Clinical Trial Protocol

	Document Number:	**c26431910 -02**
EudraCT No.	2018-004421-91	
BI Trial No.	1407-0032	
BI Investigational Medicinal Product	BI 730357	
Title	Relative bioavailability of intended commercial formulations (iCF) of BI 730357 versus BI 730357 trial formulation 1 and bioavailability comparison of three different iCF batches following oral administration in healthy subjects (an open-label, single-dose, randomised, 2-way and 3-way crossover trial)	
Lay Title	A study in healthy men and women to test if taking different formulations of BI 730357 tablets influences the amount of BI 730357 in the blood	
Clinical Phase	I	
Clinical Trial Leader	Phone: Fax:	
Principal Investigator	Phone: Fax:	
Status	Final Protocol (Revised Protocol (based on global amendment 1)	
Version and Date	Version: 2.0	Date: 07 March 2019

CLINICAL TRIAL PROTOCOL SYNOPSIS

Company name	Boehringer Ingelheim
Protocol date	21 January 2019
Revision date	07 March 2019
BI trial number	1407-0032
Title of trial	Relative bioavailability of intended commercial formulations (iCF) of BI 730357 versus BI 730357 trial formulation 1 and bioavailability comparison of three different iCF batches following oral administration in healthy subjects (an open-label, single-dose, randomised, 2-way and 3-way crossover trial)
Principal Investigator:	
Trial site	
Clinical phase	I
Trial rationale	Trial Parts 1 and 2: To define the relative bioavailability of two tablet strengths of Trial Formulation 1 (TF1) used in previous Phase 1 and Phase 2 trials and of the newly developed intended Commercial Formulations (iCF) for Phase 3 in order to bridge pharmacokinetic and safety data between the formulations and secure Phase 3 dosing. The 50 mg tablet formulations will be compared in Part 1, the 100 mg tablet formulations in Part 2. Trial Part 3: To determine clinically relevant specifications for BI 730357 particle size in the 100 mg iCF (coarse milled active pharmaceutical ingredient (API) vs. unmilled API vs. regularly milled API) and to show *in vivo* relevance of the selected *in vitro* dissolution method for the iCF.
Trial objective	Trial Parts 1 and 2: To investigate the relative bioavailability of two tablet strengths (50 mg and 100 mg) of the intended Commercial Formulation of BI 730357 (Test, T) versus the corresponding tablet strengths of Trial Formulation 1 (Reference, R) Trial Part 3: To investigate the relative bioavailability of two iCF side batches of BI 730357 with coarse milled API ($Test_{coarse\ milled}$, T_c) and unmilled API ($Test_{unmilled}$, T_u), respectively, versus the final iCF batch of BI 730357 with regularly milled API (Reference, R)
Trial design	Parts 1 & 2: Randomized, open-label, single-dose, 2-way crossover design Part 3: Randomized, open-label, single-dose, 3-way crossover design

Trial endpoints	Primary endpoints: AUC_{0-tz} and C_{max} of BI 730357 in plasma Secondary endpoints: $AUC_{0-\infty}$ of BI 730357 in plasma
Number of subjects	
total entered	43 (14 for Trial Part 1, 14 for Trial Part 2, 15 for Trial Part 3)
each treatment	14 (Trial Parts 1 and 2) or 15 (Trial Part 3)
Diagnosis	Not applicable
Main criteria for inclusion	Healthy male and female subjects, age of 18 to 50 years (inclusive), body mass index (BMI) of 18.5 to 29.9 kg/m^2 (inclusive)
Test product of Part 1	BI 730357 film-coated tablets **50 mg, iCF, final batch**
dose	50 mg
mode of admin.	Oral with 240 mL of water after an overnight fast of at least 10 h
Reference product of Part 1	BI 730357 film-coated tablets **50 mg, TF1**
dose	50 mg
mode of admin.	Oral with 240 mL of water after an overnight fast of at least 10 h
Test product of Part 2	BI 730357 film-coated tablets **100 mg, iCF, final batch**
dose	200 mg
mode of admin.	Oral with 240 mL of water after an overnight fast of at least 10 h
Reference product of Part 2	BI 730357 film-coated tablets **100 mg, TF1**
dose	200 mg
mode of admin.	Oral with 240 mL of water after an overnight fast of at least 10 h
Test products of Part 3	BI 730357 film-coated tablets **100 mg, iCF side batch with coarse milled API**; BI 730357 film-coated tablets **100 mg, iCF side batch with unmilled API**
dose	100 mg
mode of admin.	Oral with 240 mL of water after an overnight fast of at least 10 h
Reference Product of Part 3	BI 730357 film-coated tablets **100 mg, iCF final batch with regularly milled API**
dose	100 mg
mode of admin.	Oral with 240 mL of water after an overnight fast of at least 10 h
Duration of treatment	One day (single dose) for each treatment (separated by wash-out phases of at least 10 days)

Statistical methods	Relative bioavailability will be estimated by the ratios of the geometric means (test/reference) for the primary and secondary endpoints. Additionally, their two-sided 90% confidence intervals (CIs) will be provided. This method corresponds to the two one-sided t-tests procedure, each at a 5% significance level. Since the main focus is on estimation and not testing, a formal hypothesis test and associated acceptance range is not specified. The statistical model will be an analysis of variance (ANOVA) on the logarithmic scale including effects for 'subjects' and 'treatment'. CIs will be calculated based on the residual error from the ANOVA. Descriptive statistics will be calculated for all endpoints.

FLOW CHART FOR ALL TRIAL PARTS

Period	Visit	Day	Planned time (relative to BI 730357 administration) [h:min]	Approximate clock time of actual day [h:min]	Event and comment	Safety laboratory [8]	PK blood (BI 730357)	12-lead ECG	Vital signs (BP, PR)	Questioning for AEs and concomitant therapy [6]
SCR	1	-21 to -1			Screening (SCR)[1]	A		x	x	
1/2/3[7]	2/3/4[7]	1	-2:00	06:00	Admission to trial site	x[2,5]	x[2]	x[2]	x[2]	x[2]
			0:00	**08:00**	**Administration of BI 730357**					
			0:30	08:30			x			
			1:00	09:00			x			
			1:30	09:30			x			
			2:00	10:00	240 mL fluid intake		x			
			2:30	10:30			x			
			3:00	11:00			x			
			3:30	11:30			x			
			4:00	12:00	240 mL fluid intake, thereafter lunch [3]		x			x
			5:00	13:00			x			
			6:00	14:00			x			
			7:00	15:00	Snack (voluntary)					
			8:00	16:00			x			
			10:00	18:00	Dinner					
			12:00	20:00			x			x
		2	24:00	08:00	Breakfast (voluntary) [3], discharge from trial site	B	x	x	x	x
			34:00	18:00	Ambulatory visit		x			x
		3	47:00	07:00	Ambulatory visit		x			x
		4	71:00	07:00	Ambulatory visit		x			x
		6	119:00	07:00	Ambulatory visit		x			x
		8	167:00	07:00	Ambulatory visit		x			x
FU	5	9 to 16			End of trial (EoTrial) examination[4]	C		x	x	x

1. Subject must be informed and written informed consent obtained prior to starting any screening procedures. Screening procedures include physical examination, check of vital signs, ECG, safety laboratory (including pregnancy test in women and 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 procedure is to be performed and completed within 3h prior to drug administration.
3. If several actions are indicated at the same time, the intake of meals will be the last action.
4. At the end of trial visit the EoTrial examination includes physical examination, vital signs, ECG, safety laboratory (including pregnancy test in women), recording of AEs and concomitant therapies.
5. Only urine drug screening and alcohol breath test as well as pregnancy test in women will be done at this time.
6. AEs and concomitant therapies will be recorded throughout the trial, but will be specifically asked for at the times indicated in the Flow Chart above.
7. Two identical periods / visits in Trial Part 1 and Trial Part 2, or three identical periods / visits in Trial Part 3. All periods/visits are separated by wash-out periods of at least 10 days between administrations of BI 730357.
8. Letter A, B and C define different sets of safety laboratory examinations (see Section 5.2.3)

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ABBREVIATIONS

ADME	Absorption, distribution, metabolism, and excretion
AE	Adverse event
AESI	Adverse events of special interest
ANOVA	Analysis of variance
API	Active pharmaceutical ingredient
AUC_{0-24}	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 to 24 hours
AUC_{0-96}	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 to 96 hours
$AUC_{0-\infty}$	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity
AUC_{0-tz}	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 to the last quantifiable data point
BA	Bioavailability
BI	Boehringer Ingelheim
BMI	Body mass index (weight divided by height squared)
BP	Blood pressure
CA	Competent authority
CI	Confidence interval
CL/F	Apparent clearance of the analyte in plasma after extravascular administration
C_{max}	Maximum measured concentration of the analyte in plasma
CNS	Central nervous system
CRF	Case Report Form, paper or electronic (sometimes referred to as ‘eCRF’)
CT Leader	Clinical Trial Leader
CT Manager	Clinical Trial Manager
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
CV	Arithmetic coefficient of variation
CYP	Cytochrome P450
DILI	Drug induced liver injury
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
eCRF	Electronic case report form
eDC	Electronic data capture
EDTA	Ethylenediaminetetraacetic acid

EEG	Electroencephalogram
EMG	Electromyelogram
EoTrial	End of trial
EudraCT	European Clinical Trials Database
F	Absolute bioavailability factor
FDA	Food and Drug Administration (US)
FSH	Follicle-stimulating hormone
FU	Follow-up
f_u	Fraction unbound
GCP	Good Clinical Practice
gCV	Geometric coefficient of variation
GLP	Good Laboratory Practice
gMean	Geometric mean
HPC	Human Pharmacology Centre
hPXR	Human pregnane X receptor
IB	Investigator's Brochure
IC_{50}	50% inhibitory concentration
ICF	Informed consent form
iCF	Intended commercial formulation
ICH	International Council on Harmonisation
IEC	Independent Ethics Committee
IL	Interleukin
IPD	Important protocol deviation
IQRM	Integrated quality and risk management
IRB	Institutional Review Board
ISF	Investigator site file
λ_z	Terminal rate constant of the analyte in plasma
MDA	Methylenedioxyamphetamine
MDMA	Methylenedioxymethamphetamine
MDR	Multiple rising dose
MedDRA	Medical Dictionary for Regulatory Activities
mRNA	Messenger ribonucleic acid
MRT_{po}	Mean residence time of the analyte in the body after oral administration

NOAEL	No observed adverse event level
P-gp	P-glycoprotein
PK	Pharmacokinetic(s)
PKS	Pharmacokinetic set
PR	Pulse rate
PUVA	Psoralen ultraviolet A
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
RCTC	Rheumatology Common Toxicity Criteria
SAE	Serious adverse event
SCR	Screening
SOP	Standard operating procedure
SRD	Single-rising dose
ss	(at) steady state
T	Test product or treatment
TF1	Trial formulation 1
$t_{1/2}$	Terminal half-life of the analyte in plasma
t_{max}	Time from (last) dosing to the maximum measured concentration of the analyte in plasma
TS	Treated set
t_z	Time of last measurable concentration of the analyte in plasma
TSAP	Trial statistical analysis plan
ULN	Upper limit of normal
V_z	Apparent volume of distribution during the terminal phase after intravascular administration
V_z/F	Apparent volume of distribution during the terminal phase after extravascular administration
WOCBP	Woman of childbearing potential
XTC	Ecstasy

1. INTRODUCTION

BI 730357 It is being developed as an oral therapy for the treatment of patients with psoriasis

This trial will be performed to investigate the relative bioavailability of BI 730357 in plasma when given as different tablet formulations (iCF vs. TF1) and iCF batches of different particle size (regularly milled vs. coarse milled vs. unmilled).

1.1 MEDICAL BACKGROUND

1.2 DRUG PROFILE

1.2.1 Nonclinical data

1.2.2 Clinical data

Up to now, two Phase I trials have been completed, a first-in-human, single-rising-dose (SRD) trial and a multiple-rising dose (MRD) trial [c09228382].

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1.3 RATIONALE FOR PERFORMING THE TRIAL

Parts 1 and 2 of this trial are designed to investigate the relative bioavailability of two tablet strengths of a newly developed tablet formulation (iCF batch 1 and batch 2) of BI 730357 compared to the corresponding strengths of TF1 following oral administration in healthy male and female subjects. TF1 has already been administered and investigated in previous clinical trials. iCF is the anticipated formulation for Phase 3 and, if applicable, later in clinical practice. To allow the prediction of safety and pharmacokinetics in Phase 3 and clinical practice, comparable pharmacokinetic data between TF1 and iCF are considered essential.

PK data from SRD trial 1407.1 and MRD trial 1407-0002 revealed non-linear kinetics of BI 730357 with a less-than-dose-proportional increase of $AUC_{0-\infty}$ and C_{max}. Therefore, in accordance with regulatory guidelines [R05-1094; R10-2509] a low dose of 50 mg (with 50 mg formulations in Part 1), and a high dose of 200 mg (with 100 mg formulations in Part 2), corresponding to doses at the bottom and top end of the anticipated dose range to be tested in Phases 2 and 3, have been selected. As 50 mg was seen at the top of the dose proportional range, results obtained with 50 mg in this trial will also cover lower doses.

The aim of Part 3 is to determine clinically relevant specifications for BI 730357 particle size in the 100 mg iCF and to show *in vivo* relevance of the selected *in vitro* dissolution method for the iCF. The final iCF tablet with regularly milled API showed the fasted dissolution behavior whereas the iCF with the unmilled API showed the slowest dissolution. A relative bioavailability comparison using these two extremes (i.e. the final batch with regularly milled API and a side batch with unmilled API) and a side batch in between (e.g. with coarse milled API) would be the best option to achieve this aim.

1.4 BENEFIT - RISK ASSESSMENT

Participation in this clinical trial is without any (therapeutic) benefit for healthy subjects. Their participation, however, is of major importance for the development of BI 730357.

Subjects are exposed to risks of study procedures and risks related to the exposure to the trial medication.

1.4.1 Expected benefit to the target population

filling an unmet medical need for the introduction of new, efficacious oral treatment options in the treatment of psoriasis

1.4.2 Procedure-related risks

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

ECG electrodes may cause local and typically transient skin reactions.

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

1.4.3 Drug-related risks and safety measures

As the nature of the target and the mechanism of action of BI 730357 are well understood from pre-clinical studies, comparable compounds have been tested by other companies before (although not a lot of published data are available), and the animal models are believed to be predictive for the effects in humans, BI 730357 is not seen as a high-risk compound.

Single dose administration of BI 730357 is supported up to 800 mg by preclinical, as well as clinical safety data from first-in-human trial 1407.1 (see Section 1.2.2). In trial 1407.1, administration of a 800 mg tablet under fed (high-fat) conditions resulted in exposures This was 2.9-fold and 4.1-fold below the C_{max} and AUC_{0-24} respectively at the combined NOAEL for male and female dogs after 13 weeks of treatment (see Section 1.2.1.3).

Since preclinical data indicate that BI 730357 has phototoxicity potential, direct exposure to the sun or exposure to solarium radiation is not allowed during the entire study, and use of sunscreens is mandatory in that time (see Section 4.2.2.2).

Women of childbearing potential have to use highly effective birth control (see Section 3.3.2). In addition, negative pregnancy testing will be required at the screening visit and prior to each administration of trial medication.

1.4.4 Overall assessment of benefit-risk ratio

BI 730357 has been adequately characterised in pre-clinical studies. The non-clinical safety package supports clinical trials in males and females with administration of BI 730357 for up to 39 weeks.

Results of the SRD trial 1407.1 indicate good safety and tolerability of single oral doses of BI 730357 up to 800 mg (see IB [c09228382]).

The trial design is optimized to collect as much relevant information as possible on the pharmacokinetics of BI 730357 without exposing participating volunteers to undue risk. The potential for side effects has been assessed to be minimal and thus acceptable. However, there is always the potential for subjects receiving medication to experience adverse events (AEs), and rarely also serious adverse events (SAEs). Risks for subjects will be minimized and addressed by eligibility criteria, safety laboratory examinations, ECG and vital sign measurements, in-house observation periods and AE questioning.

If the investigator should have any clinical concern, the safety of subjects will be of upmost importance. The Investigator has the discretion to remove subjects from the trial should there be any safety concerns, or if the subjects' wellbeing is at jeopardy.

All in all, the risk of the participating volunteers is judged to be low considering particularly the good tolerability of BI 730357 seen so far and the administration of single doses already investigated. With respect to the medical need for an effective and safe treatment of psoriasis, the benefit of this trial is assessed to outweigh the potential risks.

2. TRIAL OBJECTIVES AND ENDPOINTS

2.1 MAIN OBJECTIVES, PRIMARY AND SECONDARY ENDPOINTS

2.1.1 Main objectives

The main objective of Trial Parts 1 and 2 is to investigate the relative bioavailability of two tablet strengths (50 mg and 100 mg) of the intended Commercial Formulation of BI 730357 (Test, T) versus with the corresponding tablet strengths of Trial Formulation 1 (Reference, R).

The main objective of Trial Part 3 is to investigate the relative bioavailability of two iCF side batches of BI 730357 with coarse milled API ($Test_{coarse\ milled}$, T_c) and unmilled API ($Test_{unmilled}$, T_u), respectively, versus the final iCF batch of BI 730357 with regularly milled API (Reference, R).

2.1.2 Primary endpoints

The following pharmacokinetic parameters will be determined for BI 730357:

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

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

2.1.3 Secondary endpoint

The following pharmacokinetic parameter will be determined for BI 730357:

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

2.2.2.2 Safety and tolerability

Safety and tolerability of BI 730357 will be assessed based on:

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

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

The trial consists of three parts, which will be performed in a randomised, open-label, single-dose, two-way (Parts 1 and 2) or three-way (Part 3) crossover design in healthy male and female subjects in order to compare the following test treatment and reference treatments:

Part 1

T_1 (Test $_{Part\ 1}$)	One 50 mg BI 730357 tablet as iCF, final batch
R_1 (Reference $_{Part\ 1}$)	One 50 mg BI 730357 tablet as TF1

Part 2

T_2 (Test $_{Part\ 2}$)	Two 100 mg BI 730357 tablets as iCF, final batch
R_2 (Reference $_{Part\ 2}$)	Two 100 mg BI 730357 tablets as TF1

Part 3

T_{3c} (Test $_{Part\ 3,\ coarse\ milled}$)	One 100 mg BI 730357 tablet as iCF side batch, coarse milled
T_{3u} (Test $_{Part\ 3,\ unmilled}$)	One 100 mg BI 730357 tablet as iCF side batch, unmilled
R_3 (Reference $_{Part\ 3}$)	One 100 mg BI 730357 tablet as final iCF batch, regularly milled

In Part 1 and Part 2 the iCF and TF1 will be investigated at two dose levels (at a low dose of 50 mg and a high dose of 200 mg) due to the non-linear kinetics of BI 730357.

All treatments will be administered to the subjects as single dose in the fasting state. Within each trial part the subjects will be randomly allocated to the 2 treatment sequences in Part 1 (T_1/R_1 *or* R_1/T_1) and Part 2 (T_2/R_2 *or* R_2/T_2) or to the following 3 treatment sequences in Part 3 ($R_3/T_{3c}/T_{3u}$ *or* $T_{3c}/T_{3u}/R_3$ *or* $T_{3u}/R_3/T_{3c}$). Each subject will participate either in Part 1 or Part 2 or Part 3, only.

There will be a washout interval of at least 10 days between the administrations of BI 730357. For details, refer to Section 4.1.

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

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

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

For this pharmacokinetic bioavailability trial, open-label treatment is acceptable, because the primary and secondary endpoints of this trial are pharmacokinetic endpoints derived from

measurement of plasma concentrations of BI 730357. These endpoints are not expected to be affected by knowledge of treatment.

3.3 SELECTION OF TRIAL POPULATION

It is planned that 14 healthy subjects each (at least 4 of each sex) will enter Trial Parts 1 and 2, and 15 healthy subjects (at least 4 of each sex) will enter Trial Part 3. They will be recruited from the volunteers' pool of the trial site.

A log of all subjects enrolled into the trial (i.e. who have signed informed consent) will be maintained in the Investigator Site File (ISF) irrespective of whether they have been treated with investigational drug or not.

3.3.1 Main diagnosis for trial entry

The study will be performed in healthy subjects.

3.3.2 Inclusion criteria

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

1. Healthy subjects according to the assessment of the investigator, as based on a complete medical history including a physical examination, vital signs (BP, PR), 12-lead ECG, and clinical laboratory tests
2. Age of 18 to 50 years (inclusive)
3. BMI of 18.5 to 29.9 kg/m^2 (inclusive)
4. Signed and dated written informed consent prior to admission to the study, in accordance with GCP and local legislation
5. Male subjects, or female subjects who meet any of the following criteria from at least 30 days before the first administration of trial medication until 30 days after trial completion:
   - Use of adequate contraception, e.g. any of the following methods *plus* condom: implants, injectables, combined oral or vaginal contraceptives, intrauterine device
   - Sexually abstinent
   - A vasectomised sexual partner (vasectomy at least 1 year prior to enrolment)
   - Surgically sterilised (including hysterectomy)
   - Postmenopausal, defined as at least 1 year of spontaneous amenorrhea (in questionable cases a blood sample with levels of FSH above 40 U/L and estradiol below 30 ng/L is confirmatory)

3.3.3 Exclusion criteria

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

1. Any finding in the medical examination (including BP, PR or ECG) deviating from normal and assessed as clinically relevant by the investigator

2. Repeated measurement of systolic blood pressure outside the range of 90 to 140 mmHg, diastolic blood pressure outside the range of 50 to 90 mmHg, or pulse rate outside the range of 45 to 90 bpm
3. Any laboratory value outside the reference range that the investigator considers to be of clinical relevance
4. Any evidence of a concomitant disease assessed as clinically relevant by the investigator
5. Gastrointestinal, hepatic, renal, respiratory, cardiovascular, metabolic, immunological or hormonal disorders
6. Cholecystectomy or other surgery of the gastrointestinal tract that could interfere with the pharmacokinetics of the trial medication (except appendectomy or simple hernia repair)
7. Diseases of the central nervous system (including but not limited to any kind of seizures or stroke), and other relevant neurological or psychiatric disorders
8. History of relevant orthostatic hypotension, fainting spells, or blackouts
9. Chronic or relevant acute infections
10. History of relevant allergy or hypersensitivity (including allergy to the trial medication or its excipients)
11. Use of drugs within 30 days of planned administration of trial medication that might reasonably influence the results of the trial (including drugs that cause QT/QTc interval prolongation)
12. Intake of an investigational drug in another clinical trial within 60 days of planned administration of investigational drug in the current trial, or concurrent participation in another clinical trial in which investigational drug is administered
13. Smoker (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 12 g per day for females and 24 g per day for males)
16. Drug abuse or positive drug screening
17. Blood donation of more than 100 mL within 30 days of planned administration of trial medication or intended blood donation during the trial
18. Intention to perform excessive physical activities within one week prior to the administration of trial medication or during the trial
19. Inability to comply with the dietary regimen of the trial site
20. A marked baseline prolongation of QT/QTc interval (such as QTc intervals that are repeatedly greater than 450 ms in males or repeatedly greater than 470 ms in females) or any other relevant ECG finding at screening
21. A history of additional risk factors for *Torsade de Pointes* (such as heart failure, hypokalaemia, or family history of Long QT Syndrome)

22. Subject is assessed as unsuitable for inclusion by the investigator, for instance, because the subject is not considered able to understand and comply with study requirements, or has a condition that would not allow safe participation in the study

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

23. Male subjects with WOCBP partner who are unwilling to use male contraception (condom or sexual abstinence) from time point of first administration of trial medication until 30 days after the last administration of trial medication
24. Pulse rate ranging from 45 bpm to 49 bpm (inclusive) in combination either with abnormal thyroid function (determined by medical history, physical examination, or abnormal TSH) or with signs of diseases associated with bradycardia
25. ALT (alanine transaminase) or AST (aspartate transaminase) or serum creatinine exceeds the upper limit of normal (ULN) at screening

Female subjects will not be allowed to participate, if any of the following apply:

26. Positive pregnancy test, pregnancy, or plans to become pregnant within 30 days after study completion
27. Lactation

For study restrictions, refer to Section 4.2.2.

3.3.4 Withdrawal of subjects from treatment or assessments

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

If a subject is removed from or withdraws from the trial prior to the first administration of trial medication, the data of this subject will not be entered in the case report form (CRF) and will not be reported in the clinical trial report (CTR). If a subject is removed from or withdraws from the trial after the first administration of trial medication, this will be documented and the reason for discontinuation must be recorded in the CRF; in addition, the data will be included in the CRF and will be reported in the CTR. At the time of discontinuation, a complete end of trial examination will be performed, if possible, and the information will be recorded in the CRF. If the discontinuation occurs before the end of the REP (see Section 1.2.3), the discontinued subject should if possible be questioned for AEs and concomitant therapies at or after the end of the REP in order to ensure collection of AEs and concomitant therapies throughout the REP, if not contrary to any consent withdrawal of the subject.

If it is known that a subject becomes pregnant during the trial, administration of the trial medication is to be stopped immediately, and the subject is to be removed from the trial. The subject is to be followed until she has given birth or until the end of the pregnancy. The subject's data are to be collected until the end of the trial (last visit of last subject) and reported in the CTR. For reporting of pregnancy and associated events, refer to Section 5.2.6.2.4.

3.3.4.1 Discontinuation of trial treatment

An individual subject will discontinue trial treatment if:

1. The subject wants to discontinue trial treatment, without the need to justify the decision
2. The subject has repeatedly shown to be non-compliant with important trial procedures and, in the opinion of both, the investigator and sponsor representative, is not willing or able to adhere to the trial requirements in the future.
3. The subject needs to take concomitant medication that interferes with the investigational medicinal product or other trial treatment
4. The subject can no longer receive trial treatment for medical reasons (such as pregnancy, surgery, adverse events [AEs], or diseases)
5. The subject has an elevation of AST and/or ALT ≥3-fold ULN and an elevation of total bilirubin ≥2-fold ULN (measured in the same blood sample) and/or needs to be followed up according to the DILI checklist provided in the ISF

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

Even if the trial treatment is discontinued, the subject remains in the trial and, given his/her agreement, will undergo the procedures for early treatment discontinuation and follow up as outlined in the Flow Chart and section 6.2.3.

3.3.4.2 Withdrawal of consent to trial participation

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

3.3.4.3 Discontinuation of the trial by the sponsor

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

1. Failure to meet expected enrolment goals overall or at a particular trial site
2. New toxicological findings, serious adverse events, or any safety information invalidating the earlier positive benefit-risk-assessment. More specifically, the trial will be terminated if more than 50% of the subjects have drug-related and clinically relevant AEs of moderate or severe intensity, or if at least 1 drug-related serious adverse event is reported
3. Violation of GCP or the CTP impairing the appropriate conduct of the trial
4. The sponsor decides to discontinue the further development of the investigational product

3.3.5 Replacement of subjects

In case more than 2 (Parts 1 and 2) or 3 (Part 3) subjects do not complete the trial part, the Clinical Trial Leader together with the Trial Pharmacokineticist and the Trial Statistician are to decide, if and how many subjects will be replaced. A replacement subject will be assigned a unique trial subject number, and will be assigned to the same treatment as the subject he/she replaces.

4. TREATMENTS

4.1 INVESTIGATIONAL TREATMENTS

The investigational product BI 730357 as film-coated tablet formulation has been manufactured by BI Pharma GmbH & Co. KG.

4.1.1 Identity of the Investigational Medicinal Products

*The characteristics of the test and reference products of **Part 1** are given below:*

Test product

Substance:	BI 730357
Pharmaceutical formulation:	Film-coated tablet, iCF, final batch
Source:	BI Pharma GmbH & Co. KG, Germany
Unit strength:	50 mg
Posology:	1 – 0 – 0 (treatment T_1)
Route of administration:	Oral
Duration of use:	1 day

Reference product

Substance:	BI 730357
Pharmaceutical formulation:	Film-coated tablet, TF1
Source:	BI Pharma GmbH & Co. KG, Germany
Unit strength:	50 mg
Posology:	1 – 0 – 0 (treatment R_1)
Route of administration:	Oral
Duration of use:	1 day

*The characteristics of the test and reference products of **Part 2** are given below:*

Test product

Substance:	BI 730357
Pharmaceutical formulation:	Film-coated tablet, iCF, final batch
Source:	BI Pharma GmbH & Co. KG, Germany
Unit strength:	100 mg
Posology:	2 – 0 – 0 (treatment T_2)
Route of administration:	Oral
Duration of use:	1 day

Reference product

Substance:	BI 730357
Pharmaceutical formulation:	Film-coated tablet, TF1
Source:	BI Pharma GmbH & Co. KG, Germany
Unit strength:	100 mg
Posology:	2 – 0 – 0 (treatment R_2)
Route of administration:	Oral
Duration of use:	1 day

*The characteristics of the test and reference products of **Part 3** are given below:*

Test product 1

Substance:	BI 730357
Pharmaceutical formulation:	Film-coated tablet, iCF side batch with coarse milled API
Source:	BI Pharma GmbH & Co. KG, Germany
Unit strength:	100 mg
Posology:	1 – 0 – 0 (treatment T_{3c})
Route of administration:	Oral
Duration of use:	1 day

Test product 2

Substance:	BI 730357
Pharmaceutical formulation:	Film-coated tablet, iCF side batch with unmilled API
Source:	BI Pharma GmbH & Co. KG, Germany
Unit strength:	100 mg
Posology:	1 – 0 – 0 (treatment T_{3u})
Route of administration:	Oral
Duration of use:	1 day

Reference product

Substance:	BI 730357
Pharmaceutical formulation:	Film-coated tablet, iCF final batch with regularly milled API
Source:	BI Pharma GmbH & Co. KG, Germany
Unit strength:	100 mg
Posology:	1 – 0 – 0 (treatment R_3)
Route of administration:	Oral
Duration of use:	1 day

4.1.2 Selection of doses in the trial

Results from the SRD trial 1407.1 and the MRD trial 1407-0002 showed non-linear pharmacokinetics of BI 730357 with a less-than-dose-proportional increase in AUC and C_{max}. Based on current guidelines [R05-1094; R10-2509] the planned bioavailability comparison of iCF and TF1 in Trial Parts 1 and 2 has therefore to be conducted with doses of 50 mg at the bottom and of 200 mg at the top end of the dose range to be tested in Phases 2 and 3. As 50 mg was seen at the top of the dose proportional range, results obtained with 50 mg in this trial will also cover lower doses.

For the bioavailability comparison of the three iCF batches with different particle size in Part 3, a dose of 100 mg in the middle of the anticipated therapeutic range was selected.

4.1.3 Method of assigning subjects to treatment groups

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

Subjects will be allocated to treatment sequences prior to the first administration of trial medication in the morning of Day 1 (Visit 2). For this purpose, numbers of the randomisation list will be allocated to the subjects by drawing lots. Subjects are then assigned to a treatment sequence according to the randomisation list. Once a subject number has been assigned, it cannot be reassigned to any other subject. The randomisation procedure is described in Section 7.6.

4.1.4 Drug assignment and administration of doses for each subject

This trial consists of two 2-way crossover parts (Trials Parts 1 and 2) and one 3-way crossover trial part (Trial Part 3). In Trial Parts 1 or 2, subjects will receive the 2 treatments in randomised order. In Trial Part 3, subjects will receive 3 treatments in randomised order. The treatments to be evaluated for each trial part are outlined in Tables 4.1.4: 1, 4.1.4: 2 and 4.1.4: 3 below.

Table 4.1.4: 1 Dosage and treatment schedule for Part 1

Treatment	Substance	Formulation	Unit strength	Dosage	Total dose
T_1 (Test $_{Part\ 1}$)	BI 730357	film-coated tablet, iCF final batch	50 mg	1 film-coated tablet on Day 1	50 mg
R_1 (Reference $_{Part\ 1}$)	BI 730357	film-coated tablet, TF1	50 mg	1 film-coated tablet on Day 1	50 mg

Table 4.1.4: 2 Dosage and treatment schedule for Part 2

Treatment	Substance	Formulation	Unit strength	Dosage	Total dose
T_2 (Test $_{Part\ 2}$)	BI 730357	film-coated tablet, iCF final batch	100 mg	2 film-coated tablets on Day 1	200 mg
R_2 (Reference $_{Part\ 2}$)	BI 730357	film-coated tablet, TF1	100 mg	2 film-coated tablets on Day 1	200 mg

Table 4.1.4: 3 Dosage and treatment schedule for Part 3

Treatment	Substance	Formulation	Unit strength	Dosage	Total dose
T_{3c} (Test $_{Part\ 3,\ coarse\ milled}$)	BI 730357	film-coated tablet, iCF side batch coarse milled	100 mg	1 film-coated tablet on Day 1	100 mg
T_{3u} (Test $_{Part\ 3,\ unmilled}$)	BI 730357	film-coated tablet, iCF side batch unmilled	100 mg	1 film-coated tablet on Day 1	100 mg
R_3 (Reference $_{Part\ 3}$)	BI 730357	film-coated tablet, iCF final batch regularly milled	100 mg	1 film-coated tablet on Day 1	100 mg

Administration of trial medication will be performed after subjects have fasted overnight; fasting is to start no later than 10 h before the scheduled dosing. The investigator (or authorised designee) will administer the trial medication as an oral dose together with about 240 mL of water to subjects who are in a standing position. For drug administration, the so-called four-eye principle (two-person rule) should be applied. For this, one authorised employee of the trial site should witness the administration of trial medication, and – if applicable – its preparation (e.g. reconstitution), if correct dosage cannot be ensured otherwise.

For restrictions with regard to diet, see Section 4.2.2.2.

Subjects will be kept under close medical surveillance until 24 h after drug administration. During the first 4 h after drug administration of BI 730357, subjects are not allowed to lie down (i.e. no declination of the upper body of more than 45 degrees from upright posture), except for medical reasons or for recording of 12-lead ECG and vital signs measurements.

The treatments will be separated by a wash-out phase of at least 10 days between administrations of BI 730357.

4.1.5 Blinding and procedures for unblinding

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

Emergency envelopes will not be provided, because the dose of trial medication is known to investigators and subjects.

PK samples will be labelled in such a way that treatment allocation cannot be derived by the analytical site.

4.1.6 Packaging, labelling, and re-supply

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

For details of packing and the description of the label, refer to the ISF.

The telephone number of the sponsor and the name, address and telephone number of the trial site are provided in the subject information form. The EudraCT number is indicated on the title page of this protocol as well as on the subject information and informed consent forms.

No re-supply is planned.

4.1.7 Storage conditions

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

4.1.8 Drug accountability

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

- Approval of the clinical 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 documented in the form 'Trial Staff List' may dispense medication to trial subjects. The trial medication must be administered in the manner specified in the CTP.

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

All unused medication will be disposed of locally by the trial site upon written authorisation of the Clinical Trial Leader. Receipt, usage and disposal of trial medication must be documented on the appropriate forms. Account must be given for any discrepancies.

4.2 OTHER TREATMENTS, EMERGENCY PROCEDURES, RESTRICTIONS

4.2.1 Other treatments and emergency procedures

There are no special emergency procedures to be followed. No additional treatment is planned. However, if adverse events require treatment, the investigator can authorise

symptomatic therapy. In those cases, subjects will be treated as necessary and, if required, kept under supervision at the trial site or transferred to a hospital until all results of medical evaluations are acceptable.

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

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

4.2.2.2 Restrictions on diet and life style

Poppy-seeds containing foods should not be consumed starting 3 days before the first drug administration in each treatment period, in order to avoid false-positive results in the drug screen.

While admitted to the trial site, the subjects will be instructed not to consume any foods or drinks other than those provided by the staff. Standardised meals will be served at the times indicated in the Flow Chart.

No food is allowed within 10 h before and 4 h after intake of BI 730357.

From 1 h before drug intake until lunch, fluid intake is restricted to the water administered with the drug, and an additional 240 mL of water at 2 h and 4 h post-dose (mandatory for all subjects). From lunch until 24 h post-dose, total fluid intake is restricted to 3000 mL.

Grapefruits, Seville oranges (sour or bitter oranges) and their juices, and dietary supplements and products containing St. John's wort (*Hypericum perforatum*) are not permitted from 7 days before the first administration of trial medication in Period 1 until after the last PK sample of the last period is collected.

Alcoholic beverages are not permitted from 2 days before the first administration of trial medication in period 1 until after the last PK sample of the last period is collected.

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

Smoking is not allowed during in-house confinement while admitted to the trial site.

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

Direct exposure to the sun or exposure to solarium radiation, treatment with ultraviolet light (e.g. PUVA), or medication with known phototoxicity potential (e.g, doxycycline) should be avoided from the first administration of trial medication until the EoTrial examination. The use of sunscreens is mandatory in that time.

If female subjects of child-bearing potential are included in the trial, adequate contraception is to be maintained throughout the course of the trial (see Section 3.3.2 for the definition of adequate measures).

4.3 TREATMENT COMPLIANCE

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

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. ASSESSMENTS

5.1 ASSESSMENT OF EFFICACY

Not applicable.

5.2 ASSESSMENT OF SAFETY

5.2.1 Physical examination

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

5.2.2 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.

5.2.3 Safety laboratory parameters

For the assessment of laboratory parameters, blood and urine samples will be collected by the trial site at the times indicated in the Flow Chart after the subjects have fasted for at least 10 h. For retests, at the discretion of the investigator or designee, overnight fasting is not required.

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

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

Table 5.2.3: 1 Routine laboratory tests

Functional lab group	BI test name [comment/abbreviation]	A[1]	B[1]	C[1]
Haematology	Haematocrit	X	X	X
	Haemoglobin	X	X	X
	Red Blood Cell Count/Erythrocytes	X	X	X
	White Blood Cells/Leucocytes	X	X	X
	Platelet Count/Thrombocytes (quant)	X	X	X
Automatic WBC differential, relative	Neutrophils/Leukocytes; Eosinophils/Leukocytes; Basophils/ Leukocytes; Monocytes/Leukocytes; Lymphocytes/Leukocytes	X	X	X
Automatic WBC differential, absolute	Neutrophil, absol.; Eosinophils, absol.; Basophils, absol.; Monocytes, absol.; Lymphocytes, absol.	X	X	X
Manual differential WBC (if automatic differential WBC is abnormal)	Neut. Poly (segs); Neut. Poly (segs), absol.; Neutrophils Bands; Neutrophils Bands, absol.; Eosinophils/Leukocytes; Eosinophils, absol.; Basophils/ Leukocytes; Basophils, absol.; Monocytes/ Leukocytes; Monocytes, absol.; Lymphocytes/Leukocytes; Lymphocytes, absol.			
Coagulation	Activated Partial Thromboplastin Time	X	--	X
	Prothrombin time	X	--	X
	Prothrombin time - INR (International Normalization Ratio)	X	--	X
Enzymes	AST [Aspartate transaminase] /GOT, SGOT	X	X	X
	ALT [Alanine transaminase] /GPT, SGPT	X	X	X
	Alkaline Phosphatase	X	X	X
	Gamma-Glutamyl Transferase	X	X	X
	Glutamate Dehydrogenase (GLDH)	X	X	X
	Creatine Kinase [CK]	X	--	X
	Creatine Kinase Isoenzyme MB [only if CK is elevated]	X	--	X
Hormones	Thyroid Stimulating Hormone	X	--	--
Substrates	Glucose (Plasma)	X	X	X
	Creatinine	X	X	X
	Bilirubin, Total	X	X	X
	Bilirubin, Direct	X	X	X
	Protein, Total	X	X	X
	C-Reactive Protein (Quant)	X	X	X
	Cholesterol, total	X	--	X
	Triglyceride	X	--	X
Electrolytes	Sodium	X	X	X
	Potassium	X	X	X
Urinalysis (Stix) [2]	Urine Nitrite (qual)	X	--	X
	Urine Protein (qual)	X	--	X
	Urine Glucose (qual)	X	--	X
	Urine Ketone (qual)	X	--	X
	Urobilinogen (qual)	X	--	X
	Urine Bilirubin (qual)	X	--	X
	Urine RBC/Erythrocytes (qual)	X	--	X
	Urine WBC/Leucocytes (qual)	X	--	X
	Urine pH	X	--	X
Urine sediment [2]	Only positive findings will be reported (for instance, the presence of sediment bacteria, casts in sediment, squamous epithelial cells, erythrocytes, leukocytes)			

1 A, B and C are different sets of laboratory values. The Flow Chart details at which time point which set is to be investigated.
2 Microscopic examination if erythrocytes, leukocytes, nitrite or protein are abnormal in urine

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 pregnancy tests and drug screening, it is planned to perform these tests during screening only. Pregnancy testing in women will be performed at screening, prior to each treatment period, and as part of the end of trial examination. Drug screening will be performed at screening and prior to first dosing in each treatment period.

Table 5.2.3: 2 Exclusionary laboratory tests

Functional lab group	Test name
Drug screening (urine)	Amphetamine/MDA Barbiturates Benzodiazepine Cannabis Cocaine Methadone Methamphetamines/MDMA/XTC Opiates Phencyclidine Tricyclic antidepressants
Infectious serology (blood)	Hepatitis B surface antigen (qualitative) Hepatitis B core antibody (qualitative) Hepatitis C antibodies (qualitative) HIV-1 and HIV-2 antibody (qualitative) Interferon-γ release assay to tuberculosis (qualitative), e.g. QuantiFERON®-TB Gold Test
Pregnancy test (urine)	Beta human chorionic gonadotropin (beta-HCG)

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

The laboratory tests listed in Tables 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 drug screening and pregnancy tests. These tests will be performed at the trial site using M-10/14-PDT Multiline test and HCG-K20 test, respectively, or comparable test systems.

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

5.2.4 Electrocardiogram

Twelve-lead 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 times provided in the Flow Chart.

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

All ECGs will be recorded for a 10 sec duration after subjects have rested for at least 5 min in a supine position. ECG assessment will always precede all other study procedures scheduled for the same time to avoid compromising ECG quality.

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

All locally printed ECGs will be evaluated by the investigator or a designee. Abnormal findings will be reported as AEs (during the trial) or baseline conditions (at screening) if assessed to be clinically relevant by the investigator. Any ECG abnormalities will be carefully monitored and, if necessary, the subject will be removed from the trial and will receive the appropriate medical treatment.

ECGs may be repeated for quality reasons (for instance, due to alternating current artefacts, muscle movements, or electrode dislocation) and the repeated ECG will be used for analysis. Additional (unscheduled) ECGs may be collected by the investigator for safety reasons.

5.2.5 Other safety parameters

Not applicable.

5.2.6 Assessment of adverse events

5.2.6.1 Definitions of adverse events

5.2.6.1.1 Adverse event

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

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

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

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

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

5.2.6.1.2 Serious adverse event

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

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

5.2.6.1.3 AEs considered ‘Always Serious’

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

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

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

5.2.6.1.4 Adverse events of special interest

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

The following are considered as AESIs:

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

  These lab findings constitute a hepatic injury alert and the subjects showing these lab abnormalities need to be followed up according to the 'DILI checklist' provided in the ISF. In case of clinical symptoms of hepatic injury (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.
- Severe infections (grading according to Rheumatology Common Toxicity Criteria (RCTC) developed by OMERACT [R13-3515])
- Opportunistic and mycobacterium tuberculosis infections
  These include pneumocystis jirovecii, BK virus disease including polyomavirus-associated nephropathy, cytomegalovirus, posttransplant lymphoproliferative disorder (Epstein-Barr virus), progressive multifocal leukoencephalopathy, bartonellosis (disseminated only), blastomycosis, toxoplasmosis, coccidioidomycosis, histoplasmosis, aspergillosis (invasive only), candidiasis (invasive or pharyngeal), cryptococcosis, other invasive fungi (mucormycosis (zygomycosis, rhizopus, mucor, lichtheimia), scedosporium/pseudallescheria boydii, fusarium), legionellosis, listeria monocytogenes (invasive only), tuberculosis, nocardiosis, non-tuberculous mycobacterium, salmonellosis (invasive only), hepatitis B virus reactivation, herpes simplex (invasive only), herpes zoster, strongyloides (hyperinfection syndrome and disseminated forms only), paracoccidioides, penicillium marneffei, sporothrix schenckii, cryptosporidium species (chronic only), microsporidiosis, leishmaniasis (visceral only), trypanosoma cruzi Infection (Chagas' disease) (disseminated only), campylobacteriosis (invasive only), shigellosis (invasive only), vibriosis (invasive due to vibrio vulnificus), hepatitis C virus progression.

5.2.6.1.5 Intensity (severity) of AEs

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

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

5.2.6.1.6 Causal relationship of AEs

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

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

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

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

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

5.2.6.2 Adverse event collection and reporting

5.2.6.2.1 AE collection

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

Subjects will be required to report spontaneously any AEs as well as the time of onset, end time, and intensity of these events. In addition, each subject will be regularly assessed by the

medical staff throughout the clinical trial and whenever the investigator deems necessary. As a minimum, subjects will be questioned for AEs (and concomitant therapies) at the time points indicated in the Flow Chart. Assessment will be made using non-specific questions such as 'How do you feel?'. Specific questions will be asked wherever necessary in order to more precisely describe an AE.

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

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

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

5.2.6.2.2 AE reporting to the sponsor and timelines

The Investigator must report SAEs, AESIs, and non-serious AEs which are relevant for the reported SAE or AESI, on the BI SAE form 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.

5.2.6.2.3 Information required

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

5.2.6.2.4 Pregnancy

In rare cases, pregnancy might occur in a clinical trial. Once a subject has been enrolled in the clinical trial and has taken trial medication, the investigator must report any drug exposure during pregnancy in a trial participant immediately (within 24 hours) by means of Part A of the Pregnancy Monitoring Form to the sponsor's unique entry point.

The outcome of the pregnancy associated with the drug exposure during pregnancy must be followed up and reported to the sponsor's unique entry point on the Pregnancy Monitoring Form for Clinical Trials (Part B).
The ISF will contain the Pregnancy Monitoring Form for Clinical Trials (Part A and Part B) as well as non-trial specific information and consent for the pregnant partner.

As pregnancy itself is not to be reported as an AE, in the absence of an accompanying SAE and/or AESI, only the Pregnancy Monitoring Form for Clinical Trials and not the SAE form is to be completed. If there is an SAE and/or AESI associated with the pregnancy, an SAE form must be completed in addition.

5.3 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

5.3.1 Assessment of pharmacokinetics

For the assessment of pharmacokinetics, blood samples will be collected at the time points indicated in the Flow Chart. The actual sampling times will be recorded and used for determination of pharmacokinetic parameters.

5.3.2 Methods of sample collection

5.3.2.1 Blood sampling for pharmacokinetic analysis

5.3.3 Analytical determinations

5.3.3.1 Analytical determination of analyte plasma concentration

5.4 ASSESSMENT OF BIOMARKER(S)

Not applicable.

5.5 BIOBANKING

Not applicable.

5.6 OTHER ASSESSMENTS

5.7 APPROPRIATENESS OF MEASUREMENTS

All measurements performed during this trial are standard measurements and will be performed in order to monitor subjects' safety and to determine pharmacokinetic parameters in an appropriate way. The scheduled measurements will allow monitoring of changes in vital signs, standard laboratory values, and ECG parameters that might occur as a result of administration of trial medication. The safety assessments are standard, are accepted for evaluation of safety and tolerability of an orally administered drug, and are widely used in clinical trials. The pharmacokinetic parameters and measurements outlined in Sections 2.1.2, 2.1.3, 2.2.2.1, and 5.3 are generally used assessments of drug exposure.

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

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

Study measurements and assessments scheduled to occur 'before' trial medication administration are to be performed and completed within a 3h-period prior to the trial drug administration.

The acceptable deviation from the scheduled time for vital signs, ECG, and laboratory tests will be ± 30 min on Day 1, ± 45 min on Day 2, and ± 60 min from Day 3 onwards.

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

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

Starting from 119 hours after BI 730357 administration (and beyond), a time window of ± 60 min will be allowed for PK blood sampling times.

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

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

6.2.1 Screening period

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

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

Genotyping will be performed in those volunteers whose genotypes have not been previously determined (for details, see Section 5.3).

6.2.2 Treatment periods

Each subject is expected to participate in 2 treatment periods (in Part 1 or Part 2) or 3 treatment periods (Part 3). At least 10 days will separate drug administrations in the first and second treatment period as well as in the second and third treatment period.

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

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

The safety measurements performed during the treatment period are specified in Section 5.3 of this protocol and in the Flow Chart. For details on times of all other trial procedures, refer to the Flow Chart. AEs and concomitant therapy will be assessed continuously from screening until the end of trial examination.

6.2.3 Follow-up period and trial completion

For AE assessment, laboratory tests, recording of ECG and vital signs, and physical examination during the follow-up period, see Sections 5.2.2 to 5.2.6.
Subjects who discontinue treatment before the end of the planned treatment period should undergo the EoTrial Visit.

All abnormal values (including laboratory parameters) that are assessed as clinically relevant by the investigator will be monitored using the appropriate tests until a return to a medically acceptable level is achieved. (S)AEs persisting after a subject's EoTrial Visit must be followed until they have resolved, have been sufficiently characterised, or no further information can be obtained.

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 STATISTICAL DESIGN – MODEL

The main objective of this trial is to investigate the relative bioavailability of two tablet strengths (50 mg and 100 mg) of the intended Commercial Formulation of BI 730357 (Test, T) versus with the corresponding tablet strengths of trial formulation 1 (Reference, R), and to investigate the relative bioavailability of two iCF side batches of BI 730357 with coarse milled API ($Test_{coarse\ milled}$, T_c) and unmilled API ($Test_{unmilled}$, T_u), respectively, versus final iCF batch of BI 730357 with regularly milled API (Reference, R) following oral administration on the basis of the primary and secondary pharmacokinetic endpoints, as listed in Section 2.1.2 and 2.1.3. The trial is designed to allow intra-subject comparisons and will be evaluated statistically by use of a linear model for logarithmically transformed PK endpoints.

A further objective is to evaluate and compare further pharmacokinetic parameters between the treatments, see Section 2.2.1. These further pharmacokinetic parameters will be assessed by descriptive statistics.

The assessment of safety and tolerability is a further objective of this trial, and will be evaluated by descriptive statistics for the parameters specified in Section 2.2.2.2.

7.2 NULL AND ALTERNATIVE HYPOTHESES

The relative bioavailability of BI 730357 in plasma after test versus reference treatment will be estimated by the ratios of the geometric means (test/reference), and their corresponding 2-sided 90% confidence intervals (CIs) will be provided. This method corresponds to the two one-sided t-tests procedure, each at the 5% significance level. Since the main focus is on estimation and not testing, a formal hypothesis test and associated acceptance range is not specified.

7.3 PLANNED ANALYSES

Analysis sets

Statistical analyses will be based on the following analysis sets:

- Treated set (TS): The treated set includes all subjects who were randomized and treated with at least one dose of study drug. The treated set will be used for safety analyses.
- Pharmacokinetic parameter analysis set (PKS): This set includes all subjects in the treated set (TS) who provide at least one PK endpoint that was defined as primary or secondary and was not excluded due to a protocol deviation relevant to the evaluation of PK or due to PK non-evaluability (as specified in the following subsection 'Pharmacokinetics'). Thus, a subject will be included in the PKS, even if contributes only one PK parameter value for one period to the statistical assessment. Descriptive and model based analyses of PK parameters will be based on the PKS.

Adherence to the protocol will be assessed by the trial team. Important protocol deviation (IPD) categories will be suggested in the IQRM plan, IPDs will be identified no later than in the Report Planning Meeting, and the IPD categories will be updated as needed.

Pharmacokinetics

The pharmacokinetic parameters listed in Section 2.1 for drug BI 730357 will be calculated by means of non-compartmental analysis. Non-compartmental pharmacokinetic parameters will be calculated based on actual sampling times using a validated pharmacokinetic software (Phoenix® WinNonlin® 6.3). Descriptive statistics will be used to evaluate plasma concentration data and PK parameters. The derivation of PK parameters is described in BI internal SOP (001-MCS-36-472_RD-01). Further details on analysis will be described in the TSAP.

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

Relevant protocol deviations may be

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

7.3.1 Primary endpoint analyses

Primary analyses

The primary endpoints (refer to Section 2.1.2) will be calculated according to the BI Standard Operating Procedure (SOP) 'Standards and processes for analyses performed within Clinical Pharmacokinetics/ Pharmacodynamics' (001-MCS-36-472).

The statistical model used for the analysis of the primary endpoints will be an analysis of variance (ANOVA) model on the logarithmic scale. That is, the PK endpoints will be log-transformed (natural logarithm) prior to fitting the ANOVA model. This model will include effects accounting for the following sources of variation: sequence, subjects within sequences, period and treatment. The effect 'subjects within sequences' will be considered as random, whereas the other effects will be considered as fixed. The model is described by the following equation, where p=2 for Parts 1 and 2 of the trial and p=3 for Part 3 of the trial:

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

y_{ijkm} = logarithm of response measured on subject m in sequence i receiving treatment k in period j,

μ = the overall mean,

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

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,, …, p

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

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

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

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

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 (Least Squares Means). Additionally their two-sided 90% confidence intervals will be calculated based on the residual error from the ANOVA and quantiles from the t-distribution. These quantities will then be back-transformed to the original scale to provide the point estimate and 90% CIs for each endpoint.

Further exploratory analyses

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

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

7.3.2 Secondary endpoint analyses

The secondary endpoints (refer to Section 2.1.3) will be calculated according to the BI SOP 'Standards and processes for analyses performed within Clinical Pharmacokinetics/ Pharmacodynamics' (001-MCS-36-472) and will be assessed statistically using the same methods as described for the primary endpoints.

7.3.4 Safety analyses

Safety will be analysed based on the assessments described in Section 2.2.2.2. All treated subjects (TS, refer to Section 7.3) will be included in the safety analysis. Safety analyses will be descriptive in nature and based on BI standards. No hypothesis testing is planned.

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

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

Measurements (such as ECG, vital signs, or laboratory parameters) or AEs will be assigned to treatments (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 the screening period, those between first trial medication intake and end of REP (see Section 1.2.3) will be assigned to the treatment period. Events occurring after the REP but prior to next intake or end of trial termination date will be assigned to 'follow-up'. In case of two or more treatments, the follow-up will be summarized according to the previous treatment. These assignments including the corresponding time intervals will be defined in detail in the TSAP. Note that AEs occurring after the last per protocol contact but entered before final database lock will be reported to Pharmacovigilance only and will not be captured in the trial database.

Additionally, further treatment intervals (analysing treatments) may be defined in the TSAP in order to provide summary statistics for time intervals, such as combined treatments, on-

treatment totals, or periods without treatment effects (such as screening and follow-up intervals).

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

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

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

Relevant ECG findings will be reported as AEs.

7.4 INTERIM ANALYSES

No interim analysis is planned.

7.5 HANDLING OF MISSING DATA

7.5.1 Safety

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

7.5.2 Pharmacokinetics

7.6 RANDOMISATION

Subjects will be randomised to one of the 2 treatment sequences in Part 1 (T_1/R_1 or R_1/T_1) or Part 2 (T_2/R_2 *or* R_2/T_2) in a 1:1 ratio. For Trial Part 3, subjects will be randomised to one of 3 treatment sequences ($R_3/T_{3c}/T_{3u}$ *or* $T_{3c}/T_{3u}/R_3$ *or* $T_{3u}/R_3/T_{3c}$) in a 1:1:1 ratio. The block size will be documented in the CTR.

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

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

7.7 DETERMINATION OF SAMPLE SIZE

It is planned to enter 14 subjects in Part 1, 14 subjects in Part 2 (accounting for up to 2 non PK evaluable subjects in each part), and 15 subjects in Part 3 of this trial (accounting for up to 3 non PK evaluable subjects), because these sample sizes are considered sufficient to achieve the aims of this exploratory trial parts. With this sample size, the following precision in estimating the ratio of geometric means (test/reference) can be expected with 95% probability. Precision is defined as the ratio of upper CI limit to the relative BA estimate. Note that the precision is independent of the actual ratio of geometric means.

The intra-individual coefficient of variation (gCV) is estimated from total gCV from pharmacokinetic data of the SRD part of a previous trial (Study 1407.1) using the result of 50 mg dose, 100 mg and 200 mg doses. Table 7.7:1 below presents, for each dose, the observed total gCV in this previous trial, for each primary endpoint, as well as the roughly estimated intra-individual gCV.

Table 7.7: 1 Estimated intra-individual gCV depending on observed total gCV in trial 1407.1 and assumed within-subject correlation, for C_{max} and AUC_{0-tz}

Dose	Endpoint	Observed total gCV in trial 1407.1	Assumed within-subject correlation	Estimated intra-individual gCV
50 mg	C_{max}	41.9%	0.6	26%
	AUC_{0-tz}	51.5%	0.8	22%
100 mg	C_{max}	30.7%	0.6	19%
	AUC_{0-tz}	56.8%	0.8	24%
200 mg	C_{max}	27.6%	0.6	17%
	AUC_{0-tz}	27.8%	0.8	12%

Parts 1 and 2

Assuming a gCV of 22% for BI 730357 and given a sample size of 12 subjects with evaluable data for primary analysis, the precision of the two-sided 90% confidence interval of the bioavailability ratio will be approximately 1.243, for a greater gCV of 26%, the precision would still be approximately 1.292. For a lower gCV (17%), the precision would be approximately 1.184. Table 7.7: 2 provides an overview of the achievable precision for estimating the ratio of geometric means (test/reference) applicable to Parts 1 and 2 of the trial (two-way crossover). For illustrative purposes, the expected 90% confidence intervals with 95% tolerance probability are displayed for different values of the ratios T/R of geometric means.

Table 7.7: 2 Precision that can be expected with 95% tolerance probability and illustrative two-sided 90% confidence intervals around the ratios of geometric means (T/R) for different gCVs in a two-way crossover trial with 2 treatments and 2 sequences and 2 periods (N=12)

gCV [%]	Precision upper CL / relative BA estimate	Ratio [%]*	Lower CL [%]	Upper CL [%]
17	1.184	50	42.23	59.21
17	1.184	100	84.45	118.41
17	1.184	150	126.68	177.62
17	1.184	200	168.90	236.82
22	1.243	50	40.22	62.16
22	1.243	100	80.44	124.32
22	1.243	150	120.66	186.47
22	1.243	200	160.88	248.63
26	1.292	50	38.70	64.59
26	1.292	100	77.41	129.18
26	1.292	150	116.11	193.77
26	1.292	200	154.82	258.36

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

Part 3

Assuming a gCV of 22% for BI 730357 and given a sample size of 12 subjects with evaluable data for primary analysis, the precision of the two-sided 90% confidence interval of the bioavailability ratio will be approximately 1.211, for a greater gCV of 26%, the precision would still be approximately 1.253. For a lower gCV (17%), the precision would be approximately 1.161. Table 7.7: 3 provides an overview of the achievable precision for estimating the ratio of geometric means (test/reference) applicable to part 3 of the trial (three-way crossover). For illustrative purposes, the expected 90% confidence intervals with 95% tolerance probability are displayed for different values of the ratios T/R of geometric means.

Table 7.7: 3 Precision that can be expected with 95% tolerance probability and illustrative two-sided 90% confidence intervals around the ratios of geometric means (T/R) for different gCVs in a three-way crossover trial with 3 treatments and 3 sequences and 3 periods (N=12)

gCV [%]	Precision upper CL / relative BA estimate	Ratio [%]*	Lower CL [%]	Upper CL [%]
17	1.161	50	43.08	58.03
17	1.161	100	86.16	116.06
17	1.161	150	129.24	174.09
17	1.161	200	172.32	232.12
22	1.211	50	41.27	60.57
22	1.211	100	82.54	121.15
22	1.211	150	123.82	181.72
22	1.211	200	165.09	242.29
26	1.253	50	39.90	62.66
26	1.253	100	79.80	125.32
26	1.253	150	119.70	187.98
26	1.253	200	159.59	250.64

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

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

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

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 Julious [R11-5230] using R Version 3.0.3.

8. INFORMED CONSENT, TRIAL RECORDS, DATA PROTECTION, PUBLICATION POLICY, AND ADMINISTRATIVE STRUCTURE

The trial will be carried out in compliance with the protocol, the ethical principles laid down in the Declaration of Helsinki, in accordance with the ICH Harmonized Guideline for Good Clinical Practice (GCP), relevant BI Standard Operating Procedures (SOPs), the EU regulation 536/2014, and other relevant regulations. Investigators and site staff must adhere to these principles.

Standard medical care (prophylactic, diagnostic, and therapeutic procedures) remains the responsibility of the subject's treating physician.

The investigator will inform the sponsor immediately of any urgent safety measures taken to protect the trial subjects against any immediate hazard, as well as of any serious breaches of the protocol or of ICH GCP.

The Boehringer Ingelheim transparency and publication policy can be found on the following web page: trials.boehringer-ingelheim.com. As a general rule, no trial results should be published prior to archiving of the CTR.

The terms and conditions of the insurance coverage are made available to the investigator and the subjects, and are stored in the ISF.

8.1 TRIAL APPROVAL, SUBJECT INFORMATION, INFORMED CONSENT

This trial will be initiated only after all required legal documentation has been reviewed and approved by the respective Institutional Review Board (IRB / Independent Ethics Committee (IEC and competent authority (CA) according to national and international regulations. The same applies for the implementation of changes introduced by amendments.
Prior to a subject's participation in the trial, written informed consent must be obtained from each subject (or the subject's legally accepted representative) according to ICH-GCP and to the regulatory and legal requirements of the participating country. Each signature must be personally dated by each signatory and the informed consent and any additional subject-information form retained by the investigator as part of the trial records. A signed copy of the informed consent and any additional subject information must be given to each subject or the subject's legally accepted representative.

The subject must be given sufficient time to consider participation in the trial. The investigator or delegate obtains written consent of the subject's own free will with the informed consent form after confirming that the subject understands the contents. The investigator or delegate must sign (or place a seal on) and date the informed consent form. If a trial collaborator has given a supplementary explanation, the trial collaborator also signs (or places a seal on) and dates the informed consent.

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

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

8.2 DATA QUALITY ASSURANCE

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

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

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

8.3 RECORDS

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

ClinBase™
In the Human Pharmacology Centre (HPC) – Boehringer Ingelheim's Phase I unit – the validated ClinBase™ system is used 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

In accordance with regulatory requirements, the investigator should prepare and maintain adequate and accurate source documents and trial records for each trial subject that include all observations and other data pertinent to the investigation. Source data as well as reported data should follow the 'ALCOA principles' and be attributable, legible, contemporaneous, original, and accurate. Changes to the data should be traceable (audit trail).

Data reported on the CRF must be consistent with the source data or the discrepancies must be explained.

Before providing any copy of subjects' source documents to the sponsor, the investigator must ensure that all subject identifiers (e.g., subject's name, initials, address, phone number, and social security number) have properly been removed or redacted to ensure subject confidentiality.

If the subject is not compliant with the protocol, any corrective action (e.g. re-training) must be documented in the subject file.

For the CRF, data must be derived from source documents, for example:

- Subject identification: sex, year of birth (in accordance with local laws and regulations)
- Subject participation in the trial (substance, trial number, subject number, date subject was informed)
- Dates of subject's visits, including dispensing of trial medication
- Medical history (including trial indication and concomitant diseases, if applicable)
- Medication history
- AEs and outcome events (onset date [mandatory], and end date [if available])
- SAEs (onset date [mandatory], and end date [if available])
- Concomitant therapy (start date, changes)
- Originals or copies of laboratory results and other imaging or testing results, with proper documented medical evaluation (in validated electronic format, if available)
- ECG results (original or copies of printouts)
- Completion of subject's participation in the trial (end date; in case of premature discontinuation, document the reason for it, if known)
- Prior to allocation of a subject to a treatment into a clinical trial, there must be documented evidence in the source data (e.g. medical records) that the trial participant meets all inclusion criteria and does not meet any exclusion criteria. The absence of records (either medical records, verbal documented feedback of the subject or testing conducted specific for a protocol) to support inclusion/exclusion criteria does not make the subject eligible for the clinical trial.

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

8.3.2 Direct access to source data and documents

The investigator /institution will allow site trial-related monitoring, audits, IRB/IEC review and regulatory inspections. Direct access must be provided to the CRF and all source documents/data, including progress notes, copies of laboratory and medical test results, which must be available at all times for review by the Clinical Research Associate, auditor and regulatory inspector (e.g. FDA). They may review all CRFs and informed consents. The accuracy of the data will be verified by direct comparison with the source documents described in section 8.3.1. The sponsor will also monitor compliance with the protocol and GCP.

8.3.3 Storage period of records

Trial site:
The trial site(s) must retain the source and essential documents (including ISF) according to the local requirements 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 AND SUBJECT PRIVACY

Individual subject data obtained as a result of this trial is considered confidential and disclosure to third parties is prohibited with the exceptions noted in section 8.7.

Data protection and data security measures are implemented for the collection, storage and processing of patient data in accordance with the principles 6 and 12 of the WHO GCP handbook.

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

8.5.1 Collection, storage and future use of biological samples and corresponding data

Measures are in place to comply with the applicable rules for the collection, biobanking and future use of biological samples and clinical data, in particular

- Sample and data usage has to be in accordance with the separate biobanking informed consent
- The BI-internal facilities storing biological samples from clinical trial participants as well as the external banking facility are qualified for the storage of biological samples collected in clinical trials.
- An appropriate sample and data management system, incl. audit trail for clinical data and samples to identify and destroy such samples according to ICF is in place
- A fit for the purpose documentation (biomarker proposal, analysis plan and report) ensures compliant usage
- A fit for purpose approach will be used for assay/equipment validation depending on the intended use of the biomarker data

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

8.6 TRIAL MILESTONES

The **start of the trial** is defined as the date of the enrolment of the first subject in the trial.

The **end of the trial** is defined as the 'date of the last visit of the last subject in whole trial' ('Last Subject Completed') or 'end date of the last open AE' or 'date of the last follow-up test' or 'date of an AE has been decided as sufficiently followed-up', whichever is latest.

Early termination of the trial is defined as the premature termination of the trial for any reason before the end of the trial as specified in this protocol.

Temporary halt of the trial is defined as any unplanned interruption of the trial by the sponsor with the intention to resume it.

Suspension of the trial is defined as an interruption of the trial based on a Health Authority request.

The ethics committee/competent authority in each participating EU member state will be notified about the trial milestones according to the laws of each member state.

A final report of the clinical trial data will be written only after all subjects have completed the trial in all countries (EU or non-EU), so that all data can be incorporated and considered in the report.

The sponsor will submit to the EU database a summary of the final trial results within one year from the end of a clinical trial as a whole, regardless of the country of the last patient (EU or non-EU).

8.7 ADMINISTRATIVE STRUCTURE OF THE TRIAL

The trial is sponsored by Boehringer Ingelheim (BI).

The trial will be conducted at the under the supervision of the Principal Investigator. Relevant documentation on the participating (Principal) Investigators (e.g. their curricula vitae) will be filed in the ISF.

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

- Manage the trial in accordance with applicable regulations and internal SOPs
- Direct the clinical trial team in the preparation, conduct, and reporting of the trial
- ensure appropriate training and information of Clinical Trial Manager (CT Manager), Clinical Research Associates, and investigators of participating trial sites

The trial medication (BI 730357) will be provided by the Clinical Trial Supplies Unit, BI Pharma GmbH & Co. KG, Biberach, Germany.

Safety laboratory tests will be performed by the local laboratory of the trial site (MVZ Labor Ravensburg GbR, Ravensburg, Germany).

Analyses of BI 730357 concentrations in plasma will be performed at

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

Data management and statistical evaluation will be done by BI or a contract research organization appointed by BI according to BI SOPs.

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

9. REFERENCES

9.1 PUBLISHED REFERENCES

R05-1094 Guidance for industry: bioavailability and bioequivalence studies for orally administered drug products - general considerations (revision 1). In: Rockville: U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER); 2003.

R10-2509 European Medicines Agency (EMEA). Committee for Medicinal Products for Human Use (CHMP): guideline on the investigation of bioequivalence (London, 20 January 2010, doc. ref.: CPMP/EWP/QWP/1401/98 rev. 1/corr). http://www.emea.europa.eu; 2010.

R11-5230 Julious SA. Sample sizes for clinical trials. Boca Raton: Taylor & Francis Group; 2010.

R13-3515 Woodworth T, Furst DE, Alten R, Bingham C, Yocum D, Sloan V, Tsuji W, et.al. Standardizing assessment and reporting of adverse effects in rheumatology clinical trials II: the Rheumatology Common Toxicity Criteria v.2.0. J Rheumatol 34:6. 1401-1414. 2007.

R94-1529 Chow SC, Liu JP. Design and Analysis of Bioavailability and Bioequivalence Studies. New York: Marcel Dekker Inc; 1992.

9.2 UNPUBLISHED REFERENCES

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

001-MCS-36-472_RD-01 Noncompartmental Pharmacokinetic/Pharmacodynamic Analyses of Clinical Studies. Current version.

c09228382 Investigator Brochure BI 730357. Psoriasis - 1407.P01; Current version.

10. APPENDICES

Not applicable.

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

11.1 GLOBAL AMENDMENT 1

Date of amendment		07 March 2019
EudraCT number **EU number**		2018-004421-91
BI Trial number		1407-0032
BI Investigational Medicinal Product(s)		BI 730357
Title of protocol		Relative bioavailability of intended commercial formulations (iCF) of BI 730357 versus BI 730357 trial formulation 1 and bioavailability comparison of three different iCF batches following oral administration in healthy subjects (an open-label, single-dose, randomised, 2-way and 3-way crossover trial)
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		1) 3.3.3 (exclusion criterion 24) 2) 3.3.3 (exclusion criterion 25) 3) 3.3.3 (exclusion criterion 15) 4) 1.4.2
Description of change		1) Exclusion of pulse rates ranging from 45 to 49 bpm (inclusive) in combination with abnormal thyroid function or signs of diseases associated with bradycardia 2) Exclusion of ALT, AST and serum creatinine exceeding upper limit of normal 3) Limits for alcohol consumption were lowered 4) Syncope was added as risk for using an indwelling venous catheter or venepuncture
Rationale for change		1-4) Recommended/requested by Competent Authority and IEC