Clinical Trial Protocol

	Document Number: c20427822-07
EudraCT No.:	2017-004446-15
BI Trial No.:	1416-0001
BI Investigational Product:	BI 730460
Title:	A partially randomised, single-blind, placebo-controlled trial to investigate safety, tolerability, pharmacokinetics and pharmacodynamics of single rising doses of BI 730460 administered as tablets to healthy subjects, and a randomised, open-label, single-dose, two-way cross-over bioavailability comparison of BI 730460 as tablet with and without food
Lay Title:	This study in healthy volunteers determines the amount of BI 730460 in the blood when taken as tablet. It looks at how different doses of BI 730460 are taken up in the body and how well they are tolerated. The study also tests how food influences the amount of BI 730460 in the blood.
Clinical Phase:	I
Trial Clinical Monitor:	Phone: Fax:
Principal Investigator:	Phone: Fax:
Status:	Final Protocol (Revised Protocol based on global amendment 1)
Version and Date:	Version: 7.0 Date: 24 January 2019

CLINICAL TRIAL PROTOCOL SYNOPSIS

Name of company: Boehringer Ingelheim		**Tabulated Trial Protocol**	
Name of finished product: Not applicable			
Name of active ingredient: BI 730460			
Protocol date: 04 July 2018	**Trial number:** 1416-0001		**Revision date:** 24 January 2019

Title of trial:	A partially randomised, single-blind, placebo-controlled trial to investigate safety, tolerability, pharmacokinetics and pharmacodynamics of single rising doses of BI 730460 administered as tablets to healthy subjects, and a randomised, open-label, single-dose, two-way cross-over bioavailability comparison of BI 730460 as tablet with and without food
Principal Investigator:	
Trial site:	
Clinical phase:	I
Objectives:	To investigate the safety, tolerability, pharmacokinetics (PK) including dose proportionality, and pharmacodynamics (PD) of BI 730460 (single rising dose [SRD] part), and the influence of food on the bioavailability of the tablet formulation (bioavailability [BA] part).
Methodology:	SRD part: Single rising dose, partially randomised, single-blind, placebo-controlled, parallel group design. BA part: Single dose, randomised, open-label, intra-individual two-way cross-over comparisons of the relative bioavailability of tablet fasted versus tablet fed
No. of subjects:	
total entered:	84[1]
each treatment:	SRD part: 72[1] (6 on active drug and 2 on placebo at each of 9 dose levels) BA part: 12 (all on active drug)
	[1]Additional subjects may be entered to allow testing of additional doses on the basis of experience gained during the trial conduct (e.g. preliminary PK data), provided the planned and approved highest dose will not be exceeded. Thus, the actual number of subjects entered may exceed 84 (72 in SRD part), but will not exceed 100 subjects (88 in SRD part) entered.
Diagnosis:	Not applicable
Main criteria for inclusion:	Healthy male subjects, age of 18 to 45 years (inclusive), body mass index (BMI) of 18.5 to 29.9 kg/m^2 (inclusive)

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Test products:	SRD part:	BI 730460 as film-coated tablet (2 mg, 25 mg, and 100 mg)
	BA part:	BI 730460 as film-coated tablet (25 mg) in treatment T
dose:	SRD part:	2, 8, 25, 50, 100, 200, 400, 600 and 800 mg
	BA part:	50 mg[2] [2] This dose is tentative and can be adapted based on the information obtained during the trial as long as this dose will not exceed the highest dose tested in the SRD part that has been found to have acceptable safety and tolerability. The BA part will only be started if in the SRD part a dose that is at least 4-times higher has been found to have acceptable safety and tolerability.
mode of admin.:	SRD part:	Oral with 240 mL of water in fasted state;
	BA part:	Oral with 240 mL of water in fed state (high-fat breakfast)
Comparator products:	SRD part:	Placebo tablets
	BA part:	BI 730460 as film-coated tablet (25 mg) in treatment R
dose:	SRD part:	Not applicable (matching placebo)
	BA part:	50 mg
mode of admin.:	SRD part:	Oral with 240 mL of water in fasted state
	BA part:	Oral with 240 mL of water in fasted state
Duration of treatment:	SRD part:	1 single dose
	BA part:	2 single doses separated by a washout period of at least 8 days
Criteria for safety:	Primary endpoint to assess safety and tolerability of BI 730460 is the number [N (%)] of subjects with drug-related adverse events.	
Criteria for pharmacokinetics:	Secondary endpoints: $AUC_{0-\infty}$ and C_{max} of BI 730460	
Criteria for pharmacodynamics:		

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Statistical methods:	Descriptive statistics will be calculated for all endpoints. SRD part: Dose proportionality will be explored using a regression model. A 95% confidence interval for the slope will be computed. BA part: Relative bioavailability will be estimated by the ratios of the geometric means (tablet fed / tablet fasted) for the secondary endpoints. Additionally, their two-sided 90% confidence intervals (CIs) will be provided. Since the main focus is on estimation and not testing, an ac eptance 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.		

FLOW CHART FOR THE SINGLE RISING DOSE 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 $_{blood}$ [10, 11]		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[14]		x	
2	-3 to -1	-72:00	08:00	Ambulatory visit	x[7]						x
	1	-2:00	06:00	Admission to trial site	x[2,5]				x[2]		x[2]
		-1:30	06:30					x[2,15]		x[2]	
		-1:15	06:45					x[2,15]			
		-1:00	07:00					x[2,15]			
		-0:30	07:30	Allocation to treatment[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			|		
		2:00	10:00	240 mL fluid intake		x		x[9]	|	x	x
		2:30	10:30			x			|		
		3:00	11:00			x		x[9]	|	x	x
		4:00	12:00	240 mL fluid intake, thereafter lunch[3]	x	x[8]		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	Dinner[3]		x		x[9]			
		12:00	20:00			x		x[9]		x	x
	2	24:00	08:00	Breakfast (voluntary)[3], discharge from trial site	x	x		x[9]		x	x
		34:00	18:00	Ambulatory visit		x		x[9]		x	x
	3	48:00	08:00	Ambulatory visit		x		x[9]		x	x
	4	72:00	08:00	Ambulatory visit	x	x				x	x
	5	96:00	08:00	Ambulatory visit		x				x	x
	8	168:00	08:00	Ambulatory visit	x[16]	x					x
4	9 to 13			End of trial (EOT) examination [4]	x			x[14]		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 (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 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 above.

7. Safety laboratory to be taken and to be medically evaluated within 3 days prior to administration of study drug; this ambulatory visit including the safety laboratory can be omitted, if the screening examination is performed on Days -3, -2 or -1.
8. Two blood sample for stability testing will be taken at this time point (refer to Section 5.5.2.4)
9. The ECG recording has to be performed as triplicate at this time point
10. Sampling times and periods may be adapted based on information obtained during the trial (e.g. preliminary PK data) including addition of samples and visits as long as the total blood volume taken does not exceed 500 mL per subject

13. Two blood samples should be collected: 4.3 mL in sodium citrate tubes and 4.5 mL in lithium heparin tubes.
14. The ECG will be recorded as single ECG at this time point
15. At baseline (i.e. Day 1, prior to drug administration) 3 triplicate ECGs are recorded within approximately one hour. The recordings of each first triplicate ECG should be separated by at least 15 minutes.
16. Only haematology with automatic WBC differential (refer to Table 5.2.3: 1) at this time point.

FLOW CHART FOR THE BIOAVAILABILITY 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[10]	x	
2/3*	-3 to -1	-72:00	08:00	Ambulatory visit	x[7]				x
	1	-2:00	06:00	Admission to trial site in visits 2 and 3, allocation to treatment in visit 2 only[2]	x[2,5]	x[2]	x[10,2]	x[2]	x[2]
		-0:30	07:30	Standardised Breakfast[9]					
		0:00	**08:00**	**Drug administration**					
		0:30	08:30			x			
		1:00	09:00			x			x
		1:30	09:30			x			
		2:00	10:00	240 mL fluid intake		x	x[10]	x	x
		2:30	10:30			x			
		3:00	11:00			x			
		4:00	12:00	240 mL fluid intake, thereafter lunch[3]		x	x[10]	x	x
		6:00	14:00			x			x
		8:00	16:00	Snack (voluntary)[3]		x			x
		10:00	18:00	Dinner[3]		x	x[10]	x	
		12:00	20:00			x			x
	2	24:00	08:00	Breakfast (voluntary)[3], discharge from trial site	x	x	x[10]	x	x
		34:00	18:00	Ambulatory visit		x			x
	3	48:00	08:00	Ambulatory visit		x	x[10]	x	x
	4	72:00	08:00	Ambulatory visit		x			x
	5	96:00	08:00	Ambulatory visit		x			x
	8	168:00	08:00	Ambulatory visit	x[11]	x			x
4	9 to 13			End of trial (EOT) examination[4]	x		x[10]	x	x

* Two identical treatment periods separated by a wash-out phase of at least 8 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 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 above.
7. Safety laboratory to be taken and to be medically evaluated within 3 days prior to each administration of study drug; this ambulatory visit including the safety laboratory can be omitted, if the screening examination is performed on Days -3, -2 or -1.

8. Sampling times and periods may be adapted based on information obtained during the trial (e.g. preliminary PK data) including addition of samples and visits as long as the total blood volume taken does not exceed 500 mL per subject
9. Standardised (high-fat, high-calorie) breakfast only in one treatment period under fed condition
10. The ECG will be recorded as single ECG at this time point. However, except for screening and EOT, the number of ECGs per time point may be increased to three ECGs based on the preliminary ECG results obtained during the SRD part of this trial.
11. Only haematology with, automatic WBC differential (refer to Table 5.2.3: 1) at this time point.

TABLE OF CONTENTS

ABBREVIATIONS

ADME	Absorption, distribution, metabolism, and excretion
AE	Adverse event
AESI	Adverse events of special interest
ANOVA	Analysis of variance
$AUC_{0-\infty}$	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity
BA	Bioavailability
BI	Boehringer Ingelheim
BLQ	Below limit of quantification
BMI	Body mass index (weight divided by height squared)
BP	Blood pressure
BW	Body Weight
CA	Competent authority
CI	Confidence interval
C_{max}	Maximum measured concentration of the analyte in plasma
CNS	Central nervous system
CRF	Case report form
CTP	Clinical trial protocol
CTR	Clinical trial report
CYP	Cytochrome P450
DG	Dose group
DILI	Drug induced liver injury
ECG	Electrocardiogram
EDTA	Ethylenediaminetetraacetic acid
EEG	Electroencephalograph
EOT	End of trial

FIM	First-in-man
gCV	Geometric coefficient of variation
HR	Heart rate
IC_{50}	50% inhibitory concentration
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ISF	Investigator site file
ITE	Indirect target engagement
LC-MS/MS	Liquid chromatography tandem mass spectrometry
MACS	Magnetic-activated cell sorting
MedDRA	Medical Dictionary for Regulatory Activities
mRNA	Messenger Ribonucleic Acid
NC	Not calculated
NOA	Not analysed
NOAEL	No observed adverse effect level
NOP	No peak detectable
NOR	No valid result
NOS	No sample available
PAD	Pharmacologically active dose
PCR	Polymerase chain reaction
PD	Pharmacodynamic(s)
PE	Polyethylene
PK	Pharmacokinetic(s)
PKS	Pharmacokinetic set
PP	Polypropylene
PR	Pulse rate
PUVA	Psoralen Ultraviolet A
QD	*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
REP	Residual effect period
RNA	Ribonucleic Acid
SAE	Serious adverse event
SCR	Screening
SOP(s)	Operating Procedure(s)
SRD	Single-rising dose
T	Test product or treatment
TDMAP	Trial Data Management and Analysis Plan
Th	T helper type
TMF	Trial master file
TSAP	Trial statistical analysis plan
ULN	Upper limit of normal
WOCBP	Women of childbearing potential

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

BI 730460 has not yet been tested in humans.

1.2 DRUG PROFILE

1.2.1 Nonclinical pharmacology

BI 730460 was profiled in cellular assays in primary human cells central to the pathogenesis BI 730460 provided consistent potency across all stimuli, cell types, and species tested, including in whole blood conditions. BI 730460 provided substantial inhibition of disease-relevant biomarker and histology reads in mechanistic pre-clinical *in vivo* mouse models of inflammation.

BI 730460 showed good off-target selectivity in that it exhibited

No other off-target activities were detected.

General and safety pharmacology studies have been conducted to address the core battery of CNS, cardiovascular, respiratory, renal, and liver function. The results of BI 730460 general and safety pharmacology studies demonstrated an acceptable profile for Phase I clinical trials in healthy volunteers.

the proarrhythmic risk of BI 730460 at clinical dose levels is low.

1.2.2 Toxicology

The toxicity profile of BI 730460 has been assessed in a comprehensive set of *in vitro* and *in vivo* safety pharmacology studies, genetic toxicology studies, and repeat dose studies in the rat and dog. Pivotal studies were performed in compliance with GLP. The nonclinical safety package supports administration of BI 730460 to men for up to 4 weeks duration.

General Tolerability

In repeat dose toxicity studies in rats, doses of in 20 animals/sex resulted in mortality with body weight losses in 1 male rate and 2 female rats, and in a dose reduction to 300 mg/kg/day on dosing day 7. Reduced doses of were then well tolerated. The NOAEL of a 4-week dosing period was considered to be males and females combined).

In dogs doses up to for 4 weeks were well tolerated in repeat dose toxicity studies.

Clinical pathology findings

These findings were considered non-adverse based on the magnitude of the changes and since they were not associated with tissue inflammation.

Histopathology findings

This finding was considered a non-adverse adaptive response to hepatic microsomal enzyme induction due to lack of hepatocellular necrosis or degeneration. It was associated with decreases in plasma exposures upon repeat dosing.

There was no evidence of vascular injury, erosions or ulcers in the oesophagus, stomach or larynx after the 4-week recovery period in dogs so these were all considered to be reversible findings [n00255297].

There were no vascular findings in the two-week and four-week rat studies with BI 730460, suggesting that this might be a dog-specific phenomenon that is of limited relevance to humans.

Organ System Effects

The immunotoxic potential of BI 730460 was evaluated in 2- and 4-week rat and dog studies by assessing haematology, peripheral blood immunophenotyping and microscopic evaluation of lymphoid tissues.

Genetic Toxicology

The genotoxic potential of BI 730460 was assessed in bacterial and mammalian systems. The results of the *in vitro* and *in vivo* genetic toxicology studies showed that BI 730460 was free of any genotoxic potential [c19477316].

Photosafety

In summary, non-clinical safety data of BI 730460 support clinical Phase I trials in men with daily oral administration for up to 28 days. Human exposure up to those achieved at the NOAEL of

is considered safe.

1.2.3 Nonclinical pharmacokinetics

1.2.4 Prediction of human pharmacokinetics

The compound showed equivalent *in vitro* potency in human, mouse and rat.

1.2.5 Clinical experience in humans

This is the first-in-man study. Clinical data are not available up to date for BI 730460.

To date preliminary results are available at BI from a similar small molecule

This study was completed on 15 August 2017 and consisted of 2 parts. The SRD part was a partially randomised, single-blind, placebo-controlled trial to investigate safety, tolerability, pharmacokinetics and pharmacodynamics of single rising doses of administered as oral solution (2 mg and 8 mg) and film-coated tablets (doses of 25 mg, 50 mg, 100 mg, 200 mg, 400 mg and 800 mg) to 72 healthy male volunteers. The BA part was a randomised, open label, single-dose, three-way crossover bioavailability comparison of 25 mg in 12 healthy male volunteers to explore the relative bioavailability of tablet fasted versus oral solution fasted and the influence of food on the bioavailability of tablet fasted versus tablet fed.

Safety evaluations included physical examination, vital signs, ECG, laboratory tests, and adverse events (AEs) and demonstrated that was safe and well tolerated up to the 800 mg dose. AEs, which generally reflected commonly-occurring events of short duration, and were mostly mild or moderate in severity, were distributed without discernable trend among recipients of placebo and rising dose levels of . No serious AEs were reported.

Following administration of the tablet, was absorbed with a T_{max} between about 2 to 3 hours. Thereafter, plasma concentrations decreased rapidly in a mono- or biphasic manner with an estimated terminal half-life ($t_{1/2}$) ranging from approximately 20 to 27 hours. The preliminary PK data suggest that the exposure (AUC_{0-24}) to increased in a dose-proportional manner for the oral solution between 2 and 8 mg and for the tablet up to 50 mg, and thereafter increased in a less-than-dose-proportional manner, with approximately 1.5-fold increase in exposure with each 2-fold increase in dose up to 800 mg. Comparing the exposures of tablets in the fasted state, it can be noted that an 8-fold increase in dose from 25 to 200 mg and a 16-fold increase from 25 to 400 mg only led to AUC increases of 4.4-fold and 6.6-fold, respectively. After single dosing, the steady-state trough level (C_{24}) of 140 nM for the efficacy of was only exceeded in dose groups ≥ 100 mg instead of at 25 mg as originally predicted.

Preliminary data of the BA part show an increase in exposure in the fed condition compared to the fasted condition suggesting a positive food effect for

Also other pharmaceutical companies have already tested compounds of this mode of action in Phase I or Phase II trials in the past (e.g. ClinicalTrials.gov Identifiers and). In the US, safety, tolerability, pharmacokinetics and pharmacodynamics of an investigational was investigated in two randomised, double-blind, placebo-controlled clinical trials in healthy volunteers. The first study was a SRD trial (7 dose levels) in 53 subjects. The second study was a multiple rising dose trial (5 dose levels) with once daily treatment for 10 days in 40 subjects. For these trials, final results are yet to be published and only an abstract is available from the homepage of the Journal of Immunology (http://www.jimmunol.org/ content/196/1_Supplement/71.4.abstract) [2016, vol. 196 (1 Supplement) 71.4]. According to this abstract, the investigational compound was shown to be safe and generally well tolerated at all dose levels tested.

1.2.6 Drug product

Please refer to Section 4.1. For a more detailed description of the BI 730460 profile, please refer to the current Investigator's Brochure (IB) [c19477316].

2. RATIONALE, OBJECTIVES, AND BENEFIT - RISK ASSESSMENT

2.1 RATIONALE FOR PERFORMING THE TRIAL

As a transition from preclinical investigations to clinical development in this first-in-man trial, safety, tolerability, and pharmacokinetics of BI 730460 will be assessed in healthy male volunteers using single rising oral doses in order to provide the basis for a potential ongoing clinical development of BI 730460 in the indication of psoriasis.

Healthy male subjects aged 18 - 45 years will be recruited for this study. They provide a relatively stable physiological, biochemical and hormonal basis (steady state) for studying drug effects, they show no disease-related variation and they are not taking concomitant medication.

In the single rising dose (SRD) part, within each dose group, all actively treated individuals will receive the same BI 730460 dose. The next higher dose will only be administered (to the next group) if the treatment in the preceding dose groups was safe and showed acceptable tolerability.

In the bioavailability (BA) part, BI 730460 will be administered to the subjects in a two-way-crossover fashion to gain information about the effect of food on BI 730460 to support upcoming clinical efficacy studies.

Dose selection

It is intended to investigate the following dose levels of BI 730460 in the SRD part of this trial: 2 mg, 8 mg, 25 mg, 50 mg, 100 mg, 200 mg, 400 mg, 600 mg, and 800 mg. The background for this dose selection is described in the following paragraphs.

Starting dose in this trial

It is best practice to use different methods for dose selection and to take a starting dose at the lower end of the dose range if different methods give different estimates (err on the side of caution).

Applying the respective calculation as given in the US FDA Guidance for Industry 'Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers' and assuming a no adverse effect level (NOAEL) of
a maximum recommended starting dose (MRSD) as high as 17 mg could be selected based on the toxicology data. In addition the PAD (pharmacologically active dose) approach should be used to support the selection of a safe starting dose. The lowest therapeutic dose of BI 730460 is predicted to be
and was derived from the pharmacodynamic minicircle model. Considering potential but easy monitorable and reversible effects of BI 730460 on blood pressure, it is preferable to apply a safety factor of 10 to the predicted lowest PAD, which would translate to a starting dose of 2 mg (for details see Section 5.3.8.2 of the IB).

Finally, another commonly used NOAEL-based approach, following ICH guidance M3 (R2), is to use a fraction of the NOAEL, e.g. 1/50 or 1/100 (R09-1400).

Taken together different approaches give a starting dose in the range of 2 mg , and 2 mg is finally considered as an appropriate and safe starting dose at the lower end of this range. The 2 mg dose is

and is not expected to trigger any relevant or unacceptable biological activity.

Maximum dose and dose escalation

Although, as stated above, a minimum daily dose of about is predicted to achieve therapeutic systemic exposure of BI 730460 at steady state for several reasons it is planned to explore higher doses / exposures. Subsequent clinical studies in patients might show that required therapeutic doses and exposures are significantly higher than predicted. Also, higher doses / exposures might be required for more severe disease states, for induction vs. maintenance treatment, and for other immunological indications. So while higher doses and exposures might still be well tolerated they provide a larger magnitude of therapeutic effects. Further, testing of doses higher than is also reasonable to compensate for any bioavailability and half-life lower/shorter than expected. If, for example, bioavailability was significantly less than the predicted (see section 1.2.4), the therapeutic dose could eventually turn out to be several fold higher than currently predicted (e.g. 4-fold higher as observed for BI 730357, refer to 1.2.5). And eventually, even if the therapeutic dose turns out to be as low , higher than therapeutic doses / exposures are typically explored in the well-controlled clinical environment of first-in-man (FIM) studies if supported by non-clinical safety data, in order to provide a sufficient safety margin for subsequent studies (e.g. studies with multiple dose and accumulation, drug-drug-interaction studies, studies in patients with impaired excretion function, etc.), where substantial increases in exposure may be seen.

For this study therefore 800 mg has been selected as maximum dose, but this dose will only be administered if predicted geometric mean values of C_{max} or geometric mean AUC_{0-24} do not exceed the exposures limits defined below – otherwise dose escalation will be stopped at lower doses. Based on the preclinical safety profile of BI 730460 these exposure limits are anticipated to be safe and well tolerated.

The maximum human exposure to BI 730460 in this trial will be limited to 2,900 nM for C_{max} and 49,000 nM*h for AUC_{0-24}.

The cause of death in these animals could not be determined, but due to the occurrence in only the highest dose group, the mortality was attributed to BI 730460 [c19477316].

To prevent that an exposure beyond the above predetermined safety margins will be achieved in this trial, preliminary PK data of preceding dose groups will be provided to estimate the expected exposure of the next dose group (see Section 7.3.4). The next higher dose level will only be administered, if predicted geometric mean values of C_{max} and AUC_{0-24} do not exceed 2,900 nM and 49,000 nM*h, the maximum acceptable exposure in this clinical trial.

In order to cover the anticipated dose range, a stepwise and careful dose increase up to a maximum dose of 800 mg has been selected for this trial. The escalation schedule has been chosen in a way that a decreasing escalation factor will be applied, for example, with a factor of 2 for the predicted therapeutic range and higher dose levels and with a factor of 1.5 for the last dose. This dose escalation is considered to be adequate and safe, particularly when the selected exposure safety margins are taken into consideration.

2.2 TRIAL OBJECTIVES

The primary objective of the SRD part (trial part 1) is to investigate the safety and tolerability of BI 730460 in healthy subjects following oral administration of single rising doses. The secondary objective is the exploration of the pharmacokinetics (PK) including dose proportionality, and pharmacodynamics of BI 730460 after single dosing.

The objective of the BA part (trial part 2) will be to explore the influence of food on the bioavailability of tablet fasted versus tablet fed.

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

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 a new orally available drug, which might improve the therapy in patients with psoriasis. The subjects are exposed to the risks of the study procedures and the risks related to the exposure to the trial medication.

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 paraesthesia, reduced sensibility, and/or pain for an indefinite period. The 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 (500 mL). No health-related risk to healthy subjects is expected from this blood withdrawal.

Drug-related risks and safety measures

As the nature of the target and the mechanism of action of BI 730460 are well understood, comparable compounds have been tested by BI and other companies before, and the animal models are believed to be predictive for the effects in humans, BI 730460 is not seen as a high risk compound.

The pharmacological effects of BI 730460 are dose dependent and no evidence for prolonged or irreversible effects has been observed. Exposures of BI 739460 up to 2,900 nM for C_{max} and 49,000 nM*h for AUC_{0-24} are supported by preclinical safety data.

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

- Careful dose selection as described in Section 2.1. In addition, dose escalation will be shallow and both, starting dose and maximum dose/exposure have ample safety margins with respect to the preclinical findings. Finally, dose selection was based on a sound preclinical package including 4 week toxicological studies (not only 2 weeks).
- Preliminary measurement of BI 730460 plasma concentrations and preliminary determination of PK parameters (C_{max}, AUC_{0-24} see Section 7.3.4). For precautionary reasons, drug plasma concentrations of healthy volunteers in this trial should not exceed the geometric mean C_{max} of 2,900 nM or geometric mean AUC_{0-24} of 49,000 nM*h and will be considered as a preliminary threshold (see Section 2.1). Further dose progression would only be allowed after a safety interim analysis and filing and approval of a substantial CTP amendment.
- An extensive safety laboratory will be performed including differentiation of lymphocyte subtypes (see Section 5.2.3).
- For safety reasons, during the single rising dose part 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). These two cohorts will be separated by at least 48 hours (between 1st subject of each cohort), which based on an anticipated half-life of BI 730460 of approximately 14 hours is expected to cover the period of highest risk / peak effect. The first cohort will be dosed in a single blinded, fixed sequence fashion (active - placebo - active - active) and the drug administration will be separated by at least 10 min between the first and second subject, and by at least 3 hours between the first and third subject. This design ensures that between first and second active dose of each dose level there is a time interval of at least 3 hours, which is expected to be sufficient to detect relevant acute effects of BI 730460. If BI 730460 was safe and well tolerated during these initial administrations, the remaining subjects of the respective dose level could be dosed as close as 10 minutes apart.

- A thorough ECG monitoring including continuous ECG measurement over 4 hours post dose to cover the anticipated period of highest drug exposure and additional repeated 12-lead ECGs over 48 hours following drug administration. Dose escalation would be stopped as soon as at least 2 subjects at one dose level showed relevant QT prolongation (see Section 3.3.4.2 for details).
- Although no clinically relevant hypotension is expected at the exposures anticipated in this trial (see Section 1.2.1), nevertheless, blood pressure and heart rate will be closely monitored for potential hemodynamic effects.
- The subjects will stay at the trial site (BI Human Pharmacology Centre) for at least 24 hours after study drug administration at each dose level. Based on an anticipated half-life BI 730460 of approximately this is expected to cover the period of highest risk / peak effect.
- During in house-confinement the subjects will be under medical observation and thoroughly monitored for both expected and unexpected adverse events.
- Only if the respective dose of BI 730460 was safe and showed acceptable tolerability and if no stopping criterion was met (refer to Section 3.3.4.2), the next higher dose will be given at least 6 days later (referring to the 1st subject of each dose group).
- The next higher dose will be given after careful assessment of all available safety data by the Principal Investigator (or authorised deputy) and the sponsor (see Section 3.1)
- The BA part will only be started if in the SRD part a dose that is at least 4-fold higher has shown acceptable safety and tolerability.
- As reproductive toxicity studies have not yet been conducted, women of child-bearing potential will not be enrolled in this study.
- subjects will be advised to apply protection measures such as sunscreen, and solarium radiation or treatment with ultraviolet light (e.g. PUVA) or medication with known phototoxicity potential (e.g. doxycycline) are prohibited during this clinical trial within 8 days after administration of trial medication.

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, adverse events of special interest.

In summary, although not tested in humans to date, BI 730460 has the potential to become an oral treatment for signs and symptoms of psoriasis. Based upon preclinical data for BI 730460 and clinical information from competitor compounds as well as the implemented safety measures described above, healthy subjects will not be exposed to undue risks in relation to the important information expected from this trial as a basis for further clinical development of this compound. Healthy volunteers are not expected to have any direct benefit from participation in this FIM clinical trial with BI 730460, as is the usual case in such Phase I trials. Considering the medical need of the development of a safer and more

effective treatment for patients with psoriasis, the Sponsor considers that the benefit outweighs the potential risks and justifies exposure of healthy human volunteers.

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

This first-in-man trial will be conducted in healthy male volunteers at a single centre.

A total of 84 healthy male subjects is planned to participate in 9 sequential groups of 8 subjects each during the SRD part, and in a group of 12 subjects during the BA part. However, additional subjects may be entered to allow testing of additional doses on the basis of experience gained during trial conduct (e.g. preliminary PK data), provided the planned and approved highest dose of the SRD part will not be exceeded. Thus, the actual number of subjects entered may exceed 84, but will not exceed 100 subjects entered. If required for the further evaluation of pharmacokinetics such changes may be implemented via non-substantial CTP Amendments. However, the addition of further dose groups for the evaluation of safety findings is subject to a substantial CTP Amendment requiring approval. Within each dose group of the SRD part, 6 subjects will receive the active drug and 2 will receive placebo. In the BA part, 12 subjects will receive the active drug. The dose groups to be evaluated are outlined in Table 3.1: 1 below.

Table 3.1: 1 Planned dose groups

Trial part	SRD									BA
Dose Group (DG)	1	2	3	4	5	6	7	8	9	
Dose (mg)	2	8	25	50	100	200	400	600	800	2x 50
Number of subjects	8	8	8	8	8	8	8	8	8	12
Subjects receiving placebo	2	2	2	2	2	2	2	2	2	0
Subjects receiving active drug	6	6	6	6	6	6	6	6	6	12
Subject / medication number[1]										

1 Respective reserve subject numbers will be provided. In the SRD part, the medication number matches the subject number. In the BA part, the subject numbers are assigned to the medication numbers and in ascending order.

SRD part

The first part of the trial, the SRD part, is designed as single-blind, partially randomised, and placebo-controlled within parallel dose groups. Only one dose is tested within each dose group. The groups will be treated consecutively in ascending order of doses. Each group is divided into 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 10 min later by the second subject (placebo) followed at least 2 h 50 min later by the third subject (active) followed at least 10 min later by the fourth subject (active).

If BI 730460 treatment is safe and showed acceptable tolerability in the first cohort, the subjects in the second cohort will be treated not earlier than 2 days later in a single-blind

randomised manner. In the second cohort, a time interval of at least 10 min will be maintained between each administration of the trial drug to the individual subjects. A time interval of at least 6 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 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 (refer to Section 3.3.4.2).

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

Although no formal Safety Review meeting will take place within a given dose group, safety will be continuously monitored during this trial, and an individual will only be dosed in the absence of any safety concern (i.e. no dose-limiting events occurred) and if none of the pre-specified trial-specific stopping criteria have been met (refer to Section 3.3.4.2).

The minimum data set for the Safety Review consists of the following data:

- AEs in the current and preceding dose groups up to at least 48h post dosing from at least 4 subjects on active drug per dose group, including clinically relevant findings from ancillary safety testing listed below (Note: AEs may be ongoing at the time of Safety Reviews and AE information may be subject to change prior to Database Lock)
- Results from 12-lead EGG and continuous ECG monitoring in the current and preceding dose groups and from at least 4 subjects on active drug per dose group up to at least 48h post dosing.
- Vital signs in the current and preceding dose groups and from at least 4 subjects on active drug per dose group up to at least 48h post dosing.
- Clinical laboratory tests in the current and preceding dose groups and from at least 4 subjects on active drug per dose group up to at least 24h post dosing.
- Preliminary PK data for selected time as per Section 7.3.4.
- 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.

BA part

The BA part will be performed in a randomised, open-label, single dose, two-way crossover fashion. Subjects will be administered BI 730460 as tablet in a fasting state (reference treatment R) and as tablet after a standardised high-fat breakfast (test treatment T). The two treatments will be separated by a washout period of at least 8 days between study drug administrations. Subjects will be allocated randomly to one of the two treatment sequences: R/T, T/R.

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

3.1.1 Administrative structure of the trial

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

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

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

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

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 .

The analyses of BI 730460 concentrations in plasma and urine will be performed under the responsibility of Drug Metabolism and Pharmacokinetics, BI Pharma GmbH & Co. KG, Biberach, Germany at a suitable contract research organization (CRO).

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

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

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

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

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

For single-rising dose trials, the design described in Section 3.1 is viewed favourable under the provision not to expose the subjects involved to undue risks since the main study objective is to investigate safety and tolerability of BI 730460 and the risk to subjects will be minimized by studying sequentially ascending doses. For safety reasons the first cohort of each dose level will be treated in a fixed treatment sequence (Active-Placebo-Active-Active). The dose level being investigated at any time will be known to subjects, but single-blind conditions regarding each subject's treatment (active or placebo) will be maintained for both cohorts of each dose level.

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 and tolerability. Each dose group consists of 8 subjects with 6 on active treatment, and 2 on placebo. The placebo control group includes all subjects of all dose groups treated with placebo. 6 subjects per active treatment group are in general considered as sufficient for the exploratory evaluation of pharmacokinetics.

For the BA part comparing bioavailability of BI 730460 following administration as tablet in the fasted state versus tablet under fed conditions, the crossover design is viewed favourable due to its efficiency: since each subject serves as his own control, the comparison between the treatments is based on a comparison within subjects rather than between subjects. Thus the inter-subject variability is removed from the comparison between treatments [R94-1529]. Blinding is not possible because the treatments are distinguishable.

3.3 SELECTION OF TRIAL POPULATION

It is planned that 84 healthy male will enter the study. The actual number of subjects entered may exceed the total of 84 if additional intermediate doses will be tested (see Section 3.1). Subjects will be recruited from the volunteers' pool of the trial site.

Only male subjects will be included into the study because hitherto no data on reproductive toxicology are available. With respect to the embryo-fetal risk coming from the treatment of male subjects with BI 730460, where it is theoretically possible that relevant exposure to BI 730460 may be achieved in women of childbearing potential (WOCBP) from exposure to seminal fluid, male contraception (condom or abstinence) should be used in order to avoid exposure of an existing embryo/fetus [R16-0373] (see 3.3.3, exclusion criterion 23).

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

3.3.1 Main diagnosis for study entry

The study will be performed in healthy subjects.

3.3.2 Inclusion criteria

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

1. Healthy male subjects according to the assessment of the investigator, based on a complete medical history including a physical examination, vital signs (BP, PR), 12-lead ECG, and clinical laboratory tests
2. Age of 18 to 45 years (incl.)
3. BMI of 18.5 to 29.9 kg/m^2 (incl.)
4. Signed and dated written informed consent prior to admission to the study in accordance with GCP and local legislation

3.3.3 Exclusion criteria

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

1. Any finding in the medical examination (including BP, PR or ECG) 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 for males)
16. Drug abuse or positive drug screening
17. Blood donation of more than 100 mL within 30 days prior to administration of trial medication or intended donation during the trial
18. Intention to perform excessive physical activities within one week prior to administration of trial medication or during the trial
19. Inability to comply with dietary regimen of trial site
20. A marked baseline prolongation of QT/QTc interval (such as QTc intervals that are repeatedly greater than 450 ms in males) 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. ALT (alanine transaminase) or AST (aspartate transaminase) or GGT (gammaglutamyl transferase) or serum creatinine exceeds the upper limit of normal (ULN) at screening

For study restrictions, refer to Section 4.2.2.

3.3.4 Removal of subjects from therapy or assessments

3.3.4.1 Removal of individual subjects

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

1. The subject withdraws consent for trial treatment or trial participation, without the need to justify the decision
2. The subject needs to take concomitant drugs that interfere with the investigational product or other trial medication
3. The subject is no longer able to participate for other medical reasons (such as surgery, adverse events (AEs), or diseases)
4. 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 or hypertension, or of clinically relevant changes in ECG requiring intervention.

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.
6. The subject experiences a serious adverse event
7. For BA part only: The subject experiences a drug-related AE of severe intensity

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 CRFs. If the discontinuation occurs before the end of the REP (see Section 5.2.2.2), the discontinued subject should if possible be questioned for AEs and concomitant therapies at or after the end of the REP in order to ascertain collection of AEs and concomitant therapies throughout the REP, if not contrary to any consent withdrawal of the subject. These discontinuations will be discussed in the CTR.

3.3.4.2 Discontinuation of the trial by the sponsor

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

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

in connection with absolute QT or QTc greater than 500 ms, as confirmed by a repeat ECG recording.

6. Dose escalation will be stopped, if the C_{max} or AUC_{0-24} of at least 1 subject of one dose group increases above the following exposure thresholds or if the estimated gMean exposure is expected to exceed a C_{max} of 2,900 nM or an AUC_{0-24} of 49,000 nM*h. Estimation will be done based on preliminary PK results of preceding dose groups (see Section 2.1).
7. Occurrence of severe non-serious adverse events considered as drug-related by the investigator in 2 subjects of the same cohort (4 subjects), or 2 subjects of the same dose group (8 subjects), or 2 subjects of the BA group (12 subjects)

3.3.5 Replacement of subjects

In case that there are less than 4 subjects on active per dose level in the SRD part or less than 9 subjects in the BA 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 possessing the same treatment, as the subject replaces.

4. TREATMENTS

4.1 TREATMENTS TO BE ADMINISTERED

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

4.1.1 Identity of BI investigational product and comparator products

SRD part

The characteristics of the test product are:

Substance:	BI 730460
Pharmaceutical formulation:	Film-coated tablet
Source:	BI Pharma GmbH & Co. KG
Unit strength:	2 mg
Posology:	1-0-0 (DG 1), 4-0-0 (DG 2)
Route of administration:	oral
Duration of use:	Single dose

Substance:	BI 730460
Pharmaceutical formulation:	Film-coated tablet
Source:	BI Pharma GmbH & Co. KG
Unit strength:	25 mg
Posology:	1-0-0 (DG 3), 2-0-0 (DG 4)
Route of administration:	oral
Duration of use:	Single dose

Substance:	BI 730460
Pharmaceutical formulation:	Film-coated tablet
Source:	BI Pharma GmbH & Co. KG
Unit strength:	100 mg
Posology:	1-0-0 (DG 5), 2-0-0 (DG 6), 4-0-0 (DG 7), 6-0-0 (DG 8) or 8-0-0 (DG 9)
Route of administration:	oral
Duration of use:	Single dose

The characteristics of the reference product (placebo) are:

Substance:	Placebo matching in size and weight to 2 mg tablet
Pharmaceutical formulation:	Film-coated tablets
Source:	BI Pharma GmbH & Co. KG
Unit strength:	Not applicable
Posology:	1-0-0 (DG 1), 4-0-0 (DG 2)
Route of administration:	oral
Duration of use:	Single dose

Substance:	Placebo matching in size and weight to 25 mg tablet
Pharmaceutical formulation:	Film-coated tablets
Source:	BI Pharma GmbH & Co. KG
Unit strength:	Not applicable
Posology:	1-0-0 (DG 3), 2-0-0 (DG 4)
Route of administration:	oral
Duration of use:	Single dose

Substance:	Placebo matching in size and weight to 100 mg tablet
Pharmaceutical formulation:	Film-coated tablets
Source:	BI Pharma GmbH & Co. KG
Unit strength:	Not applicable
Posology:	1-0-0 (DG 5), 2-0-0 (DG 6), 4-0-0 (DG 7), 6-0-0 (DG 8) or 8-0-0 (DG 9)
Route of administration:	oral
Duration of use:	Single dose

BA part

The characteristics of test product T and reference product Rare:

Substance:	BI 730460
Pharmaceutical formulation:	Film-coated tablet
Source:	BI Pharma GmbH & Co. KG
Unit strength:	25 mg
Posology:	2-0-0
Route of administration:	oral
Duration of use:	Single dose

4.1.2 Method of assigning subjects to treatment groups

Prior to the screening visit, subjects of the SRD part will be contacted in writing and informed about the planned visit dates. The subjects willing to participate will be recruited to dose groups according to their temporal availability. As soon as enough subjects have been allocated to 1 of the 18 dose cohorts (2 cohorts per dose group), the following subjects will be allocated to one of the other dose cohorts. Therefore, the allocation of subjects to dose cohorts is not influenced by trial personnel, but only by the subjects' temporal availability. As the study includes healthy subjects from a homogenous population, relevant imbalances between the dose groups are not expected.

The randomisation list with study subject numbers and allocated treatments (SRD part) or treatment sequences (BA part) will be provided to the trial site in advance. In both parts of the trial, 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

For the SRD part, oral doses in the range of 2 mg to 800 mg have been selected in order to assess the safety and tolerability of BI 730460 in healthy male volunteers, and to investigate the PK of this novel . The selected doses cover a safe starting dose in the sub-therapeutic range, the estimated therapeutic range and potentially supra-therapeutic doses within the levels determined by toxicological investigations (see Section 1.2 for details).

The intra-individual comparison of the BA part investigating the relative bioavailability of tablet fasted versus tablet fed are planned to be conducted with a dose of 50 mg as it is assumed that this dose covers the therapeutic range and might be used in the subsequent clinical development.

4.1.4 Drug assignment and administration of doses for each subject

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

Table 4.1.4: 1 BI 730460 and placebo treatments for the SRD part

Dose group	Substance	Pharmaceutical form	Unit strength	Number of units per administration	Total dose
1	BI 730460	film-coated tablet	2 mg	1 tablet	2 mg
2	BI 730460	film-coated tablet	2 mg	4 tablets	8 mg
3	BI 730460	film-coated tablet	25 mg	1 tablet	25 mg
4	BI 730460	film-coated tablet	25 mg	2 tablets	50 mg
5	BI 730460	film-coated tablet	100 mg	1 tablet	100 mg
6	BI 730460	film-coated tablet	100 mg	2 tablets	200 mg
7	BI 730460	film-coated tablet	100 mg	4 tablets	400 mg
8	BI 730460	film-coated tablet	100 mg	6 tablets	600 mg
9	BI 730460	film-coated table	100 mg	8 tablets	800 mg
1-9	Placebo*	film-coated tablet	--	identical to active treatment	--

* Subjects receiving placebo are equally distributed across dose groups

Table 4.1.4: 2 BI 730460 film-tablets for the BA part

Treatment	Substance	Pharmaceutical form	Unit strength	Number of units per administration	Total Dose
T (tablet fed)	BI 730460	film-coated tablet	25 mg	2 tablets	50 mg
R (tablet fasted)	BI 730460	film-coated tablet	25 mg	2 tablets	50 mg

The Investigator can decide at any time to discontinue dosing or to decrease the dose escalation by adding intermediate doses in case of intolerability or due to safety concerns.

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 in the morning of Day 1. The so-called four-eye principle (two-person rule) should be applied for administration of trial medication and – if applicable – its preparation (e.g. reconstitution), if correct dosage cannot be ensured otherwise. Administration will be performed following an overnight fast, which is to start no later than 10 h before the scheduled dosing.

In treatment T (tablet fed) of the BA part, a high-fat, high-calorie meal will be served 30 min before drug administration. The meal must be completely consumed prior to drug administration. The composition of the standardised 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
Sum[1]	984

[1] 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 h following drug administration. During the first 4 hours after drug administration subjects of the SRD part will be confined to bed with a bed inclination angle of at least 45 degrees unless lower or supine positioning is required for trial-related measurements (e.g. recording of 12-lead ECG). During the first 4 hours after drug administration subjects of the BA part will only be allowed to lie down if supine positioning is required for trial-related measurements (e.g. recording of 12-lead ECG). 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

In the present trial, treatments of the SRD part will be blinded to subjects only. With the rising dose design, single-blind conditions regarding the subjects' treatment (active or placebo) are maintained within each dose group, however the current dose level will be known to subjects and Investigators. Treatments of the BA part will be open-label.

The database of this trial will be handled open-label, because no bias with regard to data cleaning of safety measures is expected. This is considered acceptable because the potential for bias seems to be low and does not outweigh practical considerations. The bioanalyst will be blinded for the BA part only.

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

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 time the 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.

4.1.5.2 Procedures for emergency unblinding

As this trial will be conducted open-label, the treatment information will be known. Therefore, no emergency envelopes will be provided.

4.1.6 Packaging, labelling, and re-supply

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

The clinical trial supply consists of containers holding the trial medication which are labelled with trial identification. The required information according to the German Drug Law as well as Annex 13/EU GMP Guideline will be provided on the containers. Smaller boxes and/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
- Batch number
- Visit number (BA part only)

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 all unused or partially used drug supplies have been returned by the clinical trial subject and that no remaining supplies are in the Investigator's possession.

4.2 OTHER TREATMENTS, EMERGENCY PROCEDURES, RESTRICTIONS

4.2.1 Other treatments and emergency procedures

There are no special emergency procedures to be followed. No additional treatment is planned. However, in case of adverse events in need of treatment, the Investigator can authorise symptomatic therapy. In those cases, subjects will be treated as necessary and, if

required, kept under supervision at the trial site or transferred to a hospital until all medical evaluation results have returned to an acceptable level.

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

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

4.2.2.2 Restrictions on diet and life style

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

From 1 h before drug intake until lunch, fluid intake (except for the milk served with the breakfast in the BA part) is restricted to the water administered with the drug, and an additional 240 mL of water served at 2 h and 4 h post-dose (mandatory for all subjects). From lunch until discharge from the study centre, liquid intake is restricted to additional 3 litres. During the days of urine collection, subjects will be advised to drink at least 1.5 litres per day.

Alcoholic beverages, grapefruits, Seville oranges (sour or bitter oranges) and their juices, and dietary supplements and products containing St. John's wort (Hypericum perforatum) are not permitted starting 4 days before the first 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 h before until 24 h after administration of trial medication.

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, treatment with ultraviolet light (e.g. PUVA), or medication with known phototoxicity potential (e.g, doxycycline) should be avoided within 8 days after administration of trial medication. The use of sunscreens is mandatory in that time.

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

Primary endpoint to assess safety and tolerability of BI 730460 is the number [N (%)] of subjects with drug-related adverse events.

Further criteria of interest:

- AEs (including clinically relevant findings from the physical examination)

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.

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

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

If such abnormalities already pre-exist prior to trial inclusion, they will be considered as baseline conditions and should be collected in the eCRF only.

Serious adverse event

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

- Results in death
- Is life-threatening, which refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if more severe
- Requires inpatient hospitalisation
- Requires prolongation of existing hospitalisation,
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly/birth defect
- Is deemed serious for any other reason if it is an important medical event when based upon appropriate medical judgment which may jeopardise the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation or development of dependency or abuse.

AEs considered 'Always Serious'

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

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

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

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. AESIs need to be reported to the sponsor's Pharmacovigilance Department within the same timeframe that applies to SAEs, please see section 5.2.2.2.

The following are considered as AESIs:

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

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

Intensity (severity) of AEs

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

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

Causal relationship of AEs

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

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

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

5.2.2.2 Adverse event collection and reporting

AE collection

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

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

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

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

- From signing the informed consent onwards until an individual subject's end of trial:
    - All AEs (serious and non-serious) and all AESIs
    - The only exception to this rule are AEs (serious and non-serious) and AESIs in Phase I trials in healthy volunteers, when subjects discontinue from the trial due to screening failures prior to administration of any trial medication. In these cases, the subjects' data must be collected at trial site but will not be entered in the CRF or trial database and will not be reported in the CTR.

- After the individual subject's end of trial:
    - The investigator does not need to actively monitor the subject for new AEs but should only report any occurrence of cancer and related SAEs and related AESIs of which the investigator may become aware of by any means of communication, e.g. phone call. Those AEs should, however, not be reported in the CRF.

The REP for BI 730460, the time interval when measurable drug levels or PD effects are still likely to be present after last administration, is not known for this first-in-human trial at this early stage of development. Therefore, all AEs reported until the end of trial examination (last per protocol contact) will be considered on treatment; please see Section 7.3.3.

AE reporting to the sponsor and timelines

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

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

Information required

For each AE, the investigator should provide the information requested on the appropriate eCRF pages and the BI SAE form, if applicable.

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

5.2.3 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 Chart after the subjects have fasted for at least 10 h (excluding 4-hour post-dose sample). Overnight fasting is not required at the discretion of the Investigator or designee for retests.

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**	A[1]	B[2]	C[3]	D[4]
Haematology	Haematocrit	X	X	X	X
	Haemoglobin	X	X	X	X
	Red blood cells (RBC)	X	X	X	X
	White blood cells (WBC)	X	X	X	X
	Platelets	X	X	X	X
	Reticulocyte count	X	X	X	X
Automatic WBC differential (relative and absolute)	Neutrophils	X	X	X	X
	Eosinophils	X	X	X	X
	Basophils	X	X	X	X
	Monocytes	X	X	X	X
	Lymphocytes	X	X	X	X
Manual differential WBC (if automatic differential WBC is abnormal)	Polymorphnuclear neutrophils (segs), band neutrophils (stabs), eosinophils, basophils, monocytes, lymphocytes				
Coagulation	Activated partial thromboplastin time (aPTT)	X	X	--	X
	Prothrombin Time (Quick and INR)	X	X	--	X
Enzymes	Aspartate aminotransferase (AST/GOT)	X	X	--	X
	Alanine aminotransferase (ALT/GPT)	X	X	--	X
	Alkaline phosphatase (AP)	X	X	--	X
	Gammaglutamyl transferase (GGT)	X	X	--	X
	Lactate dehydrogenase	X	X	--	X
	Lipase	X	--	--	X
Electrolytes	Calcium	X	X	--	X
	Sodium	X	X	--	X
	Potassium	X	X	--	X
Substrates	Plasma glucose	X	X	--	X
	Creatinine	X	X	--	X
	Total bilirubin	X	X	--	X
	Direct bilirubin	X	X	--	X
	Total protein	X	X	--	X
	C-Reactive Protein (CRP)	X	X	--	X
	Urea in serum	X	X	--	X
	Phosphate in serum	X	X	--	X
	Total cholesterol	X	X	--	X
	Triglycerides	X	--	--	X
Hormones	Thyroid stimulating hormone (TSH)	X	--	--	--

[1] A: parameters to be determined at visit 1 (screening examination)
[2] B: parameters to be determined at visits 2 and 3 on Days -3 to -1 and Days 1 to 4 (for time points, refer to Flow Chart)
[3] C: parameters to be determined at visits 2 and 3 on Day 8 (for time point, refer to Flow Chart)
[4] D: parameters to be determined at visit 4 (end of trial examination)

Table 5.2.3: 1 Routine laboratory tests (cont.)

Functional lab group	**Test name**	A[1]	B[2]	C[3]	D[4]
Urinalysis (Stix)	Urine nitrite	X	X	--	X
	Urine protein	X	X	--	X
	Urine glucose	X	X	--	X
	Urine ketone	X	X	--	X
	Urobilinogen	X	X	--	X
	Urine bilirubin	X	X	--	X
	Urine RBC	X	X	--	X
	Urine WBC	X	X	--	X
	Urine pH	X	X	--	X
Urine sediment (microscopic examination if erythrocytes, leukocytes nitrite or protein are abnormal in urine)	Only positive findings will be reported (e.g. presence of sediment bacteria, casts in sediment, squamous epithelial cells, erythrocytes, leukocytes)			--	

[1] A: parameters to be determined at visit 1 (screening examination)
[2] B: parameters to be determined at visits 2 and 3 on Days -3 to -1 and Days 1 to 4 (for time points, refer to Flow Chart)
[3] C: parameters to be determined at visits 2 and 3 on Day 8 (for time point, refer to Flow Chart)
[4] D: parameters to be determined at visit 4 (end of trial examination)

The tests listed in Table 5.2.3: 2 are exclusionary laboratory tests that may be repeated as required. The results will not be entered in the CRF/database and will not be reported in the CTR. Except for drug screening, it is planned to perform these tests at screening only. Drug screening will be performed at screening and prior to each administration of trial medication on Day 1 (for time points refer to Flow Chart).

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) Interferon-γ release assay to tuberculosis (qualitative), e.g. QuantiFERON®-TB Gold Test

To encourage compliance with alcoholic restrictions, a breath alcohol test (Alcotest® 7410, Dräger AG, Lübeck, Germany) will be performed prior to each treatment period at time

points indicated in the Flow Chart, 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 MVZ Labor Ravensburg GbR, Elisabethenstraße 11, 88212 Ravensburg, Germany with the exception of the drug screening tests. Drug screening will be performed at the trial site using M-10/14-PDT Multiline test or comparable tests.

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

Recording

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 Chart. 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.

To achieve a stable heart rate at rest and to assure high quality recordings, the site personnel will be instructed to assure a relaxed and quiet environment so that all subjects are at complete rest.

All ECGs will be recorded for a 10-sec duration after subjects have rested for at least 5 min in a supine position. ECG recording will always precede all other study procedures scheduled for the same time (except for blood drawing from an intravenous cannula that is already in place) to avoid compromising ECG quality.

ECGs will be recorded as single ECGs or as triplicate ECGs (i.e. three single ECGs recorded within 180 sec) as indicated in the Flow Chart.

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

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

Storing

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

Data transfer

For time points specified in the Flow Chart, ECGs will be transferred electronically to a central ECG lab ( ) for evaluation.

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

Data transfer from the central ECG lab to the sponsor is described in the ECG data transfer agreement (see TMF).

Evaluation

a) Central ECG lab (SRD part only)

For the SRD part, central ECG lab evaluation will be performed post-study for the first of three replicate ECGs per time point on Days 1, 2 and 3. For baseline, where 3 triplicate ECGs are recorded, only the first triplicate ECG (i.e. 3 single ECGs) will be evaluated. This will include the determination of cardiac QRS-axis as assessed by the ECG machine's algorithm as well as the intervals RR, PR, QRS and QT measured semi-automatically. The remaining second and third replicate ECG will be stored for additional analysis if required, e.g. by authorities at a later time point.

Heart rate (HR) and the QT interval corrected for HR (QTc e.g. QTcF and QTcB) will be determined by the sponsor (see TSAP for details).

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

For blinding arrangements see Section 4.1.5.1. No more than two blinded readers will evaluate all ECGs of the study. ECGs from a particular subject should be evaluated by a single reader.

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

b) Trial site (SRD part and BA part)

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

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

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

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

5.2.4.2 Continuous ECG monitoring

Cardiac rhythm (including heart rate) will be monitored during the SRD part by means of continuous 3-lead ECG recording using the CARESCAPE Monitor B450 (GE Healthcare, Freiburg, Germany) for at least 15 min before drug administration (for baseline assessment) and for 4 h following drug administration). This continuous ECG monitoring supports the early detection of adverse events such as clinically relevant bradycardia, tachycardia, or arrhythmia at the trial site. Beyond this clinical evaluation at the trial site, no further data collection or analyses are performed based on continuous ECG monitoring.

ECG data from continuous ECG recording will not be transferred to the clinical trial database. Abnormal findings during continuous ECG recording will be recorded as AEs if judged clinically relevant by the Investigator.

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) will be measured by a blood pressure monitor (Dinamap Pro 100, GE Medical Systems, Freiburg, Germany) at the times indicated in the Flow Chart, after subjects have rested for at least 5 min in a supine position. All recordings should be made using the same type of blood pressure recording instrument on the same arm if possible.

5.2.5.2 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 (including rhythm strip of at least 15 minutes), 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.

5.3 OTHER

5.3.1 Pharmacogenomic evaluation

Pharmacogenomic investigations explore the role of genetic variation in determining an individual's response to drugs. For this purpose, a sample of at most 10 mL of blood will be taken at the screening examination from each subject whose genotype has not been previously determined. Separate informed consent for genotyping will be obtained from each volunteer prior to sampling.

DNA will be extracted from the blood sample in order to sequence genes coding for proteins that are involved in the absorption, distribution, metabolism, and excretion (ADME) of drugs.

The gene sequences to be determined include known and likely functional variations of key ADME genes and incorporate more than 90% of ADME-related genetic markers identified by the PharmaADME group (weblink.pharmaadme.org). It is not intended to include the pharmacogenomic data in the final report. However, the data may be part of the report if necessary.

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

5.5 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

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

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

5.5.1 Pharmacokinetic endpoints

The following pharmacokinetic endpoints will be determined if feasible:

5.5.1.1 Secondary endpoints

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

5.5.2 Methods of sample collection

5.5.2.1 Plasma sampling for pharmacokinetic analysis

For quantification of BI 730460 plasma concentrations, 2.7 mL of blood will be taken from an antecubital or forearm vein into an K_2-EDTA (dipotassium ethylenediaminetetraacetic acid)-anticoagulant blood drawing tube at the times indicated in the Flow Chart. Blood will be withdrawn by means of either an indwelling venous catheter or by venipuncture with a metal needle.

The EDTA-anticoagulated blood samples will be centrifuged for about 10 min at about 2000 g to 4000 g and at 4 to 8 °C. Two plasma aliquots will be obtained and stored in polypropylene (PP) 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 min, with interim storage of blood samples on crushed ice between blood collection and centrifugation. 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.

5.5.2.4 Additional blood sample for stability-testing

In order to assess the stability of the analyte in whole blood, two additional blood samples will be taken from all subjects of dose group 50 mg. Based on the knowledge gained during the trial conduct, e.g. from preliminary PK results, the chosen timing or dose group may be changed to a different one. The change will be implemented via a non-substantial CTP Amendment.

Approximately 2.4 mL blood will be taken from an antecubital or forearm vein using two 1.2 mL K_2 EDTA-blood drawing tubes at the time indicated in the Flow Chart (immediately

after the drawing of a regular blood PK sample, which is to say that no additional venous puncture will be necessary).

From each K_2-EDTA tube, one aliquot will be generated:

- One aliquot ('stability reference') will be centrifuged within 10 min after collection. Centrifugation will last for about 10 min (at about 2000 g to 4000 g and 4 to 8 °C), plasma will be separated and transferred into a freezer
- The second aliquot ('stability test') will be stored for about 4 h at room temperature and ambient light conditions (documentation of storage time necessary) and will then be centrifuged and stored according to the first sample.

At a minimum, the aliquots should be labelled with the following information: BI trial number, administered drug, subject number, planned sampling time, 'stability reference' or 'stability test'.

Until transfer to the analytical laboratory, both aliquots will be stored at about -20 °C or below at the trial site. Both aliquots will be provided to the responsible bioanalyst together with the information about sample handling (i.e. storage time of 'test sample' at room temperature). After receipt, the aliquots will be stored at the bioanalytical laboratory at about -20°C or below until analysis.

The results of the analysis of these samples will not be reported within this clinical trial but will be used for bioanalytical assay validation and therefore included in the corresponding method validation report. The remaining sample volume will be discarded upon completion of the method validation report at the latest.

5.5.3 Analytical determinations

5.5.3.1 Analytical determination of analyte plasma concentration

BI 730460 concentrations in plasma will be determined by a validated LC-MS/MS (liquid chromatography tandem mass spectrometry) assay. All details of the analytical method will be available prior to the start of sample analysis. The analysis will be performed under the responsibility of Drug Metabolism and Pharmacokinetics, BI Pharma GmbH & Co. KG, Biberach, Germany at a suitable CRO.

As described in Section 4.1.5, the bioanalyst will be blinded for the BA part only. For the SRD part he/she will be unblinded.

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

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

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

Starting from 72 h post administration a deviation from the scheduled time for PK sampling of ±70 min is acceptable.

The acceptable deviation from the scheduled time for vital signs, ECG and laboratory tests will be ± 15 min for the first 6 h after trial drug administration and ± 30 min 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 Chart at the same time as a meal, blood sampling, vital signs and 12-lead ECG recordings have to be done first. Furthermore, if several measurements including venipuncture are scheduled for the same time, venipuncture should be the last of the measurements due to its inconvenience to the subject and possible influence on physiological parameters.

For planned individual plasma concentration sampling times
refer to the Flow Chart. While these nominal times should be adhered to as closely as possible, the actual sampling times will be recorded and used for determination of pharmacokinetic 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 Blinded 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, refer to Sections 5.2.3 to 5.2.5.

Pharmacogenomic genotyping will be performed in those volunteers whose genotypes are not known (for details see Section 5.3).

6.2.2 Treatment periods

Study participants will be admitted to trial site at least 1 hour prior to administration of the trial medication. They will be kept under close medical surveillance for at least 24 hours following drug administration. Thereafter the subjects will be allowed to leave the trial site after formal assessment and confirmation of their fitness. Afterwards the study will be performed in an ambulatory fashion until the end-of-study examination.

For the SRD part, each subject will receive one dose of the respective trial medication (BI 730460 or placebo) at visit 2. The participants of the BA part will receive the respective trial medication (BI 730460) at visit 2 and 3. Details on treatments and procedures of administration are described in Section 4.1.4.

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

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

6.2.3 End of trial period

For AE assessment, laboratory tests, recording of ECG and vital signs, 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

SRD Part:

The primary objective of the first (SRD) part of this trial is to investigate the safety and tolerability of BI 730460 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) of BI 730460. Endpoints as specified in 5.5.1 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.

BA Part:

The primary objective of the second part of the study is to investigate relative bioavailability of 50 mg BI 730460 given as tablets after a standardised high-fat breakfast (Test, T) compared to 50 mg BI 730460 as tablets in a fasting state (Reference, R)

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

7.1.2 Endpoints

The primary endpoint to describe safety and tolerability of BI 730460 will be the number (% subjects) with drug-related AEs. The collection of parameters pertaining to these investigations is described in detail in Section 5.2.1.

The secondary pharmacokinetic endpoints to be used for the assessment of dose proportionality and relative bioavailability are specified in Section 5.5.1.1.

7.1.3 Model

SRD part:

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; where i = 1, 2, …, 9, j = 1, 2, …, 6;
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.

BA part: Investigation of relative bioavailability

Relative bioavailability is primarily to be determined on the basis of the parameters $AUC_{0-\infty}$ and C_{max} (cf. Section 5.5). Those parameters will be log-transformed (natural logarithm) prior to fitting the model.

The statistical model used for the analysis of $AUC_{0-\infty}$ and C_{max} 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. For tests on subject, period, and treatment effects, the denominator sum of squares will be the sum of squares for error; while for tests on sequence effects, the denominator will be the sum of squares for subjects. The model is described by the following equation

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

y_{ijkm} = logarithm of response (endpoint, see Section 7.1.3) measured on subject m in sequence i receiving treatment k in period j,

μ = the overall mean,

ζ_i = the i^{th} sequence effect, i = 1, 2

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

π_j = the j^{th} period effect, j = 1, 2

τ_k = the k^{th} treatment effect, k = 1, 2

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

The difference between the expected means for test treatment and reference treatment log(T)-log(R), will be estimated by the difference in the corresponding Least Square Means (point estimate) and two-sided 90% confidence intervals based on the t-distribution will be computed. These quantities will then be back-transformed to the original scale to give the point estimator (geometric mean) and interval estimates for the ratio between response under test and response under reference.

Pairwise comparisons will be done for tablet fed (Test, T) vs tablet fasted (Reference, R).

7.2 NULL AND ALTERNATIVE HYPOTHESES

Safety and tolerability of different dose groups of BI 730460 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.

In the SRD part, for the evaluation of dose proportionality, a two-sided 95% confidence interval (CI) of the slope will be computed. However, the CI will have to be interpreted in the perspective of the exploratory character of the study, i.e. as interval estimate for effects in the present data.

The relative bioavailability of BI 730460 will be estimated by the ratios of the geometric means (test/reference) for the secondary PK endpoints. Additionally, their two-sided 90% 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 on testing, an acceptance range was not specified, that is, no hypothesis will be tested.

7.3 PLANNED ANALYSES

7.3.1 Primary analyses

Analysis of safety and tolerability is described in Section 7.3.3.

7.3.2 Secondary analyses

The secondary parameters (see Section 5.5.1) will be calculated according to the relevant corporate procedure of the Sponsor ‘Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics’ (001-MCS-36-472, current version).

Pharmacokinetic parameters of a subject will be included in the analysis unless the subject has an important protocol violation relevant for the evaluation. Whether a protocol violation is important will be decided no later than in the Report Planning Meeting.

Reasons for exclusion of single pharmacokinetic parameters may be:

- The subject experiences emesis at or before two times median t_{max}. Median t_{max} is to be determined for the test product excluding the subjects experiencing emesis.
- The subject experiences emesis at any time during the labelled dosing interval.
- Time deviations
- Use of restricted medications

The subject set for the evaluation of PK endpoints (PKS) will include all treated subjects that provide at least one observation for at least one secondary endpoint without important protocol violations with respect to the statistical evaluation of PK endpoints. It will also be decided in the Report Planning Meeting which subjects are to be included in the PKS.

Excluded subjects will be listed with their individual plasma concentrations and individual pharmacokinetic parameters, however, will not be included in descriptive statistics for plasma concentrations, pharmacokinetic parameters or other statistical assessment.

SRD Part: Assessment of dose proportionality

Dose proportionality of the secondary pharmacokinetic endpoints will be explored based on the regression model described in Section 7.1.3. 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 ranges, where dose proportionality can be assumed.

BA Part: Assessment of relative bioavailability

Point estimates of bioavailability, the ratios of the geometric means (test/reference) for the secondary endpoints (see 5.5.1.1), and their two-sided 90% CIs will be provided.

To this end, the PK endpoints will be log transformed (natural logarithm) prior to fitting the ANOVA model (cf. 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.

7.3.3 Safety analyses

Safety analyses will be performed in accordance with BI standards.

All treated subjects (that is, all subjects who received at least one dose of study drug), will be included in the safety evaluation. Safety analyses will be descriptive in nature and will be based on BI standards.

Treatments will be compared in a descriptive way. 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. The active treatment groups will be compared to the placebo group in a descriptive way. Tabulations of frequencies/proportions will be used for the evaluation of categorical (qualitative) data, and tabulations of descriptive statistics will be used to analyse continuous (quantitative) data.

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

Measurements (such as ECG, vital signs, or laboratory parameters) or AEs will be assigned to treatments (see Section 4.1) based on the actual treatment at the planned time of the measurement or on the recorded time of AE onset (concept of treatment emergent AEs). Therefore, measurements planned or AEs recorded prior to first intake of trial medication will be assigned to 'screening', those between first trial medication intake until the end of trial visit will be assigned to the treatment period, and those after the end of trial examination will be assigned to 'post-study'. These assignments including the corresponding time intervals will be defined in detail in the TSAP.

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.

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 triplicate ECG measurements prior to drug administration. The derivation of the quantitative and qualitative ECG endpoints and their analyses will be described in the TSAP.

7.3.4 Preliminary PK analyses

A preliminary analysis of PK parameters (AUC_{0-24} and C_{max} of BI 730460) provided as individual values and geometric means of at least the first cohort per dose level, will be performed for

- all dose levels up to n-2 before proceeding to dose level n (with n ≤ 50 mg)
- all dose levels up to n-1 before proceeding to dose level n (with n > 50 mg)

(Note: 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 were available)

In contrast to the final PK/PD calculations, the preliminary analysis will be based on planned sampling times rather than on actual times, regardless of whether actual times were within the time windows or not. Therefore, minor deviations of preliminary and final results may occur. The preliminary analysis will provide individual and mean concentration/effect-time profiles and summary statistics of individual values without subject identification. The preliminary results will be distributed to the Investigator and the trial team.

Depending on preliminary data on safety, tolerability, changes of dosing schedule (e.g. additional intermediate doses) or planned times for PK -sampling, additional preliminary PK-analysis may be performed based on the request of the trial clinical monitor, the Investigator, or trial clinical pharmacokineticist. Preliminary PK data will be distributed to the Investigator. No formal interim report will be written.

No inferential statistical preliminary 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.

7.3.5 Pharmacokinetic analyses

The pharmacokinetic parameters listed in Section 5.5.1 for drug BI 730460 will be calculated according to the BI SOP 'Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics' (001-MCS-36-472).

Subjects who are not included in the PKS (refer to Section 7.3.1.) will be reported with their individual plasma / urine concentrations and individual pharmacokinetic parameters; however, they will not be included in descriptive statistics for plasma / urine concentrations, 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, (that is, to the same number of decimal places provided in the bioanalytical report).

If a predose 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 guidances. The individual pharmacokinetic parameters of such a subject will be calculated and listed separately. If a predose 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.

Every effort will be made to include all concentration data in an analysis. If not possible, a case to case decision is required whether the value should only be excluded from half-life estimation or the complete analysis.

- If a concentration is only excluded from half-life determination, it will be used for all other calculations (e.g. descriptive statistics) and for graphical presentation.

- If a concentration value is excluded from all calculations, it will not be presented graphically or used for the calculation of descriptive statistics and parameter determination. However the excluded concentration itself will be listed in the clinical trial report associated with an appropriate flag.

Descriptive statistics of parameters are calculated only when at least 2/3 of the individual parameter estimates of a certain parameter are available. If the actual sampling time will not be recorded or will be missing for a certain time point, the planned time will generally be used for this time point instead. Pharmacokinetic parameters which cannot be determined will be identified by "not calculated" (NC).

7.4 HANDLING OF MISSING DATA

7.4.1 Safety

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

7.4.2 Plasma drug concentration - time profiles

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

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

7.4.3 Pharmacokinetic parameters

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

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

7.5 RANDOMISATION

SRD part: 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.

BA part: Subjects will be randomised to one of the two treatment sequences T/R, R/T in a 1:1 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 (refer to 3.3.5).

7.6 DETERMINATION OF SAMPLE SIZE

SRD part

It is planned to include a total of 72 subjects in this study part. The planned sample size is not based on a power calculation. The size of 8 subjects per dose group (6 on active treatment, and 2 on placebo) is commonly used in single-rising dose studies of the present type and is in general considered as sufficient for the exploratory evaluation of single dose safety and pharmacokinetics [R95-0013].

Additional subjects may be entered to allow testing of additional doses on the basis of experience gained during the trial conduct (e.g. preliminary PK data), provided the planned and approved highest dose will not be exceeded. Thus, the actual number of subjects entered may exceed 72, but will not exceed 88 subjects entered in the SRD part.

BA part

It is planned to enter 12 subjects in this trial part, because this sample size is considered sufficient to achieve the aims of this exploratory trial.

With this sample size, the following precision of the ratio of geometric means (test/reference) can be expected. Precision is defined as the ratio of upper limit to relative BA estimate. Note that the precision is independent of the actual ratio of geometric means. For this First-in-Man trial, no information on intra-subject variability is available. Therefore, Table 7.6: 1 provides an overview on the achievable precision for estimating the ratio of geometric means (test/reference) for three different gCV. For illustrative purposes, the expected 90% confidence intervals with 95% coverage probability are displayed for different values of geometric means ratios T/R in the two-period two sequence crossover design.

Table 7.6: 1 Expected two-sided 90% confidence intervals for different gCVs and ratios T/R (N=12)

gCV[%]	Ratio[1] [%]	Precision (upper CI limit/relative BA)	90% CI [%]
20	80	1.219	(65.61, 97.54)
	100	1.219	(82.01, 121.93)
	125	1.219	(102.52, 152.41)
	150	1.219	(123.02, 181.89)
	200	1.219	(164.03, 243.86)
25	80	1.28	(62.52, 102.36)
	100	1.28	(78.15, 127.95)
	125	1.28	(97.69, 159.94)
	150	1.28	(117.23, 191.93)
	200	1.28	(156.31, 255.91)
30	80	1.342	(59.63, 107.33)
	100	1.342	(74.54, 134.16)
	125	1.342	(93.17, 167.71)
	150	1.342	(111.80, 201.25)
	200	1.342	(149.07, 268.33)

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

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

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

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

The calculation was performed as described by [R12-0972] using R Version 3.0.3.

8. INFORMED CONSENT, DATA PROTECTION, TRIAL RECORDS

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

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

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

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

8.1 STUDY APPROVAL, SUBJECT INFORMATION, AND INFORMED CONSENT

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

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

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

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

8.2 DATA QUALITY ASSURANCE

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

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

8.3 RECORDS

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

ClinBase™
In the Human Pharmacology Centre (HPC) – Boehringer Ingelheim's Phase I unit – the validated ClinBase™ system is operated for processing information and controlling data collected in clinical studies. In addition to its function as a procedure control system, ClinBase™ serves as data base. Instead of being entered into CRFs, selected data are directly entered into the system.

8.3.1 Source documents

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

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

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

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

8.3.2 Direct access to source data and documents

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

8.3.3 Storage period of records

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

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

8.4 EXPEDITED REPORTING OF ADVERSE EVENTS

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

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

9.1 PUBLISHED REFERENCES

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

9.2 UNPUBLISHED REFERENCES

001-MCS-36-472 Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics. Current version.

c19477316 Investigator's Brochure: BI 73046 Psoriasis. P1416.1. Current version.

c11248385-04 A partially randomised, single-blind, placebo-controlled trial to investigate safety, tolerability, pharmacokinetics and pharmacodynamics of single rising doses of BI 730357 administered as oral solution and tablets to healthy subjects, and a randomized, open-label, single-dose, three-way cross-over bioavailability comparison of BI 730357 as tablet versus oral solution and tablet with and without food. CTP. 1407.1. 05-May-2017.

n00255510-01 Prediction of BI 730460 Pharmacokinetics and Therapeutic Dose in Human. Nonclinical Expert Statement. BI 730460. 05 Oct 2017.

n00255297 BI 730460: Four-Week Oral (Gavage) Toxicity and Toxicokinetics Study in the Dog Followed by a Four-Week Recovery Period. Nonclinical Report. 17R014. Draft report available.

10. APPENDICES

Not applicable.

11. DESCRIPTION OF GLOBAL AMENDMENT

Number of global amendment		1
Date of CTP revision		17 July 2018
EudraCT number		2017-004446-15
BI Trial number		1416-0001
BI Investigational Product		BI 730460
Title of protocol		A partially randomised, single-blind, placebo-controlled trial to investigate safety, tolerability, pharmacokinetics and pharmacodynamics of single rising doses of BI 730460 administered as tablets to healthy subjects, and a randomised, open-label, single-dose, two-way cross-over bioavailability comparison of BI 730460 as tablet with and without food
To be implemented only after approval of the IRB / IEC / Competent Authorities		☐
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		☐
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		☒
Section to be changed		Title Page & Synopsis
Description of change		Change of Principal Investigator
Rationale for change		Due to change of staff

Number of global amendment		2
Date of CTP revision		24 January 2019
EudraCT number		2017-004446-15
BI Trial number		1416-0001
BI Investigational Product		BI 730460
Title of protocol		A partially randomised, single-blind, placebo-controlled trial to investigate safety, tolerability, pharmacokinetics and pharmacodynamics of single rising doses of BI 730460 administered as tablets to healthy subjects, and a randomised, open-label, single-dose, two-way cross-over bioavailability comparison of BI 730460 as tablet with and without food
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		CTP Synopsis (test products, comparator products) and Sections 3.1, 4.1.1, 4.1.2, 4.1.3, 4.1.4 and 7.1.1
Description of change		The tentative dose of the BA part of 100 mg (1 tablet of 100 mg BI 730460) was changed to 50 mg (2 tablets of 25 mg BI 730460).
Rationale for change		In accordance with the CTP, the tentative dose of the BA part of 100 mg was adapted to 50 mg. This based on the preliminary PK information obtained during the trial and indicating that 200 mg probably will be the maximum dose of the SRD part, and on the condition that the BA part may only start if an at least 4-fold dose has been assessed to have acceptable safety and tolerability in the SRD part. In contrast to the SRD part, where the subject number matches the medication number, the medication and subject numbers of the BA part do not match.

APPROVAL / SIGNATURE PAGE

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Title: A partially randomised, single-blind, placebo-controlled trial to investigate safety, tolerability, pharmacokinetics and pharmacodynamics of single rising doses of BI 730460 administered as tablets to healthy subjects, and a randomised, open-label, single-dose, two-way cross-over bioavailability comparison of BI 730460 as tablet with and without food

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Approval-Therapeutic Area		25 Jan 2019 12:19 CET
Author-Clinical Trial Leader		25 Jan 2019 14:00 CET
Approval-Team Member Medicine		25 Jan 2019 14:01 CET
Author-Clinical Pharmacokineticist		25 Jan 2019 14:25 CET
Author-Trial Statistician		25 Jan 2019 17:19 CET
Verification-Paper Signature Completion		28 Jan 2019 09:36 CET

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed