 degrees unless lower or supine position is required for trial-related measurements (e.g., recording of 12-lead ECG) or medical reasons (e.g., adverse events). For restrictions with regard to diet, see Section 4.2.2.2.

Food effect part

This part follows a two-way crossover design. All subjects will receive the two treatments in randomised order. The treatments to be evaluated are outlined in Table 4.1.4: 2.

Table 4.1.4: 2 Dosage and treatment schedule – food effect part

Treatment	Substance	Formulation	Unit strength	Dosage	Total dose
Tablet, fed (Test)	BI 705564	Film-coated tablet	10 mg	1 tablet q.d.	10 mg
Tablet, fasting (Reference)	BI 705564	Film-coated tablet	10 mg	1 tablet q.d.	10 mg

The medication will be administered as a single oral dose together with about 240 mL of water to a subject in the sitting or standing position under supervision of the investigating physician or an authorised designee. The so-called four-eye principle (two-person rule) should be applied for administration of trial medication and – if applicable – its preparation (e.g. reconstitution), if correct dosage cannot be ensured otherwise. Administration will be performed following an overnight fast starting no later than 10 hours before scheduled dosing.

In the 'fed' treatment, a high-fat, high-calorie meal will be served 30 minutes before drug administration. The meal must be completely consumed prior to drug administration. The composition of the standard high-fat, high-calorie meal will be in compliance with the FDA guidance 'Food-Effect Bioavailability and Fed Bioequivalence Studies' [R03-2269] as detailed in Table 4.1.4: 3.

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

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

[1] Alternatively liquid egg (consisting of pasteurized whole chicken egg) with an amount corresponding to 2 chicken eggs may be used.

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

Subjects will be kept under close medical surveillance until at least 24 hours following drug administration. During the first 4 hours after drug administration, they are not allowed to lie down (i.e. no declination of the upper body of more than 45 degrees from upright posture) except, if required for trial-related measurements (e.g., recording of 12-lead ECG) or for medical reasons (e.g., adverse events). For restrictions with regard to diet see Section 4.2.2.2.

The treatments will be separated by a wash-out phase of at least 10 days between drug administrations.

Single rising dose part under fed conditions

Treatments to be evaluated are outlined in Table 4.1.4: 4. The number of units for placebo corresponds to the number of units of the respective dose group.

Table 4.1.4: 4 BI 705564 and placebo treatments, oral administration

Dose group	Substance	Pharmaceutical form	Unit strength	Number of units per administration	Total daily dose
7	BI 705564	Film-coated tablet	10 mg	2 tablets	20 mg
8	BI 705564	Film-coated tablet	10 mg	4 tablets	40 mg
12**	BI 705564	Film-coated tablet	10 mg	8 tablets	80 mg
13**	BI 705564	Film-coated tablet	10 mg and 100 mg	6 tablets of 10 mg and 1 tablet of 100 mg	160 mg
7, 8, 12, 13	Placebo*	Film-coated tablet	--	Identical to active treatment	--

* Subjects receiving placebo are equally distributed across dose groups.
** For technical reasons related to drug packaging, numbers 9-11 cannot be attributed to dose groups in the SRD part under fed conditions.

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

Subjects will be kept under close medical surveillance until at least 24 hours following drug administration. During the first 4 hours after drug administration, they are not allowed to sleep and will be confined to bed with a bed inclination angle of at least 45 degrees unless lower or supine position is required for trial-related measurements (e.g., recording of 12-lead ECG) or medical reasons (e.g., adverse events). For restrictions with regard to diet, see Section 4.2.2.2.

Additional doses

Additional subjects may be entered to allow testing of additional doses on the basis of the experience gained during the conduct of the trial (e.g. preliminary PK data), provided that the planned and approved highest dose will not be exceeded (see Section 3.1). Such changes may be implemented via non-substantial CTP amendments.

Application of food

A high-fat, high-calorie meal will be served 30 minutes before drug administration. The meal must be completely consumed prior to drug administration. The composition of the standard high-fat, high-calorie meal will be in compliance with the FDA guidance ‘Food-Effect Bioavailability and Fed Bioequivalence Studies’ [R03-2269] as detailed in Table 4.1.4: 5.

Table 4.1.4: 5 Composition of the high-fat, high-calorie meal

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

[1] Alternatively liquid egg (consisting of pasteurized whole chicken egg) with an amount corresponding to 2 chicken eggs may be used.

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

Subjects will be kept under close medical surveillance until at least 24 hours following drug administration. During the first 4 hours after drug administration, they are not allowed to lie down (i.e. no declination of the upper body of more than 45 degrees from upright posture) except, if required for trial-related measurements (e.g., recording of 12-lead ECG) or for medical reasons (e.g., adverse events). 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 database of this trial will be handled open-label, because no bias with regard to data cleaning or safety measures is expected. This is considered acceptable because the potential for bias seems to be low and does not outweigh practical considerations.

Single rising dose parts under fasting and fed conditions

The treatments administered (active or placebo) will be single-blind (blinded to subjects only). However, the current dose level will be known to the subjects.

The bioanalyst or analytical laboratory and the trial pharmacokineticist may receive the randomisation codes of the single rising dose part prior to official unblinding to perform the preliminary PK analysis. He or she will treat the codes confidentially.

In addition, the drug metabolism scientist may receive the randomisation codes prior to official unblinding to perform metabolites in safety testing analysis (MIST). He or she will confirm in writing that the codes will be treated confidentially.

Within the ECG laboratory, the staff involved with interval measurements and assessments will be blinded with respect to the treatment within each dose level and also with regard to the recording date and time as well as the 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. No more than two different blinded readers will evaluate the ECGs of the study.

Food effect part

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

4.1.5.2 Procedures for emergency unblinding

As this trial will be conducted single blinded (single rising dose parts under fasting and fed conditions) and open-label (food effect part), the treatment information will be known to the investigator. Therefore, no emergency envelopes will be provided.

4.1.6 Packaging, labelling, and re-supply

Drug supplies will be provided by the

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

- BI trial number
- Name of product and strengths or identification code
- Pharmaceutical dosage form, quantity of dosage units
- Route and mode of administration
- Term ‘For Clinical Trial Use’ (domestic language)
- Sponsor name and address
- Storage conditions
- Use-by date
- Subject or medication number – only in single rising dose part
- Batch number

The telephone number of the sponsor and name, address and telephone number of the trial site are given in the subject information form. The EudraCT number is indicated on the title page of this protocol as well as on the subject information and informed consent forms. Examples of the labels will be available in the ISF.

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 according to the recommended (labelled) storage conditions. Where necessary, a

temperature log must be maintained to make certain that the drug supplies are stored at the correct temperature. If the storage conditions are found to be outside the specified range, the local clinical monitor (as provided in the list of contacts) is to be immediately contacted.

4.1.8 Drug accountability

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

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

Only authorised personnel, as documented in the form 'Trial Staff List', may dispense medication to trial subjects. The trial medication must be administered in the manner specified in the CTP. All unused medication will be disposed locally by the trial site upon written authorisation by the clinical monitor. Receipt, usage and disposal must be documented on the respective forms. Account must be given for any discrepancies.

The investigator must maintain records of the product's delivery to the trial site, the inventory at the site, the use by each subject, and the disposal of unused products.

These records will include dates, quantities, batch/ serial numbers, expiry ('use-by') dates, and the unique code numbers assigned to the investigational products and trial subjects. The investigator will maintain records that document adequately that the subjects were provided the doses specified by the CTP, and that reconcile all investigational products received from the sponsor. At the time of disposal, the investigator must verify that no remaining supplies are in the investigator's possession.

4.2 OTHER TREATMENTS, EMERGENCY PROCEDURES, RESTRICTIONS

4.2.1 Other treatments and emergency procedures

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

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

In principle, no concomitant therapy is allowed. All concomitant or rescue therapies will be recorded (including time of intake on study days) on the appropriate pages of the CRF.

Paracetamol and acetylsalicylic acid should be avoided. Ibuprofen should preferably be used for treatment of pain such as headache or toothache.

4.2.2.2 Restrictions on diet and life style

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

From 1 hour before drug intake until lunch, fluid intake is restricted to the milk served with breakfast (see Table 4.1.4: 3 and Table 4.1.4: 5), the water administered with the drug, and an additional 240 mL of water served at 2 hours and 4 hours post-dose (mandatory for all subjects).

From lunch until discharge from the study centre, liquid intake is restricted to additional 3 litres.

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

Alcoholic beverages are not permitted starting 48 hours before administration of trial medication until after the last PK sample of each study period is collected.

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

Methylxanthine-containing drinks or foods (such as coffee, tea, cola, energy drinks, and chocolate) are not allowed from 10 hours before administration of trial medication until the end of the in-house period at the trial site.

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

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

4.3 TREATMENT COMPLIANCE

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

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

5. VARIABLES AND THEIR ASSESSMENT

5.1 EFFICACY - CLINICAL PHARMACOLOGY

5.1.1 Endpoints of efficacy

No efficacy endpoints will be evaluated in this trial.

5.1.2 Assessment of efficacy

Not applicable.

5.2 SAFETY

5.2.1 Endpoints of safety

Single rising dose parts under fasting and fed conditions

Primary endpoint to assess safety and tolerability of BI 705564 is the number [N (%)] of subjects with drug-related adverse events (adverse reactions).

Further criteria of interest:

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

Food effect part

Safety and tolerability of the investigational drug will be assessed based on:

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

These parameters will be evaluated in a descriptive way only, and are therefore considered to be ‘further parameters of interest’. A confirmatory analysis is not planned (see Section 7.3).

5.2.2 Assessment of adverse events

5.2.2.1 Definitions of adverse events

Adverse event

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

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

Adverse reaction

An adverse reaction is defined as a response to a medicinal product which is noxious and unintended. Response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility. Adverse reactions may arise from use of the product within or outside the terms of the marketing authorisation or from occupational exposure. Conditions of use outside the marketing authorization include off-label use, overdose, misuse, abuse and medication errors.

Serious adverse event

A serious adverse event (SAE) is defined as any AE which:

- Results in death,
- Is life-threatening, this refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if more severe,
- Requires inpatient hospitalisation or prolongation of existing hospitalisation,
- Results in persistent or significant disability or incapacity,
- Is a congenital anomaly/birth defect, or
- Is to be deemed serious for any other reason if it is an important medical event when based upon appropriate medical judgment which may jeopardise the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions.

Medical and scientific judgement should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalisation but might jeopardise the patient or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation or development of dependency or abuse. Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

AEs considered 'Always Serious'

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

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

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

Adverse events of special interest (AESIs)

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

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

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

With the exception of DILI, no AESIs have been defined for this trial.

Intensity of AEs

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

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

Causal relationship of AEs

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

Medical judgment should be used to determine the relationship, considering all relevant factors, including pattern of reaction, temporal relationship, de-challenge or re-challenge, confounding factors such as concomitant medication, concomitant diseases and relevant history.

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

- The event is consistent with the known pharmacology of the drug.
- The event is known to be caused by or attributed to the drug class.
- A plausible time to onset of the event relative to the time of drug exposure.
- Evidence that the event is reproducible when the drug is re-introduced.
- No medically sound alternative aetiologies that could explain the event (e.g. pre-existing or concomitant diseases, or co-medications).
- The event is typically drug-related and infrequent in the general population not exposed to drugs (e.g. Stevens-Johnson syndrome).
- An indication of dose-response (i.e. greater effect size if the dose is increased, smaller effect size if dose is diminished).

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

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

5.2.2.2 Adverse event collection and reporting

AEs collection

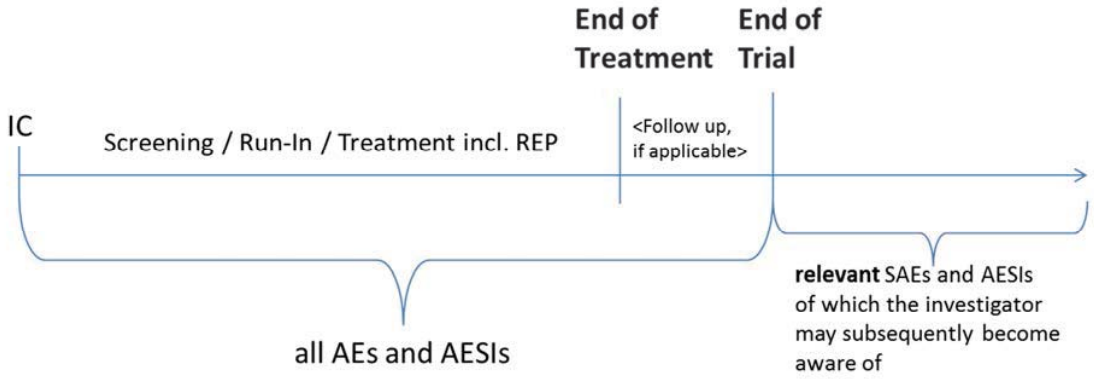
Upon enrolment into a trial, the subject's baseline condition is assessed (for instance, by documentation of medical history/concomitant diagnoses), and relevant changes from baseline are noted subsequently.

Subjects will be required to report spontaneously any AEs as well as the time of onset, end, and intensity of these events. In addition, each subject will be regularly assessed by the medical staff throughout the clinical trial and whenever the investigator deems necessary. As a minimum, subjects will be questioned for AEs (and concomitant therapies) at the time points indicated in the Flow Charts. 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 careful written record of all AEs shall be kept by the investigator in charge of the trial. Records of AEs shall include data on the time of onset, end time, and intensity of the event as well as any treatment or action required for the event and its outcome.

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

- From signing the informed consent onwards through the residual effect period (REP), until an individual subject's end of trial:
    - All AEs (serious and non-serious) and all AESIs.
    - The only exception to this rule are AEs (serious and non-serious) and AESIs in Phase I trials in healthy volunteers, when subjects discontinue from the trial due to screening failures prior to administration of any trial medication. In these cases, the subjects' data must be collected at trial site but will not be entered in the CRF or trial database and will not be reported in the CTR.
- After the individual subject's end of trial:
    - The investigator does not need to actively monitor the subject for AEs but should only report relevant SAEs and relevant AESIs of which may become aware of.



Single rising dose parts and food effect part

The REP for BI 705564, when measurable drug levels or PD effects are still likely to be present after the last administration, is not known for this first-in-human trial. Therefore, all AEs reported until the end of trial examination (last per protocol contact) will be considered on treatment; see Section 7.3.4. The follow-up period describes the period of time from the last administration of trial medication until the end of trial examination (last per protocol contact).

AE reporting to sponsor and timelines

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

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

Information required

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

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

- Worsening of the underlying disease or of other pre-existing conditions.
- Changes in vital signs, ECG, physical examination and laboratory test results, if they are judged clinically relevant by the investigator.

If such abnormalities already pre-exist prior trial inclusion they will be considered as baseline conditions.

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

5.2.3 Assessment of safety laboratory parameters

For the assessment of laboratory parameters, blood and urine samples will be collected by the trial site at the time points indicated in the Flow Charts after the subjects have fasted for at least 10 h. Overnight fasting is not required at the discretion of the investigator or designee for retests or drug screening. In the single rising dose part under fed conditions, fasting is not applicable to the post-dose safety laboratory on Day 1.

The parameters that will be determined are listed in Tables 5.2.3: 1 and 5.2.3: 2. Reference ranges will be provided in the ISF, Section 10.

Manual differential white blood cell count or urine sediment examinations will only be performed, if there is an abnormality in the automatic blood cell count or in the urinalysis, respectively.

Table 5.2.3: 1 Routine laboratory tests

Functional lab group	Test name	SCR	A[1]	B[2]	C[3]	EOT
Haematology	Haematocrit	x	x	x	x	x
	Haemoglobin	x	x	x	x	x
	Red blood cell count (RBC)	x	x	x	x	x
	Reticulocyte count	x	--	--	x	x
	White blood cell count (WBC)	x	x	x	x	x
	Platelet count	x	x	x	x	x
Automatic WBC differential (relative and absolute)	Neutrophils, eosinophils, basophils, monocytes, lymphocytes	x	x	x	x	x
Manual differential WBC (if automatic differential WBC is abnormal)	Polymorphnuclear neutrophils (segs), band neutrophils (stabs), eosinophils, basophils, monocytes, lymphocytes					
Lymphocyte differentiation (relative and absolute; except for ratio)	T cells (CD3+), T helper cells (CD3+CD4+), cytotoxic T cells (CD3+CD8+), B cells (CD19+), natural killer cells (CD16+CD56+CD3-), double-positive T cells (CD3+CD4+CD8+), CD4:CD8 ratio	x	--	--	x[4]	x
Serum immunoglobulins	IgA	x	--	--	x	x
	IgG	x	--	--	x	x
	IgM	x	--	--	x	x
Coagulation	Activated partial thromboplastin time (aPTT)	x	x	x	x	x
	Prothrombin time (Quick's test and INR)	x	x	x	x	x
	Fibrinogen	x	--	x	x	x

[1] A: Days -3 to -1
[2] B: post-dose on Day 1 (single rising dose parts)
[3] C: Days 2, 3, 8 (single rising dose parts) and Day 2 (food effect part)
[4] Not on Day 3 (single rising dose parts)

Table 5.2.3: 1 Routine laboratory tests (cont'd)

Functional lab group	Test name	SCR	A[1]	B[2]	C[3]	EOT
Enzymes	Aspartate transaminase (AST/GOT)	x	x	x	x	x
	Alanine transaminase (ALT/GPT)	x	x	x	x	x
	Alkaline phosphatase (AP)	x	--	x	x	x
	Gamma-glutamyl transferase (GGT)	x	x	x	x	x
	Glutamate dehydrogenase (GLDH)	x	--	--	x	x
	Creatine kinase (CK); CK-MB only if CK is elevated	x	--	x	x	x
	Lactate dehydrogenase (LDH)	x	x	x	x	x
	Lipase	x	x	x	x	x
	Amylase	x	x	x	x	x
Hormones	Thyroid stimulating hormone (TSH)	x				
Substrates	Plasma glucose	x	--	x	x	x
	Creatinine	x	x	x	x	x
	Total bilirubin	x	x	x	x	x
	Direct bilirubin	x	x	x	x	x
	Total protein	x	--	x	x	x
	C-Reactive Protein (CRP)	x	x	x	x	x
	Uric acid	x	--	x	x	x
	Total cholesterol	x	--	--	x	x
	Triglycerides	x	--	--	x	x
Electrolytes	Sodium	x	x	x	x	x
	Potassium	x	x	x	x	x
	Calcium	x	--	x	x	x
Urinalysis (Stix)	Urine nitrite	x	x	--	x	x
	Urine protein	x	x	--	x	x
	Urine glucose	x	x	--	x	x
	Urine ketone	x	x	--	x	x
	Urobilinogen	x	x	--	x	x
	Urine bilirubin	x	x	--	x	x
	Urine erythrocytes	x	x	--	x	x
	Urine leukocytes	x	x	--	x	x
	Urine pH	x	x	--	x	x
Urine sediment (microscopic examination if erythrocytes, leukocytes nitrite or protein are abnormal in urine)	Only positive findings will be reported (for instance, the presence of sediment bacteria, casts in sediment, squamous epithelial cells, erythrocytes, leukocytes)					

[1] A: Days -3 to -1
[2] B: post-dose on Day 1 (single rising dose parts)
[3] C: Days 2, 3, 8 (single rising dose parts) and Day 2 (food effect part)
[4] Not on Day 3 (single rising dose parts)

The tests listed in Table 5.2.3: 2 are exclusionary laboratory tests which may be repeated as required. The results will not be entered in the CRF/database and will not be reported in the CTR. It is planned to perform these tests during screening only. Drug screening will be performed at screening and prior to each treatment period.

Table 5.2.3: 2 Exclusionary laboratory tests

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

To encourage compliance with alcoholic restrictions, a breath alcohol test (Alcotest® 7410, Dräger AG, Lübeck, Germany) will be performed prior to each treatment period, and may be repeated at any time during the study at the discretion of an investigator or designee. The results will not be included in the CTR.

The laboratory tests listed in Table 5.2.3: 1 and 5.2.3: 2 will be performed at with the exception of the drug screening tests. These tests will be performed at the trial site using e.g. AccuSign® DOA 10, MAHSAN®-Kombi/DOA10, or M-10/14-PDT test.

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

5.2.4 Electrocardiogram

5.2.4.1 12-lead resting ECG

Twelve-lead resting ECGs (I, II, III, aVR, aVL, aVF, V1 - V6) will be recorded using a computerised electrocardiograph (CardioSoft EKG System, GE Medical Systems, Freiburg, Germany) at the time points given in the Flow Charts.

In order to achieve a stable heart rate at rest and to assure high quality recordings at comparable resting phases, all ECGs will be recorded for a 10-second duration after the subjects have rested for at least 5 minutes in a supine position. The site personnel will be instructed to assure a relaxed and quiet environment so that all subjects are at complete rest during the recordings. ECG assessment will always precede all other study procedures of the same time point (except blood drawing from an intravenous cannula which is already in place) to avoid impact of sampling on the ECG quality.

All ECGs will be stored electronically on the Electrode placement will be performed according to the method of Wilson, Goldberger and Einthoven modified by Mason and Likar (hips and

shoulders instead of ankles and wrists). Precise electrode placement will be marked with an indelible mark on the skin to allow reproducible placement throughout the study.

All locally printed ECGs will be evaluated by the investigator or a designee.

ECGs may be repeated for quality reasons (like alternating current artefacts, muscle movements, electrode dislocation). For time points with triple ECGs, all three single ECGs will be repeated. For the repeats due to quality reasons, only the repeated ECG recordings will be sent to the central ECG lab, whereas the initially recorded ECGs will be discarded.

Additional (unscheduled) ECGs may be collected by the investigator for safety reasons. These ECGs are assigned to the prior scheduled time point. Unscheduled ECGs will not be included into the statistical analysis of interval lengths.

For the inclusion or exclusion (see Section 3.3) of a subject and for the assessment of cardiac safety during the study, the QT and QTcB values generated by the ECG machines or their manual corrections by the investigators will be used. In doubtful cases, ECGs may be sent upfront for centralised evaluation (see below). In this case, these centrally measured results would overrule any other results obtained.

Abnormal findings 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.

Single rising dose parts under fasting and fed conditions: Triple ECGs will be recorded (three single ECGs within 180 sec) at all time points in Visit 2. At Visits 1 and 4, single ECGs will be recorded.

Food effect part: It is planned that single ECGs will be recorded for all time points. However, the number of ECGs per time point may be increased to three ECGs based on preliminary ECG results obtained during the single rising dose part of the study.

Single rising dose parts only

In the single rising dose parts, a centralised evaluation (during study and/or post study) of all 12-lead ECGs recorded at Visit 2 will be performed by an independent ECG laboratory. This analysis will include the determination of cardiac axis (automatically) as well as the intervals RR, PR, QRS and QT measured semi-automatically.

With the exception of the first triple ECG (used as baseline before the first drug administration), only the first of the three replicate ECGs at a single assessment time will be evaluated. The remaining second and third replicate ECGs will be stored for additional analyses if required, e.g. by authorities at a later time point.

For each QT interval, the RR interval preceding the QT will be measured to calculate the respective frequency corrected QTc intervals ‘QTcF’ according to Fridericia’s formula ($QTcF = QT/ RR^{1/3}$) and ‘QTcB’ according to Bazett’s formula ($QTcB = QT/ RR^{1/2}$). The QTcF correction will be used for evaluation and reporting. Abnormalities detected during centralised ECG evaluation will not necessarily qualify as AE. All 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, or if that lead is not measurable, then lead I will be used. The lead actually used will be reported in the CTR.

For blinding arrangements see Section 4.1.5.

Assessed ECGs will comply with the ICH E14 guidance document and supplements [R05-2311, R13-0801, R13-4095] as well as the FDA requirements for annotated digital ECGs [R09-4830].

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 minutes before (for baseline assessment) and 4 hours following drug administration using patient monitors (e.g. Carescape B450, GE Healthcare, Freiburg, Germany). Abnormal findings will be recorded as AEs if judged clinically relevant by the Investigator but no other data will be transferred to the database.

5.2.5 Assessment of other safety parameters

5.2.5.1 Vital signs

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

5.2.5.2 Medical examinations

At screening, the medical examination will include demographics including 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, and a physical examination. At the end of trial examination, it will include review of vital signs, 12-lead ECG, laboratory tests, and a physical examination.

5.4 APPROPRIATENESS OF MEASUREMENTS

All measurements performed during this trial are standard measurements and will be performed in order to monitor subjects' safety and to determine pharmacokinetic and biomarkers in an appropriate way. The scheduled measurements will allow monitoring of changes in vital signs, standard laboratory values, and ECG parameters that might occur as a result of administration of trial medication. The safety assessments are standard, are accepted for evaluation of safety and tolerability of an orally administered drug, and are widely used in clinical trials. The pharmacokinetic parameters and measurements outlined in Section 5.5 are generally used assessments of drug exposure. The biomarkers and measurements, outlined in Section 5.6, are of exploratory nature only.

5.5 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

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

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

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

5.5.1 Pharmacokinetic endpoints

5.5.1.1 Primary endpoints

Single rising dose parts under fasting and fed conditions

Not applicable

Food effect part

The following primary endpoints will be determined for BI 705564:

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

5.5.1.2 Secondary endpoints

Single rising dose parts under fasting and fed conditions

The following secondary endpoints will be determined for BI 705564:

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

Food effect part

The following secondary endpoints will be determined for BI 705564:

- $AUC_{0-\infty}$

5.5.2 Methods of sample collection

5.5.2.1 Plasma sampling for pharmacokinetic analysis

For quantification of BI 705564 plasma concentrations, 2.7 mL of blood will be taken from an antecubital or forearm vein into a K_3-EDTA (tripotassium ethylenediaminetetraacetic acid)-anticoagulant blood drawing tube at the times indicated in the Flow Charts. Blood will be withdrawn by means of either an indwelling venous catheter or by venipuncture with a metal needle.

The EDTA-anticoagulated blood samples will be centrifuged for about 10 minutes at about 2000 g to 4000 g and at 4 to 8 °C. Two plasma aliquots will be obtained and stored in polypropylene tubes. The first aliquot should contain at least 0.5 mL plasma. The process from blood collection until transfer of plasma aliquots into the freezer should be completed within 90 minutes, with interim storage of blood samples and aliquots in ice water or on ice or cryoblocks. For each aliquot the time when the sample was placed in the freezer will be documented. Until transfer on dry ice to the analytical laboratory, the aliquots will be stored upright at about -20°C or below at the trial site. The second aliquot will be transferred to the analytical laboratory after the bioanalyst has acknowledged safe arrival of the first aliquot. At

the analytical laboratory the plasma samples will be stored at about -20°C or below until analysis.

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

After completion of the trial the plasma samples may be used for further methodological investigations**,** e.g. for stability testing, assessment of metabolites. However, only data related to the analyte and/or its metabolite(s) including anti-drug antibodies (if applicable) will be generated by these additional investigations. The study samples will be discarded after completion of the additional investigations but not later than 5 years upon the final study report has been signed.

5.5.2.3 Urine sampling for pharmacokinetic analysis (single rising dose parts under fasting and fed conditions)

A blank urine sample will be collected before administration of trial medication (within the 3 hours 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 Charts will be collected in 2 liters polyethylene (PE) containers and stored at room temperature. Subjects are told to empty their bladders at the end of each sampling interval.

The urine weight/volume for each collection interval will be documented (however, no correction for the specific gravity of urine is done, i.e. 1 liter is defined to be equal to 1 kg). Two 0.5 mL aliquots will be stored in polypropylene (PP) tubes for bioanalytical measurement. In case more than one collection container is used in an interval, the contents of all containers are to be mixed before aliquots are prepared. Mixing should be done by transferring the entire content of all collection containers into a single PE/PP or glass container, and stirring the mixed fractions for about 1 minute (manually or using a stir bar or other stirring device out of PE, PP, Teflon or glass).

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

Until transfer on dry ice to the analytical laboratory, the urine samples will be stored at about -20°C or below at the trial site. The second aliquot will be transferred after the bioanalyst has acknowledged safe arrival of the first aliquot. At the analytical laboratory the plasma samples will be stored at about -20°C or below until analysis.

After completion of the trial the urine samples may be used for further methodological investigations, e.g. for stability testing, assessment of metabolites. However, only data related to the analyte and/or its metabolite(s) will be generated by these additional investigations. The study samples will be discarded after completion of the additional investigations but not later than 5 years upon the final study report has been signed.

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

Exact times of measurements outside the permitted time windows will be documented. The acceptable time windows for screening and end of trial examination are given in Flow Chart 1 and Flow Chart 3 for the single rising dose part under fasting and fed conditions, respectively, and Flow Chart 2 for the food effect part.

Study measurements and assessments scheduled to occur 'before' trial medication administration on Day 1 are to be performed and completed within a 3 h-period prior to the trial drug administration (including blank values for PK and biomarkers).

Starting from 72 h post administration a deviation from the scheduled time for PK and biomarker sampling of ±70 min is acceptable. The biomarker samples planned time Day 6 (single rising dose parts) may be taken on day 5 (up to 26 h earlier).

The acceptable deviation from the scheduled time for vital signs, ECG and laboratory tests will be ± 15 minutes for the first 4 hours after trial drug administration and ± 30 minutes thereafter. Starting from 72 h post administration a deviation from the scheduled time for vital signs, ECG and laboratory tests of ±70 min is acceptable.

If scheduled in the Flow Charts at the same time as a meal, blood sampling, vital signs and 12-lead ECG recordings have to be done first. Furthermore, if several measurements including venipuncture are scheduled for the same time, venipuncture should be the last of the measurements due to its inconvenience to the subject and possible influence on physiological parameters.

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

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

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

6.2.1 Screening period

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

For information regarding laboratory tests (including drug and virus screening), ECG, vital signs, and physical examination, see Sections 5.2.3 to 5.2.5.

6.2.2 Treatment periods

Single rising dose parts under fasting and fed conditions

Each subject will receive one dose of the respective trial medication (BI 705564 or placebo) at Visit 2.

Study participants will be admitted to the trial site in the morning of Day 1 and kept under close medical surveillance for at least 24 hours following drug administration. Subjects will then be allowed to leave the trial site after formal assessment and confirmation of their fitness by the investigator or designee. On all other study days, the study will be performed in an ambulatory fashion.

For details on time points and procedures for collection of plasma and urine samples for PK analysis, see Flow Chart 1, Flow Chart 3 and Section 5.5.2.

Safety measurements performed during the treatment period are specified in Section 5.2, Flow Chart 1 and Flow Chart 3. For details on time points for all other trial procedures, refer to Flow Chart 1 and Flow Chart 3. AEs and concomitant therapy will be assessed continuously from screening until the end of trial examination.

Food effect part

Each subject is expected to participate in two treatment periods. The treatment periods will be separated by at least 10 days between drug administrations.

On Day 1 of each treatment period study participants will be admitted to the trial site and kept under close medical surveillance for at least 24 hours following drug administration. Subjects will then be allowed to leave the trial site after formal assessment and confirmation of their fitness. On all other study days, the study will be performed in an ambulatory fashion.

For details on time points and procedures for collection of plasma samples for PK analysis, see Flow Chart 2 and Section 5.5.2.

Safety measurements performed during the treatment period are specified in Section 5.2 and Flow Chart 2. For details on time points for all other trial procedures, see Flow Chart 2. AEs and concomitant therapy will be assessed continuously from screening until the end of trial examination.

6.2.3 End of trial period

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

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

All abnormal values (including laboratory parameters) that are judged clinically relevant by the investigator will be monitored using the appropriate tests until a return to a medically acceptable level is achieved. (S)AEs persisting after subject's end of trial must be followed

up until they have resolved, have been sufficiently characterized, or no further information can be obtained.

The end of the trial as a whole is defined by the ‘last regular visit completed by last subject’ or ‘end date of the last open AE’ or ‘date of the last follow-up test’ or ‘date of an AE has been decided as sufficiently followed-up’, whichever is latest.

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 STATISTICAL DESIGN – MODEL

7.1.1 Objectives

Single rising dose parts under fasting and fed conditions

The primary objective of these parts of the trial is to investigate the safety and tolerability of BI 705564 by using descriptive statistics for all endpoints comparing active dose groups to placebo.

The primary endpoint is defined in Section 5.2.1. Inferential statistics is not planned (as explained in Section 7.2).

The secondary objective is the exploration of the pharmacokinetics (PK) and pharmacodynamics (PD) of BI 705564. Endpoints as specified in 5.5.1 (for PK) and 5.7.1 (for PD) will be analysed by descriptive statistics. Secondary endpoints, as defined in Section 5.5.1.1, will be subjected to analysis of dose proportionality by use of the power model.

Food effect part

The primary objective of this part of the trial is to investigate a possible food effect, comparing the tablet formulation under fasting (Reference R) to that under fed conditions (Test, T) following oral administration. The trial is designed to allow an intra-subject comparison and will be evaluated statistically by use of an appropriate linear model.

The secondary objective is the evaluation and comparison of several pharmacokinetic parameters between treatments. They will be assessed by descriptive statistics.

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

7.1.2 Endpoints

Single rising dose parts under fasting and fed conditions

Safety and tolerability will be determined on the basis of the parameters specified in Section 5.2.1. PK and PD endpoints are specified in Sections 5.5.1 (for PK) and 5.7.1 (for PD).

Food effect part

Food effect is to be determined on the basis of the primary and secondary pharmacokinetic endpoints (AUC_{0-tz}, C_{max} and $AUC_{0-\infty}$, see Section 5.5.1).

Safety and tolerability will be determined on the basis of the parameters specified in Section 5.2.1.

7.1.3 Model

Single rising dose parts under fasting and fed conditions

Endpoints will be analysed by descriptive statistics. Inferential statistics is not planned (as explained in Section 7.2).

Secondary endpoints, as defined in Section 5.5.1.1, will be subjected to analysis of dose proportionality by use of the power model.

Food effect part

The statistical model used for the analysis of primary and key secondary endpoints will be an ANOVA (analysis of variance) model on the logarithmic scale. This model will include effects accounting for the following sources of variation: 'sequence', 'subjects within sequences', 'period' and 'treatment'. The effect 'subjects within sequences' will be considered as random, whereas the other effects will be considered as fixed. The model is described by the following equation:

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

where

y_{ijkm} = logarithm of response (endpoint, see Section 7.1.2) measured on subject m in sequence i receiving treatment k in period j,

μ = the overall mean,

ζ_i = the ith sequence effect, i = 1, 2,

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

π_j = the jth period effect, j = 1, 2,

τ_k = the kth treatment effect, k = 1, 2,

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

7.2 NULL AND ALTERNATIVE HYPOTHESES

Single rising dose parts under fasting and fed conditions

Safety and tolerability of 10 different dose groups of BI 705564 (6 in SRD part under fasting conditions and 4 in SRD part under fed conditions) are to be determined on the basis of the

investigated parameters in comparison to placebo. It is not planned to test any statistical hypotheses with regard to these variables in a confirmatory sense. Instead, they will be described in their entirety and evaluated by descriptive statistical methods.

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

Food effect part

The food effect of the BI 705564 tablet will be estimated by the ratios of the gMeans (test/reference) for the primary and secondary PK endpoints. Additionally, their two-sided 90% confidence intervals (CIs) will be provided. This method corresponds to the two one-sided t-tests procedure, each at the 5% significance level. Since the main focus is on estimation and not testing, an acceptance range was not specified, that is, no hypothesis will be tested.

7.3 PLANNED ANALYSES

All individual data will be listed.

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

7.3.1 Primary analyses

Single rising dose parts under fasting and fed conditions

Analysis of safety and tolerability is described in Section 7.3.4.

Food effect part

The pharmacokinetic endpoints listed in Section 5.5.1 will be calculated according to the BI Standard Operating Procedure (SOP) ‘Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics’ [001-MCS-36-472].

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

Relevant protocol violations may be

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

Plasma 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).
- The subject experiences emesis at any time during the labelled dosing interval.
- A pre-dose concentration is >5% of the C_{max} value of that subject.
- Missing samples/concentration data at important phases of PK disposition curve.

The PK parameter analysis set (PKS) includes all subjects in the Treated Set (TS) who provide at least one primary or secondary PK parameter that was not excluded according to the description above. 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. Point estimates of bioavailability, the ratios of the gMeans (test/ reference) for the primary and secondary endpoints (see Sections 5.5.1.1 and 5.5.1.2), and their two-sided 90% confidence intervals (CIs) will be provided.

To this end, the PK endpoints will be log transformed (natural logarithm) prior to fitting the ANOVA model (see Section 7.1.3). For each endpoint, the difference between the expected means for log(T) - log(R) will be estimated by the difference in the corresponding adjusted means (LeastSquares Means), and a two-sided 90% confidence interval based on the t-distribution will be computed. These quantities will then be back-transformed to the original scale to provide the point estimate and 90% CIs for each endpoint.

7.3.2 Secondary analyses

Single rising dose parts under fasting and fed conditions

The secondary parameters (see Section 5.5.1) will be calculated according to the BI Standard Operating Procedure (SOP) 'Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics' [001-MCS-36-472]. Analyses will be performed for BI 705564.

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

For more information on relevant protocol violations and the definition of the PKS, see Section 7.3.1. Excluded subjects will be listed with their individual plasma concentrations. Individual pharmacokinetic parameters, however, will not be included in descriptive statistics for plasma concentrations, pharmacokinetic parameters or other statistical assessment.

Assessment of dose proportionality

Dose proportionality will be assessed using the secondary pharmacokinetic endpoints as specified in Section 5.5.1.2. Two separate analyses will be performed, one for the doses under fasting conditions, and one for the doses under fed conditions.

The basic model for the investigation of dose proportionality will be a power model that describes the functional relationship between the dose and PK endpoints.

$$\exp(Y_{ij}) = \alpha' * \exp(X_i)^{\beta} * \varepsilon'_{ij}$$

The model consists of a regression model applied to log-transformed data. The corresponding ANCOVA model includes the logarithm of the dose as a covariate.

Together with $\alpha' = \exp(\alpha)$ and $\varepsilon'_{ij} = \exp(\varepsilon_{ij})$, taking natural logarithms converts this model to a linear form as follows:

$$Y_{ij} = \alpha + \beta * X_i + \varepsilon_{ij}$$

where

Y_{ij}	logarithm of the pharmacokinetic endpoint for subject j at dose level i; j = 1, 2, …, N;
α	intercept parameter;
β	slope parameter;
X_i	logarithm of dose i;
ε_{ij}	random error associated with subject j at dose level i (assumed to be independent and identically normally distributed).

This equation can be fit as a linear regression model.

Based on the estimate for slope parameter (β), a 2-sided 95% CI for the slope will be computed. Perfect dose proportionality would correspond to a slope of 1. The assumption of a linear relationship between the log-transformed pharmacokinetic endpoint and the log-transformed dose will be checked.

If dose proportionality over the entire dose range investigated cannot be shown, an attempt will be made to identify dose range(s), where dose proportionality can be assumed.

Graphical displays: To support the analyses of dose proportionality, graphical representations of the data might be created. These might include (but are not limited to) individual time-courses of trough plasma concentrations and the gMean plasma concentration time profiles.

Food effect part

The secondary parameters (see Section 5.5.1) will be calculated according to the BI SOP 'Standards and processes for analyses performed within Clinical Pharmacokinetics/ Pharmacodynamics' [001-MCS-36-472] and will statistically be assessed using the same methods as described for the primary endpoints.

7.3.4 Safety analyses

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

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

Treatments will be compared in a descriptive way.

In the single rising dose parts, the placebo control group in the safety evaluation will consist of all placebo treated subjects, regardless of the dose group in which they were treated and regardless of whether they participated in the single rising dose part under fed or under fasting conditions; the active treatment groups will be compared to the placebo group in a descriptive way. To explore potential differences between placebo subjects under fasting and under fed conditions, these two subgroups will be compared descriptively.

In all (single rising dose – fasting and fed - and food effect) parts, 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 ECG, vital signs, or laboratory parameters) or AEs will be assigned to treatments (see Section 4.1) based on the actual treatment at the planned time of the measurement or on the recorded time of AE onset (concept of treatment emergent AEs).

Therefore, measurements planned or AEs recorded prior to first intake of trial medication will be assigned to 'screening', those between first trial medication intake until the end of trial visit will be assigned to the treatment period. These assignments including the corresponding time intervals will be defined in detail in the TSAP. Please note that AEs occurring after the last per protocol contact but entered before database lock will be reported to drug safety only and will not be captured in the trial database.

Additionally, further treatment intervals (analysing treatments) may be defined in order to provide summary statistics for time intervals, such as combined treatments, on-treatment totals or periods without treatment effects (such as screening and post-study 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 5.2.2.1) and other significant AEs (according to ICH E3) will be listed separately.

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

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

For the single rising dose parts (under fasting and fed conditions) of the study, a centralised evaluation of all 12-lead ECGs recordings (see Section 5.2.4) will be the basis for the derivation of further ECG parameters based on the ECG variables QT, HR, QTcF, QTcB, PR, QRS, and RR. The baseline value of an ECG variable is defined as the mean of the triple ECG measurements prior to drug administration. The derivation of the quantitative and qualitative ECG endpoints and their analyses will be described in the TSAP.

7.3.5 Interim analyses

Single rising dose parts under fasting and fed conditions

Preliminary safety analysis

No formal interim safety analysis is planned. However, if safety reasons require a preliminary safety analysis of ECG data, a part of the staff of the ECG laboratory may be unblinded. This part of the staff is strictly separated from the other part of the staff, which is involved with interval measurements and assessments of single ECGs (they keep blinded).

Preliminary PK analyses

A preliminary analysis of PK parameters (C_{max} and AUC_{0-24} of BI 705564) provided as individual values and gMeans at least of the first cohort per dose level, will be performed for each dose group before proceeding to the next higher level. Data from the first cohorts of the above mentioned dose levels will be sufficient as long as the data from at least 2 subjects on active are available.

In contrast to the final PK calculations, the preliminary analysis will be based on planned sampling times rather than on actual times, regardless of whether actual times were within the time windows or not. Therefore, minor deviations of preliminary and final results may occur.

The preliminary results will be distributed to the investigator and the trial team.

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

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

Food effect part

Preliminary PK analyses

A preliminary analysis of PK parameters (C_{max} and AUC_{0-24} of BI 705564), provided as individual values and gMeans, will be performed before proceeding to the next higher level. Data from at least 6 subjects are needed to be available before proceeding to the next higher level.

In contrast to the final PK calculations, the preliminary analysis will be based on planned sampling times rather than on actual times, regardless of whether actual times were within the time windows or not. Therefore, minor deviations of preliminary and final results may occur.

The preliminary results will be distributed to the investigator and the trial team.

No formal preliminary PK/PD report will be written.

Note: Due to global amendment No 4, only one dose level (10 mg) is given in the food effect part. Therefore, proceeding to the next higher level in the food effect part is not applicable.

7.3.6 Pharmacokinetic analyses

The pharmacokinetic parameters listed in Section 5.5.1 for drug BI 705564 will be calculated according to the BI SOP 'Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics' [001-MCS-36-472].

Subjects who are not included in the PKS (see Section 7.3.1) will be reported with their individual plasma (single rising dose parts under fasting and fed conditions, and food effect part) and urine (single rising dose parts, only) concentrations and individual pharmacokinetic parameters; however, they will not be included in descriptive statistics for plasma (single rising dose parts under fasting and fed conditions and food effect part) and urine (single rising dose parts, only) concentrations or pharmacokinetic parameters.

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

If a pre-dose concentration value is greater than 5% of C_{max}, the subject's pharmacokinetic data will be not included in any statistical evaluations, in accordance with international guidance. The individual pharmacokinetic parameters of such a subject will be calculated and listed separately. If a pre-dose concentration is above BLQ, but less than or equal to 5% of the subject's C_{max} value, the subject's data without any adjustments will be included in all pharmacokinetic measurements and calculations.

7.4 HANDLING OF MISSING DATA

7.4.1 Safety

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

7.4.2 Plasma/urine drug concentration - time profiles

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

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

7.4.3 Pharmacokinetic parameters

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

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

7.5 RANDOMISATION

Single rising dose parts under fasting and fed conditions

Each dose group will be divided into two cohorts. The subjects of the first cohort will not be randomised to maintain a treatment sequence of active-placebo-active-active due to safety reasons. In the second cohort of each dose level the subjects will be assigned to active or placebo treatment using a 3:1 allocation ratio.

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

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

Food effect part

Subjects will be randomised to one of the two treatment sequences in a 1:1 ratio. The block size will be documented in the CTR.

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

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

7.6 DETERMINATION OF SAMPLE SIZE

Single rising dose part under fasting conditions

It is planned to include a total of 48 subjects in this part of the 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 studies of the present type and is in general considered as sufficient for the exploratory evaluation of single dose safety and pharmacokinetics [R95-0013].

Single rising dose part under fed conditions

It is planned to include a total of 32 subjects in this part of the 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 studies of the present type and is in general considered as sufficient for the exploratory evaluation of single dose safety and pharmacokinetics [R95-0013].

Food effect

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

With a sample size of 12 subjects, the following precision of the ratio of gMeans (test/ reference) can be expected. Precision is defined as the ratio of upper to lower confidence interval limit. Note that the precision is independent of the actual ratio of gMeans.

For this trial, no information on intra-subject variability is available from previous trials. Therefore, Table 7.6: 1 provides an overview on the achievable precision for estimating the ratio of gMeans (test/ reference) for three different gCV. For illustrative purposes, the expected 90% confidence intervals with 95% coverage probability are displayed for different values of gMeans ratios T/R in the two-period two-sequence crossover design.

Table 7.6: 1 Precision that can be expected with 95% tolerance probability and illustrative two-sided 90% confidence intervals around the ratios of gMeans (T/R) for different gCVs in a 2x2 crossover trial in one dose group (N=12).

gCV [%]	Precision upper CL / relative BA estimate	Ratio [%]*	Lower CL [%]	Upper CL [%]
20	1.22	80	65.61	97.54
20	1.22	100	82.01	121.93
20	1.22	125	102.52	152.41
20	1.22	150	123.02	182.89
20	1.22	200	164.03	243.86
25	1.28	80	62.52	102.36
25	1.28	100	78.15	127.95
25	1.28	125	97.69	159.94
25	1.28	150	117.23	191.93
25	1.28	200	156.31	255.91
30	1.34	80	59.63	107.33
30	1.34	100	74.54	134.16
30	1.34	125	93.17	167.71
30	1.34	150	111.80	201.25
30	1.34	200	149.07	268.33

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

The calculation was performed as described by Julious [R11-5230] using R Version 3.2.2.

8. INFORMED CONSENT, DATA PROTECTION, TRIAL RECORDS

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

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

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

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

8.1 STUDY APPROVAL, SUBJECT INFORMATION, AND INFORMED CONSENT

This trial will be initiated only after all required legal documentation has been reviewed and approved by the respective Institutional Review Board (IRB) / Independent Ethics Committee (IEC) and competent authority (CA) according to national and international regulations. The same applies for the implementation of changes introduced by amendments.

Prior to a subject's participation in the trial, written informed consent must be obtained from each subject (or the subject's legally accepted representative) according to ICH GCP and to the regulatory and legal requirements of the participating country. Each signature must be personally dated by each signatory and the informed consent and any additional subject information form are to be retained by the investigator as part of the trial records. A copy of the signed and dated written informed consent and any additional subject information must be given to each subject or the subject's legally accepted representative.

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

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

8.2 DATA QUALITY ASSURANCE

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

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

8.3 RECORDS

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

8.3.1 Source documents

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

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

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

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

8.3.2 Direct access to source data and documents

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

8.3.3 Storage period of records

Trial site
The trial site must retain the source and essential documents (including ISF) according to the national or local requirements (whichever is longer) valid at the time of the end of the trial.

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

8.4 EXPEDITED REPORTING OF ADVERSE EVENTS

BI is responsible to fulfil their legal regulatory reporting obligation and in accordance to the requirements defined in this CTP.

8.5 STATEMENT OF CONFIDENTIALITY

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

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

8.6 COMPLETION OF TRIAL

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

9. REFERENCES

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10. APPENDICES

10.1 RECONSTITUTION INSTRUCTION(S)

10.1.1 Drug Supplies Overview

a) BI 705564 Powder for Oral Solution 20 mg (target solution concentration BI 705564: 0.25 mg/mL), provided in 100 mL amber glass bottles with plastic screw cap.

b) Solvent for Oral Solution 80 mL (HP-ß-Cyclodextrin 100 mg/mL) provided in 100 mL glass vials with flip-tear seal.

c) Empty appropriately labeled amber glass bottle, 100 mL with plastic screw-cap.

10.1.2 Required Equipment and Dosing aids - Overview

a) Mechanical (orbital) shaker for bottles (e.g. Bühler Typ KL2).

b) Dosing dispensers/syringes and bottle adapters.

For the withdrawal of respective volume aliquots from the final Oral Solution to be administered, amber BAXA/BAXTER ExactaMed Syringes should be used in a size as close as possible to the required dose volume. For this purpose, a range of syringe sizes from 1 mL up to 60 mL should be stocked at the trial site.

In order to ease the withdrawal of the oral solution from the glass bottles with the amber BAXA/BAXTER ExactaMed syringes, BAXA/BAXTER bottle adapters and dispenser tip caps should be used and stocked in the trial site, preferably BAXA/BAXTER Press-In Bottle Adaptors (PIBA™) or BAXA/BAXTER Adapta Cap Bottle Adapters (E-28 mm)

Possible BAXA Med Oral amber dispensers:

- BAXA/BAXTER ExactaMed amber oral dispenser 1 mL
- BAXA/BAXTER ExactaMed amber oral dispenser 3 mL
- BAXA/BAXTER ExactaMed amber oral dispenser 5 mL
- BAXA/BAXTER ExactaMed amber oral dispenser 10 mL
- BAXA/BAXTER ExactaMed amber oral dispenser 20 mL
- BAXA/BAXTER ExactaMed amber oral dispenser 35 mL
- BAXA/BAXTER ExactaMed amber oral dispenser 60 mL

Only CE certified syringes are to be used!

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

Number of global amendment		1
Date of CTP revision		13 APR 2017
EudraCT number		2017-000324-98
BI Trial number		1408-0001
BI Investigational Product(s)		BI 705564
Title of protocol		Safety, tolerability, pharmacokinetics and pharmacodynamics of single rising oral doses of BI 705564 (single-blind, partially randomised, placebo-controlled parallel group design) and food effect on a tablet formulation of BI 705564 (open-label, randomised, single-dose, two-period, two-sequence crossover design) in healthy male subjects
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		- Flow Chart - 5.5.2.3 - 5.6.2 - 6.1
Description of change		- Addition of explanatory footnote to “Day -3 to -1” safety laboratory in food effect part [Change in Flow Chart (2)]. - Correction of time window of “Day 6” biomarker blood withdrawal [Changes in Flow Chart (1) and in Section 6.1]. - Algorithm to stop further biomarker sampling in a dose group beyond 48 h was changed from “dose group” to “cohort” [Changes in

		footnote 14 of Flow Chart (1) and Section 5.6.2] - Tween is added to urine containers for urine sampling for pharmacokinetic analyses [Change in Section 5.5.2.3).
Rationale for change		- Explanatory footnote to "Day -3 to -1" safety laboratory in food effect part was added to align procedures with those of the single rising dose part. - Time window of "Day 6" biomarker blood withdrawal was corrected for logistical reasons. - Change from dose group to cohort (in the algorithm to stop further biomarker sampling) due to logistical reasons. - Tween is added to prevent adsorption of drug to the wall of the urine collection containers.

Number of global amendment		2
Date of CTP revision		03 MAY 2017
EudraCT number		2017-000324-98
BI Trial number		1408-0001
BI Investigational Product(s)		BI 705564
Title of protocol		Safety, tolerability, pharmacokinetics and pharmacodynamics of single rising oral doses of BI 705564 (single-blind, partially randomised, placebo-controlled parallel group design) and food effect on a tablet formulation of BI 705564 (open-label, randomised, single-dose, two-period, two-sequence crossover design) in healthy male subjects
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		5.5.2.3
Description of change		**10 mL** instead of 40 mL of 10% Tween 20 solution will be added to each 2 liter collection container prior to the start of urine sampling
Rationale for change		Change needed due to analytical issues during the course of method validation at

Number of global amendment		3
Date of CTP revision		08 AUG 2017
EudraCT number		2017-000324-98
BI Trial number		1408-0001
BI Investigational Product(s)		BI 705564
Title of protocol		Safety, tolerability, pharmacokinetics and pharmacodynamics of single rising oral doses of BI 705564 (single-blind, partially randomised, placebo-controlled parallel group design) and food effect on a tablet formulation of BI 705564 (open-label, randomised, single-dose, two-period, two-sequence crossover design) in healthy male subjects
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		- Clinical Trial Protocol (CTP) Synopsis - Flow Chart (Single Rising Dose [SRD] Part) - Section 2.1.4 - Section 2.1.5 - Section 3.1
Description of change		- Statements that food effect part will be performed after the single rising dose part were deleted (in CTP Synopsis, Section 2.1.4, Section 2.1.5, and Section 3.1)
Rationale for change		- For logistical reasons, the lower dose group of the food effect part (10 mg) will be pulled forward, without having terminated the SRD part. This is possible, as the necessary safety window, defined in Section 2.1.4 of this CTP,

		has been explored in the SRD part of this study.

Number of global amendment		4
Date of CTP revision		11 SEP 2017
EudraCT number		2017-000324-98
BI Trial number		1408-0001
BI Investigational Product(s)		BI 705564
Title of protocol		Safety, tolerability, pharmacokinetics and pharmacodynamics of single rising oral doses of BI 705564 (single-blind, partially randomised, placebo-controlled parallel group design) and food effect on a tablet formulation of BI 705564 (open-label, randomised, single-dose, two-period, two-sequence crossover design) in healthy male subjects
To be implemented only after approval of the IRB / IEC / Competent Authorities		☒
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		☐
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		☐
Section to be changed		- Synopsis - Flow Chart - Table of contents - Sections 1.2.1, 1.2.2, 1.2.3.2, 1.2.3.6, 1.2.4.1, and 1.2.5 - Sections 2.1, 2.1.2, 2.1.3, 2.1.4, 2.1.5, 2.2, 2.3.2.1, 2.3.2.5, and 2.3.2.7 - Sections 3, 3.1, 3.2, 3.3, 3.3.4.2, and 3.3.5 - Sections 4, 4.1.1, 4.1.2, 4.1.4, 4.1.5.1, 4.1.5.2, and 4.2.2.2 - Sections 5.2.1, 5.2.2.2, 5.2.3, 5.2.4.1, 5.5.1.1, 5.5.1.2, 5.5.1.3, 5.5.2.2, 5.5.2.3, 5.5.2.4, 5.6.1, and 5.6.2 - Sections 6.1 and 6.2.2 - Sections 7.1.1, 7.1.2, 7.1.3, 7.2, 7.3.1, 7.3.2, 7.3.3, 7.3.4, 7.3.5, 7.3.6, 7.3.7, 7.5, and 7.6

		- Section 9
Description of change		- Single rising dose part under fed conditions added, with single doses of 20 mg, 40 mg, 80 mg, and 160 mg BI 705564 or placebo, given following a high-fat, high-calorie breakfast. Design and study procedures in the single rising dose part under fed conditions are identical to the pre-existing single rising dose part under fasting conditions with the following exceptions: o Addition of high-fat, high-calorie breakfast prior to administration of BI 705564 o Modification of sampling for blood for o No stability samples will be taken o No samples for metabolite identification will be taken. o Safety laboratory at time point +4 h is not at fasting conditions (due to the breakfast taken before administration of BI 705564) - Up to 2 additional dose groups may be investigated in the single rising dose part under fed conditions. - No additional dose groups may be investigated in the single rising dose part under fasting conditions. - Number of subjects changed: Total entered number increased from 88 to 92; number in single rising dose part under fasting condition reduced from 64 to 48; number in food effect part reduced from 24 to 12; number of subjects in single rising dose part under fed conditions added as 32 subjects. Additional subjects can be included in single rising dose part under fed conditions (up to 16 additional subjects) in order to test up to 2 additional doses, provided the planned and approved highest dose will not be exceeded, i.e. the total number of subjects in the trial (all three parts together) may be higher than 92 but not higher than 108 subjects.

		- Test product BI 705564 as 100 mg tablet and corresponding placebo tablet are not applicable to the amended single rising dose part under fasting conditions. - In the single rising dose part under fasting conditions, doses 120 mg and 160 mg are not given (dose groups 7 and 8 in the single rising dose part under fasting conditions are deleted). - In the food effect part, only one dose (10 mg) is tested. The dose of 40 mg is not tested in the food effect part. - Flow Chart 3 added. - Minor editorial changes. - Update of IB reference to version 2. - Deletion of statement that doses will be increased with decreasing escalation factors. - Change of wording of primary objective in order to include both the single rising dose part under fasting and the part under fed conditions. - Change of risk minimization wording to explain that in the single rising dose part under fed conditions, escalation factors of 2 are chosen. - Addition of Section 7.3.3 to explain statistical comparison of PK data from single rising dose part fed and single rising dose part fasting. - Determination of sample size for single rising dose part under fasting conditions and for food effect part corrected to reflect the changes in subject numbers in the trial parts; determination of sample size for single rising dose part under fed conditions added. - - Drug test “M-10/14-PDT test” added.
Rationale for change		

		- Doses of 120 mg and 160 mg in the single rising dose part under fasting conditions are not justified, as no further increase of systemic plasma exposure parameters of BI 705564 is expected. - Additional dose groups are not applicable to the single rising dose part under fasting conditions, as this was not done in this part, and the single rising dose part under fasting conditions is completed. - The 40 mg food effect part is neither covered by available safety data from the single rising dose part under fasting conditions, nor is it required, due to addition of a single rising dose part under fed conditions.
		- New drug test added, because name of drug test has been changed (however, test remains identical; only change of name).

APPROVAL / SIGNATURE PAGE

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Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Author-Trial Clinical Monitor		13 Sep 2017 16:29 CEST
Author-Trial Statistician		13 Sep 2017 19:06 CEST
Approval-Therapeutic Area		13 Sep 2017 22:58 CEST
Verification-Paper Signature Completion		14 Sep 2017 11:14 CEST
Approval-Clinical Program		14 Sep 2017 12:08 CEST
Author-Trial Clinical Pharmacokineticist		18 Sep 2017 16:13 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed