Clinical Trial Protocol

	Document Number:	**c22193484-01**
EudraCT No.	2018-003103-19	
BI Trial No.	1407-0033	
BI Investigational Medicinal Product	BI 730357	
Title	Investigation of pharmacokinetics and absolute oral bioavailability of BI 730357 administered as an oral dose with an intravenous microtracer dose of BI 730357 BS (C-14) in healthy male volunteers	
Lay Title	A study in healthy men to measure the amount of BI 730357 in the blood when taken as a tablet	
Clinical Phase	I	
Clinical Trial Leader	Phone: Fax:	
Principal Investigator	Phone: Fax:	
Status	Final Protocol	
Version and Date	Version: 1.0	Date: 29 Nov 2018

CLINICAL TRIAL PROTOCOL SYNOPSIS

Company name	Boehringer Ingelheim
Protocol date	29 Nov 2018
Revision date	Not applicable
BI trial number	1407-0033
Title of trial	Investigation of pharmacokinetics and absolute oral bioavailability of BI 730357 administered as an oral dose with an intravenous microtracer dose of BI 730357 BS (C-14) in healthy male volunteers
Principal Investigator:	
Trial site	
Clinical phase	I
Trial rationale	This trial is intended to examine the absolute oral bioavailability of BI 730357 as tablet formulation for oral administration. The data are considered necessary to further understand the pharmacokinetics of BI 730357.
Trial objective	To determine the absolute oral bioavailability of BI 730357 after administration of 50 mg BI 730357 as tablet and 100 µg BI 730357 BS (C-14) as intravenous microtracer
Trial design	Non-randomized, open-label, single period, single arm design
Trial endpoints:	Primary endpoints: $AUC_{0-\infty}$ [C-14]BI 730357 BS (after i.v. administration) $AUC_{0-\infty}$ BI 730357 (after p.o. administration) Secondary endpoints: None defined.
Number of subjects **total entered** **each treatment**	 6 * 6 * * In case a subject vomits within 12 hours after administration of 50 mg BI 730357 as tablet on Day 1 or a subject drops out for other reasons, an additional subject may be entered and dosed in order to ensure at least 6 subjects completed the trial as per protocol. Thus, as up to 2 additional subjects may be entered, the actual number of subjects entered may increase up to a maximum of 8 subjects.
Diagnosis	Not applicable

Main criteria for inclusion	Healthy male subjects, age of 18 to 65 years (inclusive), body mass index (BMI) of 18.5 to 29.9 kg/m^2 (inclusive)
Test product 1 (T)	BI 730357 film-coated tablet (test treatment T)
dose	50 mg
mode of admin.	Oral with 240 mL of water after an overnight fast of at least 10 h
Test product 2 (R)	BI 730357 BS (C-14) as intravenous solution (reference treatment R)
dose	100 µg infusion consisting of 98.0 µg unlabelled BI 730357 mixed with 2.0 µg labelled [C-14]BI 730357 BS in 10 mL i.v. solution (10 µg BI 730357 BS (C-14) / mL) The radioactive dose per infusion has been calculated to not exceed 0.3 µCi = 0.01 MBq.
mode of admin.	Intravenous infusion of 15 min starting at 1.25 hours (i.e. around t_{max}) after an orally administered dose of 50 mg BI 730357 (as tablet)
Duration of treatment	Oral dose (test treatment T): Single oral dose, Day 1 Intravenous dose (reference treatment R): Single i.v. infusion of microtracer dose over 15 min, Day 1
Statistical methods	Absolute bioavailability (F) will be estimated by the ratio of the geometric means (test treatment T / reference treatment R) for the primary endpoints (dose normalized) $AUC_{0-\infty}$. Additionally, their two-sided 90% confidence intervals (CIs) will be provided. This method corresponds to the two one-sided t-tests procedure, each at the 5 % significance level. Since the main focus is on estimation and not testing, an acceptance range was not specified. The statistical model will be an ANOVA on the logarithmic scale including the fixed effect for 'formulation' and 'subject' as a random effect. CIs will be calculated based on the residual error from ANOVA. Descriptive statistics will be calculated for all endpoints.

FLOW CHART

Visit	Day	Planned time (relative to first drug administration) [h:min]	Approximate clock time of actual day [h:min]	Event and comment	Safety laboratory	PK_{plasma} BI 730357	PK_{plasma} [C-14]BI 730357 BS	12-lead ECG	Vital signs (BP, PR)	Local tolerability assessment	Questioning for AEs and concomitant therapy[7]
1	-21 to -2			Screening (SCR)[1]	x			x	x		
2	-1	-18:00	14:00	Admission to trial site	x[5]						▲
		-14:00	18:00	Dinner							
		-10:30	21:30	Light supper (voluntary)[8]							
	1	-2:00	06:00			x[2,3]	x[3]	x[3]	x[3]		
		0:00	08:00	**Drug administration (50 mg BI 730357 as tablet, oral)**							
		1:00	09:00			x					
		1:15	09:15	Start of IV infusion containing BI 730357 BS (C-14)							
		1:20	09:20				x				
		1:25	09:25				x				
		1:30	09:30	Stop of IV infusion		x	x				
		1:45	09:45				x			x	
		2:00	10:00	240 mL fluid intake		x	x	x			
		2:30	10:30			x	x				
		3:30	11:30			x	x				
		4:00	12:00	240 mL fluid intake				x	x		
		5:00	13:00	Lunch[4]		x	x				
		7:00	15:00			x	x				
		11:00	19:00	Dinner							
		12:00	20:00			x	x				
	2	24:00	08:00	Breakfast (voluntary)[4], discharge from trial site	x	x	x	x	x	x	
	4	72:00	08:00	Ambulatory visit[9]		x	x				
	6	120:00	08:00	Ambulatory visit[9]	x	x	x				
	8	168:00	08:00	Ambulatory visit[9]		x	x				▼
3	9 to 15			End-of-trial (EoTrial) examination[6]	x			x	x		x

1. Subject must be informed and written informed consent obtained prior to starting any screening procedures. Screening procedures include physical examination, check of vital signs, ECG, safety laboratory (including drug screening), demographics (including determination of body height and weight, smoking status and alcohol history), relevant medical history, concomitant therapy and review of inclusion/exclusion criteria.
2. Including pharmacogenomics sample
3. The time is approximate; the procedure is to be performed and completed within 3 h prior to drug administration.
4. If several actions are indicated at the same time point, the intake of meals will be the last action.
5. Safety lab including urine drug and alcohol screening.
6. At the end-of-trial visit, the EoTrial examination includes physical examination, vital signs, ECG, safety laboratory, recording of AEs and concomitant therapies.
7. AEs and concomitant therapies will be recorded throughout the trial; during in-house days subjects will be specifically asked for twice daily.

8. To be consumed within 30 min to allow 10 h fasting prior to drug administration.
9. The planned time is approximate; the ambulatory visit and the respective procedures are to be performed within a time window of +/- 3 hours to the planned time.

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ABBREVIATIONS

ADME	Absorption, distribution, metabolism, and excretion
AE	Adverse event
AESI	Adverse events of special interest
ALCOA	Attributable, legible, contemporaneous, original, accurate
AMS	Accelerator mass spectometry
ANOVA	Analysis of variance
$AUC_{0-\infty}$	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity
BA	Bioavailability
BCS	Biopharmaceutics Classification System
BI	Boehringer Ingelheim
BMI	Body mass index (weight divided by height squared)
BP	Blood pressure
BS	base
C_{max}	Maximum measured concentration of the analyte in plasma after oral administration
CA	Competent authority
CI	Confidence interval
CNS	Central nervous system
CRF	Case Report Form, paper or electronic (sometimes referred to as ‘eCRF’)
CRO	Contract Research Organisation
CTL	Clinical Trial Leader
CTM	Clinical Trial Manager
CTP	Clinical trial protocol
CTR	Clinical trial report
CTSU	Clinical Trial Supplies Unit

DILI	Drug induced liver injury
ECG	Electrocardiogram
eCRF	Electronic case report form
eDC	Electronic data capture
EDTA	Ethylenediaminetetraacetic acid
EoTrial	End of trial
EudraCT	European Clinical Trials Database
FU	Follow-up
GCP	Good Clinical Practice
gMean	Geometric mean
hERG	Human-ether-à-go-go related gene
hLXRα	human liver X receptor α
IB	Investigator's brochure
iCF	intended clinical formulation
ICRP	International Commission on Radiological Protection
IC50	50% inhibitory concentration
IEC	Independent Ethics Committee
IPD	Important protocol deviation
IQRM	integrated quality and risk management
IRB	Institutional Review Board
ISF	Investigator site file
LC-MS/MS	Liquid chromatography with tandem mass spectrometry
MDA	Methylenedioxyamphetamine
MDMA	Methylenedioxymethamphetamine
MedDRA	Medical Dictionary for Regulatory Activities
MRD	Multiple-rising dose
NOAEL	No observed adverse effect level
PK	Pharmacokinetic(s)
PKS	Pharmacokinetic set
PP	Polypropylene
PR	Pulse rate
QT	Time between start of the Q-wave and the end of the T-wave in an electrocardiogram
QTc	QT interval corrected for heart rate using the method of Fridericia (QTcF) or Bazett (QTcB)

R	Reference treatment
REP	Residual effect period
RORα	Retinoic acid related orphan receptor α (protein)
RORβ	Retinoic acid related orphan receptor β (protein)
RORγ	Retinoic acid related orphan receptor γ (full length protein)
RORγt	Retinoic acid related orphan receptor γt (splice variant of RORγ protein)
SAE	Serious adverse event
SCR	Screening
SOP	Standard operating procedure
SRD	Single-rising dose
T	Test product or treatment
t_{max}	Time from (last) dosing to the maximum measured concentration of the analyte in plasma
TS	Treated set
TSAP	Trial statistical analysis plan
ULN	Upper limit of normal
XTC	Ecstasy

1. INTRODUCTION

BI 730357 is an antagonist at the retinoic acid-related orphan receptor γt (RORγt). It is being developed as an oral therapy for the treatment of patients with psoriasis (PsO) as well as psoriatic arthritis (PsA), ankylosing spondylitis (AS), asthma, and Crohn's disease (CD). RORγ antagonism is a novel mechanism of action.

1.1 MEDICAL BACKGROUND

Retinoic acid-related orphan receptor γt (RORγt) is a nuclear hormone receptor/transcription factor expressed in T helper 17 (Th17) cells and in distinct subsets of lymphoid cells, including natural killer cells, innate lymphoid cells, and γδ T-cells. Upon cell activation, in response to multiple activation signals including cytokines and T cell receptor engagement, RORγt regulates the transcription of interleukin (IL)-17A, IL-17F, and IL-22 genes, and of IL-23 receptor gene. Emerging clinical science indicates a pivotal role for the Th17 axis in the pathogenesis of PsO, and other immunologically-mediated diseases. By blocking RORγt-mediated transcription of critical pro-inflammatory cytokines, and IL-23R, and consequently their downstream signaling, RORγt antagonism could prove efficacious in the treatment of Th17-mediated diseases [c09228382].

1.2 DRUG PROFILE

1.2.1 Non-clinical data

1.2.1.1 Non-clinical pharmacokinetics and metabolism

1.2.1.2 Safety pharmacology

1.2.1.3 Toxicology

Repeated dose toxicology

Genetic Toxicology

Phototoxicity

1.2.2 Clinical data

Up to now, BI 730357 has clinically been tested by Boehringer Ingelheim in a completed first-in- human trial, a multiple-rising dose trial (report in preparation) and a human ADME (hADME) trial (being analyzed) [c09228382; c14109663-03; c22159106-02].

- In the first-in-human trial BI 730357 was administered in doses ranging from 2 mg through 800 mg to a total of 84 healthy male volunteers. The maximum dose given under fasted conditions was 400 mg as tablet.
- The multiple-rising-dose trial tested administration of BI 730357 over 14 to 28 days with daily doses of 25 to 400 mg. The highest dose tested under fasting conditions was 200 mg dose for 28 days.
- The hADME trial tested the metabolism of a 50 mg dose of radioactively labelled BI 730357 BS (C-14) administered as an oral solution.

1.2.2.1 Clinical pharmacokinetics

1.2.2.2 Clinical safety

1.2.3 Residual Effect Period

The Residual Effect Period (REP) of BI 730357 is 7 days. This is the period after the last dose with measurable drug levels and/or pharmacodynamic effects still likely to be present.

1.3 RATIONALE FOR PERFORMING THE TRIAL

This trial is intended to examine the absolute oral bioavailability of BI 730357 using an intravenous [C-14]-microtracer approach. The data are considered necessary to further understand the pharmacokinetics of BI 730357.

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.

Procedure-related risks

The use of an indwelling venous catheter for the purpose of intravenous infusion or blood sampling may result in mild bruising, and in rare cases, in transient inflammation of the wall of the vein, or nerve injury, potentially resulting in paraesthesia, reduced sensibility, and/or pain for an indefinite period. The same risks apply for venepuncture with the purpose of blood sampling or safety laboratory assessment.

The solvent for the intravenous infusion containing a mixture of labelled and unlabelled BI 730357 is 10% PEG 400 in saline. Therefore, in case of inadvertent paravenous drug administration apart from local swelling no tissue damage is expected.

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.

Drug-related risks and safety measures

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

Risks related to oral BI 730357 administration

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 up to 400 mg BI 730357 under fasted conditions is supported by preclinical, as well as clinical safety data from first-in-human trial 1407.1, the multiple-rising-dose trial 1407-0002 and the hADME trial 1407-0031 (see Section 1.2.2):

Administration of a microtracer dose of 100 µg BI 730357 BS (C-14) as infusion is expected to only marginally increase the systemic exposure to BI 730357.

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).

As with other immune-targeted therapies, impaired host defense is a theoretical target-related toxicity, potentially resulting in increased risk of infection and/or malignancy. Th17 cells play an important role in defense against extracellular bacteria and fungi at mucosal surfaces [R16-3166, R16-3149]. IL-17 antagonists are associated with increased infections [R13-2643]. Homozygous, but not heterozygous RORγ knockout mice have a high incidence of T-cell lymphoma, thought to originate in the thymus [R16-2630]. While the translatability of the knockout phenotype to pharmacological RORγ antagonism and to humans is unknown, this raises the hypothetical concern for clinical T-cell lymphoma risk. The exact cause of T-cell lymphomas in RORγ knockout mice is not fully understood, but changes in homeostasis in the thymus, such as thymocyte apoptosis and proliferation, are thought to play a role. AEs and SAEs consistent with malignancy, and specifically those representing lymphoma, are to be carefully monitored and evaluated throughout the BI 730357 clinical development program, and monitoring of peripheral blood lymphocyte subsets integrated into clinical trials.

As with all drugs, the potential for hypersensitivity and allergic reactions has to be taken into consideration when BI 730357 is administered.

Risks related to intravenous administration of BI 730357 BS (C-14) solution

No intravenous route is planned for therapeutic use of BI 730357. Therefore, in accordance with the guideline on non-clinical safety studies on microdose trials (ICH-M3(R2), [R15-0594]), the intravenous microtracer dose of 100 µg BI 730357 BS (C-14) is considered

to be adequately qualified by the existing oral toxicity studies where adequate exposure margins have been reached. An investigation of intravenous local tolerance of the drug substance is not recommended in this situation because the administered dose is very low (100 µg maximum) and no novel i.v. vehicle is used.

BI 730357 is labelled with isotope [^{14}C] which is necessary for the purpose of this microtracer trial in order to distinguish the intravenously administered labelled drug from the unlabelled oral drug. The radioactive dose per infusion will be approximately 0.01 MBq. The mean radiation burden per subject has been calculated to be 0.001 mSv [c25209040] and thereby falls into the ICRP 1 category (trivial level of risk).

Summary of benefit-risk assessment

In the first-in-human trial 1407.1, administration of single doses up to 400 mg BI 730357 under fasted conditions and up to 800 mg under fed conditions was safe and well tolerated [c16462083-01]. In the current trial, it is planned that healthy male volunteers will receive a single oral dose of 50 mg BI 730357 as a tablet and an intravenous microdose of 100 µg BI 730357 BS (C-14) as infusion. The dose of 50 mg is at the lower end of the anticipated therapeutic dose range and was selected based on safety aspects as well as solubility limitations. Each participant will receive only one infusion containing a radioactive dose <0.1 mSv (ICRP 1 category, negligible radio burden).

Trial participants are healthy volunteers from a broad age range to allow the trial to achieve the study goals. 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.

The risk associated with the expected maximal radiation burden falls in ICRP category 1 with minor level risk and in WHO Category 1, i.e. within variations of natural background radioactivity. This is considered to be acceptable.

The investigation of the absolute bioavailability of this BCS class II compound contributes substantially to a better understanding of BI 730357's pharmacokinetics. The results of this trial are necessary for the further development of BI 730357. Successful development of BI 730357 is expected to provide a new valuable treatment option for patients suffering from psoriasis and Th17-mediated diseases.

The risks of the participating volunteers are minimized and justified when compared to the potential benefits of this trial.

2. TRIAL OBJECTIVES AND ENDPOINTS

2.1 MAIN OBJECTIVES, PRIMARY AND SECONDARY ENDPOINTS

2.1.1 Main objectives

The main objective of this trial is to investigate the absolute oral bioavailability of 50 mg BI 730357 administered as tablet (test treatment, T) compared with 2 µg of [C-14]BI 730357 BS administered as intravenous microtracer. The total dose administered i.v. is a mixture of 2 µg labelled [C-14]BI 730357 BS mixed with 98 µg of unlabelled BI 730357 (reference treatment, R).

2.1.2 Primary endpoints

The following pharmacokinetic parameters will be determined in plasma for [C-14]BI 730357 BS after intravenous administration and for BI 730357 after oral administration:

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

2.1.3 Secondary endpoints

No secondary endpoints are defined for this trial.

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

This Phase 1 study will be performed as a non-randomised, open-label, single period, single arm trial in healthy male subjects in order to compare the test treatment (T) to the reference treatment (R). Treatment T will be one oral tablet of 50 mg BI 730357 (intended clinical formulation (iCF)). Treatment R will be an intravenous microtracer infusion of 100 µg BI 730357 BS (C-14) consisting of 2 µg labelled [C-14]BI 730357 BS mixed with 98 µg unlabelled BI 730357 in 10 mL i.v. solution (10 µg BI 730357 BS (C-14) /mL). Both treatments will be given in the fasted state. For details, refer to Section 4.1.

Drug administration in treatment R will start 1.25 hours after drug administration in treatment T, i.e. at the time of the expected t_{max} of treatment T.

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

To investigate the absolute bioavailability, a single arm, single period trial design using a microtracer approach* was considered the favorable design compared to the traditional cross-over design for the following reasons:

- Like with a traditional cross-over design, each subject serves as his own control removing inter-subject variability. Additionally, day-to-day variability within a subject is also eliminated as potential confounding variable since each subject is exposed to the two treatments in parallel, i.e. treatment R will be administered at t_{max} of treatment T
- Expected favorable safety due to very low exposure levels after an intravenous microdose
- The radioactive dose per infusion has been calculated not to exceed 0.3 µCi = 0.01 MBq (radiation burden per subject ~ 0.001 mSv), and thus falls into the ICRP 1 category. The radiation burden is negligible [R15-3219].
- Shortened duration of the clinical trial

The open-label treatment is not expected to bias results since the study endpoints are derived from measurements of plasma concentrations of the analytes.

*In this context 'microtracer' is defined as an intravenous dose of an isotopically labelled drug in an absolute bioavailability study administered as 1% of the pharmacologic dose or 0.1 mg, whichever is lower [R17-1799].

3.3 SELECTION OF TRIAL POPULATION

It is planned that 6 healthy male subjects will enter the study. They will be recruited from the volunteers' pool of the trial site or, if necessary, via advertisement. In case a subject vomits within 12 h after administration of treatment T or a subject drops out for other reasons, up to 2 additional subjects may be entered and dosed to assure that 6 subjects will complete the study as per protocol. Thereby, the actual number of subjects entered may increase up to a maximum of 8.

The current trial is designed to investigate the absolute oral bioavailability of BI 730357. Healthy male subjects are an ideal population for the objectives of this trial, since they provide relatively stable physiological, biochemical and hormonal conditions, i.e. the absence of disease-related variations and relevant concomitant medications.

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

3.3.1 Main diagnosis for trial entry

The study will be performed in healthy subjects.

3.3.2 Inclusion criteria

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

1. Healthy male subjects according to the assessment of the investigator, as based on a complete medical history including a physical examination, vital signs (BP, PR), 12-lead ECG, and clinical laboratory tests
2. Age of 18 to 65 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. Subjects who are sexually active must use, with their partner, highly effective contraception from the time of administration of trial medication until 4 months after administration of trial medication. Adequate methods are:
   - Condoms *plus* use of hormonal contraception by the female partner that started at least 2 months prior to administration of trial medication (e.g. implants, injectables, combined oral or vaginal contraceptives, intrauterine device) *or*
   - Condoms *plus* surgical sterilization (vasectomy at least 1 year prior to enrolment) *or*
   - Condoms *plus* surgically sterilised partner (including hysterectomy) *or*
   - Condoms *plus* intrauterine device *or*
   - Condoms *plus* partner of non-childbearing potential (including homosexual men)

     Subjects are required to use condoms to prevent unintended exposure of the partner to the study drug via seminal fluid. Male and female condoms must not be used together.

Alternatively, true abstinence is acceptable when it is in line with the subject's preferred and usual lifestyle. If a subject is usually not sexually active but becomes active, whit their partner, they must comply with the contraceptive requirements detailed above.

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 139 mmHg, diastolic blood pressure outside the range of 45 to 89 mmHg, or pulse rate outside the range of 40 to 100 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. Clinically significant gastrointestinal (including known or suspected inflammatory bowel disease), 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 5 cigarettes or 1 cigar or 1 pipe per day)
14. Inability to refrain from smoking on specified trial days
15. Average intake of more than 24 units of alcohol per week (1 unit of alcohol equals approximately 250 mL of beer, 100 mL of wine or 35 mL of spirits)
16. Drug abuse or positive drug screening
17. Blood donation or loss of more than 100 mL within 60 days of planned administration of trial medication or intended blood donation during the trial. Donation or loss of more than 1.5 litres of blood in the 10 months prior to planned administration of trial medication.
18. Intention to perform excessive physical activities within 4 days 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 QTcF intervals that are repeatedly greater than 450 msec in males) 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 criterion applies:

23. Unwillingness to adhere to the rules of UV-light protection as described in Section 4.2.2.2
24. A positive QuantiFERON-TB Gold Test

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.

Since the risks of drug exposure of a (pregnant) female partner of a male study participant via the seminal fluid are yet unknown, adequate contraception as outlined in Section 3.3.2 is a prerequisite for participation in the study.

3.3.4.1 Discontinuation of trial treatment

An individual subject will discontinue trial treatment if:

1. The subject wants to discontinue trial treatment, without the need to justify the decision.
2. The subject has repeatedly shown to be non-compliant with important trial procedures and, in the opinion of both, the investigator and sponsor representative, is not willing or able to adhere to the trial requirements in the future.

3. The subject needs to take concomitant medication that interferes with the investigational medicinal product or other trial treatment.
4. The subject can no longer receive trial treatment for medical reasons (such as surgery, adverse events (AEs), or diseases).
5. The subject has an elevation of AST and/or ALT ≥3-fold ULN and an elevation of total bilirubin ≥2-fold ULN (measured in the same blood sample) and/or needs to be followed up according to the DILI checklist provided in the ISF.

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

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

3.3.5 Replacement of subjects

In case a subject vomits within 12 h after oral trial drug administration suggesting an incomplete absorption of the tablet or a subject drops out for other reasons, an additional subject may be entered and dosed to ensure that 6 subjects will complete the study as per protocol. In total, no more than 2 subjects will be replaced.

In case some subjects do not complete the trial, the Trial Clinical Monitor together with the Trial Pharmacokineticist and the Trial Statistician are to decide, if and how many subjects will be replaced. Replacement of subjects and dosing of additional subjects as described above should always be done in mutual agreement with the principal investigator. A replacement subject will be assigned a unique trial subject number.

4. TREATMENTS

4.1 INVESTIGATIONAL TREATMENTS

The investigational unlabelled product for test treatment T has been manufactured by BI Pharma GmbH & Co. KG. BI 730357 50 mg film-coated tablets are the intended commercial formulation (iCF) and will be administered orally.

Radiolabelled BI 730357 BS (C-14) for reference treatment R is administered as an intravenous solution. The powder used for intravenous solution contains radiolabelled [C-14]BI 730357 BS and unlabelled BI 730357 and both components are manufactured and mixed by BI Pharma GmbH & Co. KG. The intravenous solution from this mixture is made by

4.1.1 Identity of the Investigational Medicinal Products

The characteristics of the investigational medicinal product (1) for test treatment T are given below:

Name:	BI 730357 intended commercial formulation (iCF)
Substance:	BI 730357
Pharmaceutical formulation:	Film-coated tablet
Source:	BI Pharma GmbH & Co. KG, Germany
Unit strength:	50 mg
Posology:	1-0-0
Route of administration:	oral
Duration of use:	single dose

The characteristics of the investigational medicinal product (2) for reference treatment R are given below:

Name:	BI 730357 BS (C-14) intravenous solution
Substance:	BI 730357 mixed with [C-14] BI 730357 BS
Pharmaceutical formulation:	Intravenous solution
Source:	
Unit strength:	100 µg BI 730357 - consisting of 2 µg labelled [C-14]BI 730357 BS mixed with 98 µg unlabelled BI 730357 - in 10% PEG 400 in saline solution of 10 mL volume (concentration of BI 730357 BS (C-14): 10 µg/mL)
Posology:	1-0-0
Route of administration:	intravenous
Duration of use:	single infusion over 15 min

4.1.2 Selection of doses in the trial

The oral dose of BI 730357 tested in this trial is one single dose of 50 mg. This dose is below the highest doses (single dose up to 400 mg under fasted and up to 800 mg under fed conditions) already tested in healthy volunteers in previous trials [c16462083-01]. The dose of 50 mg was tested in the single rising dose study and was safe and well-tolerated (see Section 1.2). A dose of 50 mg is considered adequate for the objectives of the current trial.

Using the microtracer approach to investigate the absolute bioavailability, the intravenously administered dose is not expected to significantly add to the systemic drug concentrations arising from the oral administration [R17-1799]. The oral dose (50 mg BI 730357) is ~500-fold higher than the intravenously infused dose (100 µg). Therefore, exposure of BI 730357 resulting from the infusion is considered negligible (see Section 1.4).

The radioactive dose administered via infusion has been calculated to not exceed 0.3 µCi=0.01 MBq, and thus falls into the ICRP 1 category (negligible radiation burden) [R18-1905].

4.1.3 Method of assigning subjects to treatment groups

This is an open-label, phase I, single-dose study. All subjects receive the same treatment. Once a subject number has been assigned, it cannot be reassigned to any other subject.

4.1.4 Drug assignment and administration of doses for each subject

This trial is a non-randomised, open-label, single period, single arm trial. All subjects will receive the same treatments. The treatments to be evaluated are outlined in Table 4.1.4: 1 below.

Table 4.1.4: 1 Dosage and treatment schedule

Treatment	Substance	Formulation	Unit strength	Dosage	Total dose
T (Test)	BI 730357	Film-coated tablet	50 mg	1 tablet as single dose on Day 1	50 mg
R (Reference)	BI 730357 BS (C-14)	i.v. solution	10 µg/mL	i.v. infusion of 10 mL over 15 min on Day 1	100 µg

Administration of treatment T will be performed after subjects have fasted overnight; fasting is to start no later than 10 h before the scheduled dosing.

The oral medication (treatment T) will be administered as a single oral dose together with about 240 mL of water to a subject in the sitting/standing position under supervision of the investigating physician or an authorised designee.

From administration of treatment T until 5 hours thereafter, subjects are not allowed to lie down (i.e. no declination of the upper body of more than 45 degrees from upright posture) except when needed for study assessments or when indicated by the investigator. During the intravenous infusion subjects will be in a semi supine position.

The microtracer (treatment R) will be administered starting 1.25 h after treatment T as a constant intravenous infusion over 15 min to a subject in semi supine position under supervision of the investigating physician or an authorised designee. Start and end time of the infusion will be recorded. For administration of the intravenous microtracer solution an indwelling catheter is placed into an arm vein of the subject and will be kept patent with a saline infusion. A second indwelling catheter used for collection of blood samples will be placed on the contralateral arm. The handling instructions for the intravenous microtracer will be filed in the ISF.

For drug administrations, 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.

Subjects will be kept under close medical surveillance until 24 h after administration of treatment T. The in-house stay can be extended in case considered medically necessary by the investigator.

4.1.5 Blinding and procedures for unblinding

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

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

4.1.6 Packaging, labelling, and re-supply

The investigational product for treatment T (BI 730357, 50 mg tablets) will be provided by BI. Drug supply will be packaged and labelled in accordance with local law and the principles of Good Manufacturing Practice.

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

Both components (radiolabeled [C-14]BI 730357 BS mixed with unlabeled BI 730357) used for manufacturing of the intravenous solution will be provided to by the Isotope Chemistry of Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach, Germany. The final container used for administration of the radiolabeled drug product will be a syringe for intravenous infusions and will be labeled according to GMP Annex 13/EU GMP Guideline and local drug law.

For details of packaging 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 local clinical monitor (as provided in the list of contacts) is to be contacted immediately.

4.1.8 Drug accountability

pharmacy will receive the investigational medicinal product 1 (50 mg BI 730357 film-coated tablet) delivered from the sponsor once the below mentioned requirements are fulfilled. pharmacy will deliver investigational medicinal products 1 and 2 to the investigator upon availability of a valid prescription from the investigator. The investigator also will not order the investigational medicinal products from the pharmacy before these requirements are fulfilled:

- Approval of the clinical trial protocol by the IRB / ethics committee
- Availability of a signed and dated clinical trial contract between the sponsor and the investigational site
- Approval/notification of the regulatory authority, e.g. competent authority
- Availability of a signed and dated clinical trial protocol
- Availability of a licence for clinical research using radioactive isotopes

Only authorised personnel documented in the form 'Trial Staff List' may dispense medication to trial subjects. The trial medication must be administered in the manner specified in the CTP.

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

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

4.2 OTHER TREATMENTS, EMERGENCY PROCEDURES, RESTRICTIONS

4.2.1 Other treatments and emergency procedures

There are no special emergency procedures to be followed. No additional treatment is planned. However, if adverse events require treatment, the investigator can authorise symptomatic therapy. In those cases, subjects will be treated as necessary and, if required, kept under supervision at the trial site or transferred to a hospital until all results of medical evaluations are acceptable.

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

In principle, no concomitant therapy is allowed except for paracetamol. Limited doses of paracetamol (up to 2 grams per day) are allowed prior to entry in the clinic and until the end of trial after prescription by a physician to treat aches and pains. However, in case of adverse events in need of treatment, a concomitant therapy will be permitted. In case of AEs the volunteers will be treated as necessary and if required will be kept under constant supervision at the trial centre or transferred to hospital until all the results of the evaluations have returned to a medically acceptable level. All concomitant or rescue therapies will be recorded (including time of intake on study days) on the appropriate pages of the CRF.

In case concomitant therapy is necessary, drugs that might reasonably influence the results of the trial, that might prolong the QT/QTc interval,
or that might otherwise negatively affect the safety of the subjects, should be avoided if possible.

4.2.2.2 Restrictions on diet and life style

While admitted to the trial site, the subjects will be instructed not to consume any foods or drinks other than those provided by the staff. Standardised meals will be served at the times indicated in the Flow Chart. When not fasting, meals and snacks (such as decaffeinated coffee, herbal tea, fruit, and biscuits) will be provided according to standard operating procedures (SOPs).

Subjects are to be fasted for at least 10 h prior to administration of treatment T. No food is allowed for at least 5 h after treatment T. For fasting times before safety laboratory investigations see Section 5.2.3.

From 1 h before administration of treatment T 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 after treatment T, total fluid intake is restricted to 3000 mL.

Green tea, 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 admission to the trial site until after the last PK is collected.

Poppy-seed containing products should not be consumed within 2 days before screening and starting 2 days before admission to the trial site until after the last PK sample is collected.

Alcoholic beverages are not allowed within 48 hours before screening and before admission to the trial site and during in-house confinement at the trial site. During ambulatory phases alcohol consumption is restricted to 2 units per days.

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

Methylxanthine-containing drinks or foods (such as coffee, tea, cola, energy drinks, or chocolate) are not allowed from 24 h before admission to the trial site and during in-house confinement at the trial site.

Excessive physical activity (such as competitive sport) should be avoided within 96 h before screening and starting 96 h before admission to the trial site until the end-of-trial examination.

Direct exposure to the sun or exposure to solarium radiation should be avoided during the entire study. When exposed to sunlight, study participants should protect skin areas not covered by clothes by using sun-protection creams and lip balms with sun protection factor 30 or higher with protection against UV-A and UV-B. Patients should wear sun glasses when exposed to direct sun or other sources of UV-light. These protection measures must be applied until the end of study.

Adequate contraception is to be maintained throughout the course of the trial and for a defined time period afterwards (see Section 3.3.2 for 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. ASSESSMENT

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

5.2.2 Vital signs

Systolic and diastolic blood pressures (BP) as well as pulse rate (PR) or heart rate (heart rate is considered to be equal to pulse rate) will be measured by a blood pressure monitor (Dinamap CareScape VC150, GE Healthcare) 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 4 h (at admission on Day -1, only) or at least 10 h (all other time points). Subjects do not need to have fasted for drug screening and for infectious serology at the discretion of the investigator. Overnight fasting is not required at the discretion of the investigator or designee for re-tests.

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

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

Table 5.2.3: 1 Routine laboratory tests

Functional lab group	BI test name [comment/abbreviation]	A	B
Haematology	Haematocrit	X	X
	Haemoglobin	X	X
	Red Blood Cell Count/Erythrocytes	X	X
	Reticulocytes, absol.	X	X
	White Blood Cells/Leucocytes	X	X
	Platelet Count/Thrombocytes (quant)	X	X
Automatic WBC differential, relative	Neutrophils/Leukocytes; Eosinophils/Leukocytes; Basophils/ Leukocytes; Monocytes/Leukocytes; Lymphocytes/Leukocytes	X	X
Automatic WBC differential, absolute	Neutrophil, absol.; Eosinophils, absol.; Basophils, absol.; Monocytes, absol.; Lymphocytes, absol.	X	X
Manual differential WBC (if automatic differential WBC is abnormal)	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
	INR (International Normalization Ratio)	X	X
Enzymes	AST [Aspartate transaminase] /GOT, SGOT	X	X
	ALT [Alanine transaminase] /GPT, SGPT	X	X
	Alkaline Phosphatase	X	X
	Gamma-Glutamyl Transferase	X	X
	Creatine Kinase [CK]	X	X
	Creatine Kinase Isoenzyme MB [only if CK is elevated]	X	X
	Lactic Dehydrogenase	X	X
	Lipase	X	X
	Amylase (total)	X	X
Hormones	Thyroid Stimulating Hormone	X	--
Substrates	Glucose (Serum)	X	X
	Creatinine	X	X
	Bilirubin, Total	X	X
	Bilirubin, Direct	X	X
	Protein, Total	X	X
	Albumin	X	X
	Alpha glycoprotein acid	X	X
	C-Reactive Protein (Quant)	X	X
	Uric Acid	X	X
	Urea	X	X
	Cholesterol, total	X	X
	Triglyceride	X	X
Electrolytes	Sodium	X	X
	Potassium	X	X
	Magnesium	X	X
	Calcium	X	X

Table 5.2.3: 1 Routine laboratory tests (cont.)

Functional lab group	BI test name [comment/abbreviation]	A	B
Urinalysis (Stix)	Urine Nitrite (qual) Urine Protein (qual) Urine Glucose (qual) Urine Ketone (qual) Urobilinogen (qual) Urine Bilirubin (qual) Urine RBC/Erythrocytes (qual) Urine WBC/Leucocytes (qual) Urine pH	X X X X X X X X X	X X X X X X X X X
Urine sediment (microscopic examination if erythrocytes, leukocytes nitrite or protein are abnormal in urine)	Only positive findings will be reported (for instance, the presence of sediment bacteria, casts in sediment, squamous epithelial cells, erythrocytes, leukocytes)		

A: parameters to be determined at Visit 1 (screening examination)
B: parameters to be determined at Visit 2, Day -1, Day 2 and Day 6, and at Visit 3 (end-of-trial examination)

The tests listed in Table 5.2.3: 2 are exclusionary laboratory tests that may be repeated as required. The results will not be entered in the CRF/database and will not be reported in the CTR. Except for drug screening, it is planned to perform these tests during screening only. Drug screening will be performed at screening and on Day -1 of the treatment period.

To encourage compliance with alcoholic restrictions, an alcohol test in urine will be performed at screening and on Day -1 prior to the 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 the safety laboratory of
. The drug and alcohol screening tests will be performed using the ADVIA Chemistry XPT system.

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

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 Alcohol
Infectious serology (blood)	Hepatitis B surface antigen (qualitative) Hepatitis B core antibody (qualitative) Hepatitis C antibodies (qualitative) HIV-1 and HIV-2 antibody (qualitative) QuantiFERON-TB Gold

5.2.4 Electrocardiogram

5.2.4.1 12-lead resting ECG

Recording

Twelve-lead resting ECGs (I, II, III, aVR, aVL, aVF, V1 - V6) will be recorded using a computerised electrocardiograph (Mortara ELI 250 Rx) at the times provided in the Flow Chart. Electrode placement will be performed according to the method of Wilson, Goldberger and Einthoven.

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 as single 10-second ECGs as indicated in the Flow Chart and after subjects have rested for at least 5 min in a supine position. ECG recording will always precede all other study procedures scheduled for the same time to avoid compromising ECG quality.

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.

Storage

All ECGs will be stored electronically.

Evaluation

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

For the inclusion or exclusion (see Section 3.3) of a subject and for the assessment of cardiac safety during the study, the QT and QTcF values generated by the computerised ECG system or their manual corrections by the investigators will be used.

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.

5.2.5 Other safety parameters

5.2.5.1 Local tolerability

Local tolerability will be assessed by the investigator on the basis of swelling, induration, heat, redness, pain, and other findings and reported as AE in case of clinical relevant findings.

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 Section 5.2.6.2, subsections 'AE Collection' and '**AE reporting to sponsor and timelines'**.

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

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

5.2.6.1.4 Adverse events of special interest

The term adverse events of special interest (AESI) relates to any specific AE that has been identified at the project level as being of particular concern for prospective safety monitoring and safety assessment within this trial, e.g. the potential for AEs based on knowledge from other compounds in the same class. AESIs need to be reported to the sponsor's Pharmacovigilance Department within the same timeframe that applies to SAEs, 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:
  - An elevation of AST (aspartate transaminase) and/or ALT (alanine transaminase) ≥3-fold ULN combined with an elevation of total bilirubin ≥2-fold ULN measured in the same blood sample, or
  - Aminotransferase (ALT, and/or AST) elevations ≥10-fold ULN

  These lab findings constitute a hepatic injury alert and the subjects showing these lab abnormalities need to be followed up according to the 'DILI checklist' provided in the

ISF. 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 PVAN, CMV, posttransplant lymphoproliferative disorder (EBV), progressive multifocal leucoencephalopathy, 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), HBV 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), HCV 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

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

The outcome of the pregnancy associated with the drug exposure during pregnancy must be followed up and reported to the sponsor's unique entry point on the Pregnancy Monitoring Form for Clinical Trials (Part B).

The ISF will contain the Pregnancy Monitoring Form for Clinical Trials (Part A and Part B) as well as non-trial specific information and consent for the pregnant partner.

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

5.3 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

5.3.1 Assessment of pharmacokinetics

For the assessment of pharmacokinetics, 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

For quantification of BI 730357 concentrations in plasma, 3 mL of blood will be drawn from an antecubital or forearm vein into a K_2-EDTA (dipotassium ethylenediaminetetraacetic acid)-anticoagulant blood drawing tube at the times indicated in the Flow Chart.

For quantification of [C-14]BI 730357 plasma concentrations, an additional 3 mL K_2-EDTA tube will be collected as indicated in the Flow Chart. Blood will be withdrawn by means of either an indwelling venous catheter or by venepuncture with a metal needle.

The EDTA-anticoagulated blood samples will be centrifuged and obtained plasma will be split into aliquots. The first aliquots should contain at least 0.5 mL of plasma. The volume of the second aliquots may be less than 0.5 mL plasma. The process from blood collection until transfer of plasma aliquots into the freezer should be completed in less than 60 min with interim storage of blood samples and aliquots on ice water. The time each aliquot was placed in the freezer will be documented. Until transfer on dry ice to the analytical laboratory, the aliquots will be stored frozen and in an upright position at about -20°C or below at the trial site. The second aliquot will be transferred to the analytical laboratory after the bioanalyst has acknowledged safe arrival of the first aliquot.

For detailed description of blood sampling, sample handling, sample preparation, sample storage, tube labelling and sample shipment refer to the laboratory manual.

At a minimum, the sample tube labels should list BI trial number, subject number, visit, and planned sampling time.

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

5.3.3 Analytical determinations

5.3.3.1 Analytical determination of analyte plasma concentration

- Concentrations of unlabelled BI 730357 in plasma will be determined by a validated LC-MS/MS (liquid chromatography tandem mass spectrometry) assay. The analyses will be performed at:

- Concentrations of [C-14]BI 730357 BS in plasma will be determined by a validated AMS (accelerator mass spectrometry) assay. The analyses will be performed at:

Since this is an open label study, the bioanalyst will be unblinded during sample analysis.

5.6 APPROPRIATENESS OF MEASUREMENTS

All measurements performed during this trial are standard measurements and will be performed in order to monitor subjects' safety and to determine pharmacokinetic parameters in an appropriate way. The scheduled measurements will allow monitoring of changes in vital

signs, standard laboratory values, and ECG parameters that might occur as a result of administration of trial medication. The safety assessments are standard, are accepted for evaluation of safety and tolerability of an orally and intravenously administered drug, and are widely used in clinical trials. The pharmacokinetic parameters and measurements outlined in Section 5.4 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 on Day 1 are to be performed and completed within a 3 h-period prior to the trial drug administration.

The acceptable deviation from the scheduled time for vital signs, ECG, and laboratory tests will be ± 30 min on Day 1 and ± 180 min on the following days of Visit 2.

If several activities, including 12-lead ECG and meal intake, are scheduled at the same time point in the Flow Chart, ECG should be the first and meal intake the last activity. 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.

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

Screening visit is defined as Visit 1.

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 5.2.1 to 5.2.5.

6.2.2 Treatment period

Each subject is expected to participate in one treatment period (Visit 2).

On Day -1 of Visit 2, study participants will be admitted to the trial site and kept under close medical surveillance for at least 24 h following administration of treatment T. 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 5.2.1 to 5.2.5.
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 absolute bioavailability of 50 mg BI 730357 administered as tablet (test treatment, T) compared with 2 µg of labelled [C-14]BI 730357 BS administered as intravenous microtracer (mixed with 98 µg unlabelled BI 730357), (reference treatment, R) on the basis of the primary pharmacokinetic endpoints, as listed in Sections 2.1.2 . The trial is designed to allow intra-subject comparisons and will be evaluated statistically by use of an appropriate linear model.

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 absolute bioavailability of 50 mg orally administered BI 730357 compared with 2 µg of labelled [C-14]BI 730357 administered as intravenous microtracer (mixed with 98 µg unlabelled BI 730357) will be estimated by the ratio of the geometric means (test/reference) for the dose-normalized primary PK endpoints. Additionally, their 2-sided 90% confidence intervals (CIs) will be provided. This method corresponds to the two one-sided t-test 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.

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

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 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 he contributes only one PK parameter value for the study 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 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 according to the relevant SOP of the Sponsor (001-MCS-36-472).

Plasma concentration data and parameters of a subject will be included in the statistical pharmacokinetic (PK) analyses if they are not flagged for exclusion due to a protocol 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

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

- The subject experienced emesis that occurred at or before two times median t_{max} of the respective treatment (median t_{max} is to be determined excluding the subjects experiencing emesis),
- A predose concentration is >5% C_{max} value of that subject
- Missing samples/concentration data at important phases of PK disposition curve

Plasma concentration data and parameters of a subject which is flagged for exclusion will be reported with its individual values but will not be included in the statistical analyses. Descriptive and inferential statistics of PK parameters will be based on the PKS.

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

7.3.1 Primary endpoint analyses

Primary analyses

The statistical model used for the analysis of the primary endpoints will be an analysis of variance (ANOVA) model on the logarithmic scale. That is, the 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: 'subjects' and 'formulation'. The

effect 'subjects' will be considered as random, whereas 'formulation' will be considered as fixed. The model is described by the following equation:

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

y_{km} = logarithm of response (dose normalized primary endpoint, see Section 2.1.2) measured on subject m receiving formulation k,

μ = the overall mean,

s_m = the effect associated with the m^{th} subject,
m = 1, 2, ..., n

τ_k = the k^{th} formulation effect (either tablet or i.v.), k = 1, 2,

e_{km} = the random error associated with the m^{th} subject who received formulation k.

Point estimates for the ratio 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.

7.3.2 Secondary endpoint analysis

Not applicable.

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 (test treatment) and beginning of reference treatment will be assigned to the test treatment period. Those between the start of infusion until the end of REP (see Section 1.2.3) will be assigned to the combined test/reference treatment period. Events occurring after the REP but prior to next intake or end of trial termination date will be assigned to 'follow-up'. These assignments including the corresponding time intervals will be defined in detail in the TSAP. Note that AEs occurring after the last per protocol contact but entered before 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. Additionally, differences from baseline will be evaluated.

Vital signs or other safety-relevant data will be assessed with regard to possible on-treatment changes from baseline.

Relevant ECG findings will be reported as AEs.

7.4 INTERIM ANALYSES

No interim analysis is planned.

7.5 HANDLING OF MISSING DATA

7.5.1 Safety

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

7.5.2 Pharmacokinetics

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

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

7.6 RANDOMISATION

Randomisation is not applicable in this open-label, single arm study. All subjects will receive the same treatment. Consecutive subject numbers will be assigned via the EDC system.

7.7 DETERMINATION OF SAMPLE SIZE

For this clinical trial, no prospective calculations of statistical precision or power have been made. The planned sample size of 6 subjects is judged as being adequate to get reliable results regarding the trial objectives. In case of observing dropouts, the sample size may increase to a maximum of 8 to have at least 6 subjects who completed the trial as per protocol.

For replacement rules, refer to Section 3.3.5.

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 directive 2001/20/EC and other relevant regulations. Investigators and site staff must adhere to these principles.

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

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

The Boehringer Ingelheim transparency and publication policy can be found on the following web page: trials.boehringer-ingelheim.com. The rights of the investigator and of the sponsor with regard to publication of the results of this trial are described in the investigator contract. As a general rule, no trial results should be published prior to archiving of the CTR.

The terms and conditions of the insurance coverage will be described in the ICF and also 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.

8.3.1 Source documents

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

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

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

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

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

- Subject identification: sex, year of birth (in accordance with local laws and regulations)
- Subject participation in the trial (substance, trial number, subject number, date subject was informed)
- Dates of subject's visits, including dispensing of trial medication

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

8.3.2 Direct access to source data and documents

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

8.3.3 Storage period of records

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

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

8.4 EXPEDITED REPORTING OF ADVERSE EVENTS

BI is responsible to fulfil their legal and regulatory reporting obligation 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, storage and future use of biological samples and clinical data, in particular

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

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

8.6 TRIAL MILESTONES

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

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

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

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

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

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

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

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

8.7 ADMINISTRATIVE STRUCTURE OF THE TRIAL

The trial is sponsored by Boehringer Ingelheim (BI).

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

BI has appointed a Trial Clinical Monitor, 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 (CTM), Clinical Research Associates, and investigators of participating trial sites

The non-labelled trial medication (intended commercial formulation (iCF) of 50 mg BI 730357) will be provided by the Clinical Trial Supplies Unit (CTSU), BI Pharma GmbH & Co. KG, Biberach, Germany.

The radio-labelled trial medication (intravenous microtracer solution) will be provided by
.

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

The analyses of unlabelled BI 730357 concentrations in plasma will be performed at the Department of Drug Metabolism and Pharmacokinetics, BI Pharma GmbH & Co. KG, Biberach, Germany.

The analyses of labelled [C-14]BI 730357 BS concentrations in plasma via AMS analysis will be conducted 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 organisation appointed by BI according to BI SOPs.

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

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c25209040 radiation-burden-calculation-report-v-2. 1407-0031. 2018 Jul 05.

10. APPENDICES

Not applicable.

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

This is the original protocol.

11.1 GLOBAL AMENDMENT 1

Date of amendment		
EudraCT number **EU number**		
BI Trial number		
BI Investigational Medicinal Product(s)		
Title of protocol		
To be implemented only after approval of the IRB / IEC / Competent Authorities		☐
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		☐
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		☐
Section to be changed		
Description of change		
Rationale for change		

11.2 GLOBAL AMENDMENT 2

Date of amendment		
EudraCT number **EU number**		
BI Trial number		
BI Investigational Medicinal Product(s)		
Title of protocol		
To be implemented only after approval of the IRB / IEC / Competent Authorities		☐
To be implemented immediately in order to eliminate hazard – IRB / IEC /		☐

Competent Authority to be notified of change with request for approval	
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only	☐

Section to be changed		
Description of change		
Rationale for change		

APPROVAL / SIGNATURE PAGE

Document Number: c22193484 **Technical Version Number:1.0**

Document Name: clinical-trial-protocol

Title: Investigation of pharmacokinetics and absolute oral bioavailability of BI 730357 administered as an oral dose with an intravenous microtracer dose of BI 730357 BS (C-14) in healthy male volunteers

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Author-Clinical Trial		05 Dec 2018 07:45 CET
Author-Trial Statistician		05 Dec 2018 08:15 CET
Author-Trial Clinical Pharmacokineticist		05 Dec 2018 09:03 CET
Approval-Team Member Medicine		05 Dec 2018 14:12 CET
Approval-Therapeutic Area		05 Dec 2018 18:57 CET
Verification-Paper Signature Completion		10 Dec 2018 07:52 CET

(Continued) Signatures (obtained electronically)

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