Clinical Trial Protocol

	Document Number: c22159106-02
EudraCT No.:	2018-001837-41
BI Trial No.:	1407-0031
BI Investigational Product:	BI 730357
Title:	A phase I, open-label, single-dose trial to investigate metabolism and pharmacokinetics of BI 730357 BS (C-14) administered as oral solution in healthy male volunteers
Lay Title:	A study in healthy men to test how BI 730357 is processed by the body
Clinical Phase:	I
Trial Clinical Monitor:	Phone: Fax:
Principal Investigator:	Phone: Fax:
Status:	Final Protocol (Revised Protocol (based on global amendment 1))
Version and Date:	Version: 2.0 Date: 25 September 2018

CLINICAL TRIAL PROTOCOL SYNOPSIS

Name of company: Boehringer Ingelheim		**Tabulated Trial Protocol**	
Name of finished product: Not applicable			
Name of active ingredient: BI 730357			
Protocol date: 27 July 2018	**Trial number:** 1407-0031		**Revision date:** 25 September 2018

Title of trial:	A phase I, open-label, single-dose trial to investigate metabolism and pharmacokinetics of BI 730357 BS (C-14) administered as oral solution in healthy male volunteers
Principal Investigator:	
Trial site:	
Clinical phase:	I
Objectives:	To investigate the basic pharmacokinetics of BI 730357 and [^{14}C]-radioactivity, including mass balance, excretion pathways and metabolism following a single oral dose of 50 mg BI 730357 BS (C-14) given to healthy male volunteers
Methodology:	Open-label, single dose, non-randomized, single period design
No. of subjects:	
total entered:	6*
each treatment:	6* * In case a subject vomits within 8 hours after administration of trial drug on Day 1, additional subjects may be entered and dosed in order to have 6 evaluable subjects. Thus, the actual number of subjects entered may increase up to 8.
Diagnosis:	Not applicable
Main criteria for inclusion:	Healthy male subjects, age of 18 to 65 years, body mass index (BMI) of 18.5 to 29.9 kg/m^2
Test product:	BI 730357 BS (C-14) oral solution
dose:	50 mg • In 10 mL oral solution (5 mg/mL) • containing a radioactive dose of approximately 3.7 MBq (100 µCi)
mode of admin.:	Oral with 240 mL of water after an overnight fast of at least 10 h
Comparator product:	Not applicable
Duration of treatment:	Single dose

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Name of finished product: Not applicable			
Name of active ingredient: BI 730357			
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Criteria for pharmacokinetics:	*Primary endpoints:* Mass balance recovery of total [^{14}C]-radioactivity in urine and faeces: Amount of radioactivity excreted as a percentage of the administered dose (fe_{0-t2}) for urine and faeces, $fe_{urine,\ 0-t2}$ and $fe_{faeces,\ 0-t2}$ *Secondary endpoints:* Assessment of the pharmacokinetics of an oral solution formulation of BI 730357 BS (C-14) by calculation of the following parameters for total [^{14}C]-radioactivity and BI 730357 in plasma: C_{max} and AUC_{0-tz}		
Criteria for safety:	Adverse events (AEs) including clinically relevant findings from the physical examination, safety laboratory tests, 12-lead electrocardiogram (ECG), vital signs (blood pressure [BP], pulse rate [PR])		
Statistical methods:	Descriptive statistics and graphical displays		

FLOW CHART

Visit	Day	Planned time (relative to drug administration [h:min]	Approximate clock time of actual day [h:min]	Event and comment	Safety laboratory	PK blood / plasma [2]	PK urine [6]	PK faeces [7]	Blood sampling for metabolic profiling [16]	12-lead ECG	Vital signs (BP, PR)	Questioning for AEs and concomitant therapy [9]
1	-21 to -1			Screening (SCR)[1]	x					x	x	
2	-2	-48:00	08:00					x[14]				▲
	-1	-18:00	14:00	Admission to trial site	x[5]		x					┃
		-14:00	18:00	Light Supper (voluntary)								┃
		-10:30	21:30	Snack (voluntary)[17]								┃
	1	-2:00	06:00		x[3]	x[3,15]			x[3]	x[3]	x[3]	┃
		0:00	**08:00**	**Drug administration**			▲	▲				┃
		0:30	08:30			x	┃	┃				┃
		1:00	09:00			x	┃	┃	x			┃
		1:30	09:30			x	┃	┃				┃
		2:00	10:00	240 mL fluid intake	x[8]	x	┃	┃	x			┃
		4:00	12:00	240 mL fluid intake, thereafter lunch[4]	x[8]	x	┼	┃	x	x	x	┃
		8:00	16:00	Snack (voluntary)[4]		x	┼	┃	x			┃
		11:00	19:00	Dinner			┃	┃				┃
		12:00	20:00		x[8]	x	┼	┃	x	x	x	┃
	2	24:00	08:00		x[8]	x	┼	┼	x		x	┃
	3	48:00	08:00			x	┼	┼	x			┃
	4	72:00	08:00			x	┼	┼	x			┃
	5	96:00	08:00				┼	┼				┃
	6	120:00	08:00			x	┼	┼				┃
	7	144:00	08:00				┼	┼				┃
	8	168:00	08:00		x	x	┼	┼				┃
	9	192:00	08:00				┼	┼				┃
	10	216:00	08:00			x	┼	┼				┃
	11	240:00	08:00				┼	┼				┃
	12	264:00	08:00			x	┼	┼				┃
	13	288:00	08:00				┼	┼				┃
	14	312:00	08:00			x	┼	┼				┃
	15	336:00	08:00	Discharge from trial site[9]	x		▼	▼		x	x	┃
	20	461:00	13:00	Start home collection				▲				┃
	21	485:00	13:00	Admission to trial site[11,12]		x	▲	┼				┃
	22	509:00	13:00	Discharge from trial site[11]			▼	▼				┃
	27	629:00	13:00	Start home collection				▲				┃
	28	653:00	13:00	Admission to trial site[11,12]		x	▲	┼				┃
	29	677:00	13:00	Discharge from trial site[11]			▼	▼				┃
	34	797:00	13:00	Start home collection				▲				┃
	35	821:00	13:00	Admission to trial site[11,12]	x	x	▲	┼				┃
	36	845:00	13:00	Discharge from trial site[11]			▼	▼				┃
	41	965:00	13:00	Start home collection				▲				┃
	42	989:00	13:00	Admission to trial site[11,12]		x	▲	┼				┃
	43	1013:00	13:00	Discharge from trial site[11]			▼	▼				┃

	48	1133:00	13:00	Start home collection				▲				▼
	49	1157:00	13:00	Admission to trial site[11,12]		x	▲	┼				
	50	1181:00	13:00	Discharge from trial site[11]			▼	▼				
3	16 to 50			End-of-trial (EoTrial) examination[10,13]	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. Pharmacokinetics (PK): BI 730357 in plasma; [^{14}C]-radioactivity in whole blood and plasma (see Section 5.5.2.2). Blood sampling for an individual subject can be stopped if [^{14}C]-radioactivity in plasma is below limit of detection (<LLOQ 10 dpm/mL) at two consecutive sampling time points for this subject (earliest stopping after 168 h).
3. The time is approximate; the respective 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. Urine collection intervals (for PK/[^{14}C]-radioactivity assessment and metabolic profiling; planned time): on Day -1 or Day 1 predose (blank) sample, on Day 1 prior to start of urine collection voiding of the bladder, 0-4 , 4-8, 8-12, 12-24, 24-48, 48-72, 72-96, 96-120, 120-144, 144-168, 168-192, 192-216, 216-240, 240-264, 264-288, 288-312 and 312-336 hours after administration of BI 730357 BS (C-14). Thereafter, if warranted, 24 h collections are to be performed every 7 days starting on Day 21. Urine sampling for PK/[^{14}C]-radioactivity will be stopped when release criteria for radioactivity recovery (see Section 3.1) have been met (earliest stopping on Day 15). "┼" means end of last collection interval, start of following collection interval. For details on sample usage please refer to Section 5.5.2.5.
7. All stools (for [^{14}C]-radioactivity and metabolic profiling) will be collected quantitatively in portions up to 336 hours (sampling intervals of 0-24, 24-48, 48-72, 72-96, 96-120, 120-144, 144-168, 168-192, 192-216, 216-240, 240-264, 264-288, 288-312 and 312-336 hours) after administration of BI 730357 BS (C-14). Thereafter, if warranted, 24 h collections are to be performed every 7 days starting on day 20. A blank sample will be collected before drug administration on Day -2, Day -1 or Day 1 (see Section 5.5.2.6). Faeces sampling for [^{14}C]-radioactivity assessment will be stopped when the release criteria for radioactivity recovery (see Section 3.1) have been met (earliest stopping on day 15). "┼" means end of last collection interval, start of following collection interval. For details on sample usage please refer to Section 5.5.2.6.
8.
9. AEs and concomitant therapies will be recorded throughout the trial; during in-house days subjects will be specifically asked for twice daily.
10. End-of-trial (EoTrial) examination to be performed within 1 to 7 days after last discharge from the study centre, or, if all once-weekly 24 h sampling periods are needed, prior to discharge on Day 50. End-of-trial examination includes physical examination, vital signs, ECG, safety laboratory, recording of AEs and concomitant therapies.
11. The planned times for admission, discharge, start and end of the urine and faeces collection intervals are approximate. The procedures are to be performed within a time window of +/- 4 h to the planned time.
12. Subjects are to collect faeces at home within 24 h intervals before admission to once-weekly in-house collection intervals. Home collection intervals: Day 20-21, 27-28, 34-35, 41-42, and 48-49. If faeces are collected in the subsequent in-house collection interval, faeces collected at home will be discarded. If no faeces is collected in the subsequent in-house collection interval (no defecation), faeces collected at home will be used instead for analysis.
13. For definition of the individual subject's end of trial see Section 6.2.3
14. Subjects will collect a pre-dose faeces sample at home or at the site in specific containers provided by
15. Including pharmacogenomics sample
16. Metabolic profiling sampling times may be adapted based on information obtained during the trial (e.g. levels of radioactivity in each urine and/or plasma sample) as long as the overall blood volume stays the same.
17. To be consumed within 30 min to allow 10 h fasting prior to drug administration.

TABLE OF CONTENTS

ABBREVIATIONS

ADME	Absorption, distribution, metabolism, and excretion
AE	Adverse event
AESI	Adverse events of special interest
AS	ankylosing spondylitis
AUC_{0-tz}	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 to the last quantifiable data point
BI	Boehringer Ingelheim
BLQ	Below limit of quantification
BMI	Body mass index (weight divided by height squared)
BP	Blood pressure
BS	base
CA	Competent authority
CL	Total clearance of the analyte in plasma after intravascular administration
C_{max}	Maximum measured concentration of the analyte in plasma
CNS	Central nervous system
CRF	Case report form
CTP	Clinical trial protocol
CTR	Clinical trial report
DILI	Drug induced liver injury
ECG	Electrocardiogram
EDC	Electronic data capture
EDTA	Ethylenediaminetetraacetic acid
EoTrial	End of trial
fe_{0-t2}	Fraction of administered drug (% of dose) excreted over the time interval from 0 to t2 (where t2 is the last quantifiable data point across all subjects)
hERG	Human-ether-à-go-go related gene

hLXRα	human liver X receptor α
IB	Investigator's brochure
IBD	inflammatory bowel disease
IC50	50% inhibitory concentration
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ISF	Investigator site file
LC-MS/MS	Liquid chromatography tandem mass spectrometry
LLOQ	Lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
MRD	Multiple-rising dose
NOA	Not analysed
NOAEL	No observed adverse effect level
NOP	No peak detectable
NOR	No valid result
NOS	No sample available
PK	Pharmacokinetic(s)
PKS	Pharmacokinetic set
PR	Pulse rate
PSA	psoriatic arthritis
PSO	Psoriasis
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)
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(s)	Operating Procedure(s)
SRD	Single-rising dose
ss	(at) steady state
SUSAR	Suspected Unexpected Serious Adverse Reaction

TDMAP	Trial Data Management and Analysis Plan
TMF	Trial master file
t_z	Time of last measurable concentration of the analyte in plasma
TSAP	Trial statistical analysis plan
ULN	Upper limit of normal
Vd	Volume of distribution

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.

This trial is a mass balance study that aims at an in-depth understanding of metabolism and pharmacokinetics of BI 730357 including quantitative determination of elimination pathways and drug metabolites.

1.1 MEDICAL BACKGROUND

Retinoic acid-related orphan receptor γt (RORγt) is a nuclear hormone receptor/transcription factor expressed in 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 [c09228382-06].

1.2 DRUG PROFILE

1.2.1 Nonclinical data

1.2.1.2 Safety pharmacology

1.2.1.3 Toxicology

1.2.1.4 Non-clinical pharmacokinetics and metabolism

1.2.2 Clinical Data

Clinical pharmacokinetics and metabolism

Clinical safety

2. RATIONALE, OBJECTIVES, AND BENEFIT - RISK ASSESSMENT

2.1 RATIONALE FOR PERFORMING THE TRIAL

This trial is intended to examine basic pharmacokinetics of BI 730357, its metabolite and [^{14}C]-radioactivity, including mass balance, excretion pathways and metabolism following a single oral dose of BI 730357 BS (C-14) in healthy male volunteers.

The data are necessary for in-depth understanding of the pharmacokinetics of BI 730357 including quantitative determination of elimination pathways and drug metabolites and are required for submission to regulatory authorities.

2.2 TRIAL OBJECTIVES

The main objectives of the study are as follows:

- To assess the mass balance recovery of [^{14}C]-radioactivity in urine and faeces after a single oral dose of 50 mg BI 730357 BS (C-14) in healthy male subjects

The secondary objective of the study is as follows:

- To determine PK parameters of [^{14}C]-radioactivity, BI 730357 after single dose oral administration of BI 730357 BS (C-14) in healthy male subjects
- To determine the routes and rates of elimination of BI 730357

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

2.3 BENEFIT - RISK ASSESSMENT

Participation in this study is without any (therapeutic) benefit for healthy subjects. Their participation in the study, however, is of major importance to the development of BI 730357. The subjects are exposed to the risks of the study procedures and the risks related to the exposure to the trial medication and the intake of BI 730357 BS (C-14).

Procedure-related risks

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

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

Drug-related risks and safety measures

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

Risks related to 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 (see Section 1.2.2).

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. Based on the data obtained with BI 730357 so far, and based on the fact that in the current study a single dose of 50 mg will be used, the increased risk of infection and/or malignancy is considered to be extremely small.

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 administration of [C-14]-labelled BI 730357

BI 730357 BS (C-14) is labelled with the isotope [^{14}C], which is necessary for the purposes of this mass balance trial. Therefore, subjects will be exposed to ionizing radiation. The effective dose each subject receives from the administration of 3.7 MBq is approximately 0.14 mSv (see Appendix 10.1).

The radioactive dose proposed for administration in the planned human ADME study of 3.7 MBq is lower than the limit specified by:

- WHO Category 1 (<0.5 mSv – within variations of natural background radioactivity),

and lower than the limit proposed by:

- ICRP Category 2a (<1 mSv – risk defined as minor).

For biomedical investigations in order to study the disposition, metabolism and excretion of new chemical entities in a small group of healthy volunteers, an effective dose of 0.1-1.0 mSv is considered acceptable [R18-1905, R15-3219].

Although it is common sense that any increase in the amount of radiation absorbed carries the risk of developing delayed serious and possibly fatal conditions, the risk associated with the administered dose of radiation in this trial is small and considered acceptable.

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 was safe and well tolerated [c16462083-01]. In the current trial, it is planned that subjects will receive a single oral dose of 50 mg partially radioactive labelled BI

730357. 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 trial participant will receive only one radioactive dose.

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 2a with minor level risk and in WHO Category 1, i.e. within variations of natural background radioactivity. This is considered to be acceptable.

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.

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

The study will be performed as a non-randomized, open-label, single-arm, single-dose trial in healthy male subjects in order to investigate the basic pharmacokinetics of BI 730357, and [^{14}C]-radioactivity, including mass balance, excretion pathways and metabolism following a single oral dose of 50 mg BI 730357 BS (C-14).

A total of 6 healthy male subjects is planned to participate in the trial.

The planned radioactive dose per subject is 3.7 MBq (100.0 µCi, 0.14 mSv). This is equivalent to 0.038 mSv/MBq (please refer to Appendix 10.1).

On Day 1, subjects will receive the drug product, that is, 50 mg BI 730357 BS (C-14) and will then stay in the study centre up to the morning of Day 15 for collection of samples of blood, urine and faeces. Subjects will be readmitted to the study centre for 24 h collection intervals of urine and faeces on Days 21, 28, 35, 42, and 49, if release criteria have not been met before. Within 24 h before each of these once-weekly in-house collection intervals, subjects are to collect faeces at home. This 24-h interval home collection faeces will be used for analysis in case no defecation occurs in the subsequent 24 h in-house collection interval. Otherwise it will be discarded.

For determination of whether release criteria have been reached for individual subjects, [^{14}C]-radioactivity will be measured in excreta (urine and faeces). The actual recovery results will be reported as a percentage of the administered dose.

If one of the following release criteria is true (i.e., release criteria have been met), 24 h collection intervals after Day 15 will not be performed / will be stopped:

- Greater than or equal to 90% of the administered dose has been recovered in urine and faeces combined over the investigational period

or

- If <1% of the dose administered has been collected in urine and faeces within 2 separate, consecutive 24-h intervals,

  and

  Concentration of total radioactivity in plasma and in blood is <5% of C_{max} of total radioactivity in plasma

If a subject is unable to attend one of these ambulatory visits, they may be allowed to reschedule the visit if needed. Irrespective of whether release criteria have been met or not after collection interval day 49-50, no further collections are planned.

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

3.1.1 Administrative structure of the trial

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

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

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

The radiolabelled trial medication (drug product, BI 730357 BS (C-14) will be provided by
.

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

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

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

The metabolite profiling and the identification in urine, plasma and faeces will be performed at BI and/or at a suitable Contract Research Organisation (CRO) under the responsibility of Boehringer Ingelheim (BI) Pharmaceutical Inc., Ridgefield, USA.

Concentrations of [^{14}C]-radioactivity in blood, plasma, urine, faeces (and vomit if applicable) will be determined 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 according to BI SOPs and/or by a suitable CRO under the responsibility of the Department of Biostatistics and Data Sciences, BI Pharma GmbH & Co. KG, Biberach, Germany.

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

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

This is a standard design for a [^{14}C]-human study for investigation of absorption, metabolism, and excretion including determination of mass balance.

Inclusion of a control groups is not required for this investigation.

Therefore, following 14 days in-house excreta collection after dosing, subjects will return on a weekly basis for in-house 24-h collection intervals for up to 7 weeks after dosing as long as release criteria are not met (Section 3.1).

Blinding is not necessary, because all subjects receive the same treatment.

3.3 SELECTION OF TRIAL POPULATION

It is planned that 6 healthy male subjects will enter the study. They will be recruited from the pool of volunteers from the trial site's database, or if necessary, via advertisement. In case a subject vomits within 8 h after trial drug administration assuming an incomplete absorption of the radiolabelled compound, an additional subject may be entered and dosed to assure that 6 evaluable 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 basic pharmacokinetics of BI 730357 including absorption, metabolism, and elimination and quantitative determination of excretion mass balance.

Healthy 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. having given informed consent) will be maintained in the ISF at the investigational site irrespective of whether they have been treated with investigational drug or not.

3.3.1 Main diagnosis for study entry

The study will be performed in healthy subjects.

3.3.2 Inclusion criteria

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

1. Healthy male subjects according to the assessment of the investigator, based on a complete medical history including a physical examination, vital signs (BP, PR), 12-lead ECG, and clinical laboratory tests
2. Age of 18 to 65 years (incl.)
3. BMI of 18.5 to 29.9 kg/m2 (incl.)
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, with 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) is deviating from normal and judged as clinically relevant by the investigator
2. Repeated measurement of systolic blood pressure outside the range of 90 to 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 judged 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 and/or surgery of the gastrointestinal tract that could interfere with the pharmacokinetics of the trial medication (except appendectomy and simple hernia repair)
7. Diseases of the central nervous system (including but not limited to any kind of seizures or stroke), and other relevant neurological or psychiatric disorders
8. History of relevant orthostatic hypotension, fainting spells, or blackouts
9. Chronic or relevant acute infections
10. History of relevant allergy or hypersensitivity (including allergy to the trial medication or its excipients)
11. Use of drugs within 30 days prior to administration of trial medication if that might reasonably influence the results of the trial (incl. QT/QTc interval prolongation)
12. Participation in another trial where an investigational drug has been administered within 60 days prior to planned administration of trial medication, or current participation in another trial involving administration of investigational drug

13. Smoker (more than 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 of more than 100 mL within 60 days prior to administration of trial medication or intended donation during the trial
18. Intention to perform excessive physical activities within 4 days prior to administration of trial medication or during the trial.
19. Inability to comply with dietary regimen of trial site
20. A marked baseline prolongation of QT/QTc interval (such as QTcF intervals that are repeatedly greater than 450 ms in males) or any other relevant ECG finding at screening
21. A history of additional risk factors for Torsades de Pointes (such as heart failure, hypokalemia, or family history of Long QT Syndrome)
22. Subject is assessed as unsuitable for inclusion by the investigator, for instance, because considered not able to understand and comply with study requirements, or has a condition that would not allow safe participation in the study

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

23. Participation in another ADME study with a radiation burden of 0.1-1.0 mSv in the period of 1 year prior to screening or 1.1-2.0 mSv in the past 2 years or 2.1-3.0 mSv in the past 3 years etc.
24. Exposure to radiation for diagnostic reasons (except dental X-rays and plain X-rays of thorax and bony skeleton (excluding spinal column) in the period of 1 year prior to screening)
25. Irregular defecation pattern (less than a mean of one bowel movement per 2 days)

For study restrictions, refer to Section 4.2.2.

3.3.4 Removal of subjects from therapy or assessments

3.3.4.1 Removal of individual subjects

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

1. The subject withdraws consent for trial treatment or trial participation, without the need to justify the decision
2. The subject needs to take concomitant drugs that interfere with the investigational product or other trial medication
3. The subject is no longer able to participate for other medical reasons (such as surgery, adverse events (AEs), or diseases)
4. The subject shows an elevation of AST and/or ALT ≥3-fold ULN combined with an elevation of total bilirubin ≥2-fold ULN (measured in the same blood sample) and/or needs to be followed up according to the 'DILI checklist' provided in the ISF.

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

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

If a subject is removed from or withdraws from the trial prior to first administration of trial medication, the data of this subject will not be entered in the case report form (CRF) or trial database and will not be reported in the clinical trial report (CTR). If a subject is removed from or withdraws from the trial after administration of trial medication, this will be documented and the reason for discontinuation must be recorded in the CRF. In this case, the data will be included in the CRF/trial database and will be reported in the CTR. At the time of discontinuation a complete end-of-trial examination will be performed if possible and the information will be recorded in the CRFs. If the discontinuation occurs before the end of the REP (see Section 1.2), the discontinued subject should be questioned for AEs and concomitant therapies at or after the end of the REP if possible to ascertain collection of AEs and concomitant therapies throughout the REP, if subject had not withdrawn consent. These discontinuations will be discussed in the CTR.

3.3.4.2 Discontinuation of the trial by the sponsor

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

1. New toxicological findings, 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 one drug-related serious adverse event is reported. In this case, collection of pharmacokinetic samples and other scheduled activities should continue, if possible without undue risk to already dosed volunteer(s), but no further administrations of investigational drug will be done.
2. The expected enrolment goals overall are not met
3. Violation of GCP, or the CTP, or the contract with BI by a trial site or investigator, disturbing the appropriate conduct of the trial
4. The sponsor decides to discontinue the further development of the investigational product.

The investigator / the trial site will be reimbursed for reasonable expenses incurred in case of trial termination (except in case of the third reason).

3.3.5 Replacement of subjects

In case a subject vomits within 8 h after trial drug administration assuming an incomplete absorption of the radiolabelled compound an additional subject may be entered and dosed to ensure that 6 evaluable subjects will complete the study as per protocol.

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 study subject number.

4. TREATMENTS

4.1 TREATMENTS TO BE ADMINISTERED

The oral solution contains a mixture of [C-14]BI 730357 BS, i.e. pure ^{14}C-labelled "hot" drug substance, and BI 730357 BS, i.e. unlabelled "cold" drug substance and the mixture is manufactured by BI Pharma GmbH & Co. KG. The oral solution from this mixture is made by

4.1.1 Identity of BI investigational product

The characteristics of the test product are given below:

Name:	BI 730357 BS (C-14) oral solution 5 mg/mL (10 mL; 3.7 MBq)
Substance:	BI 730357 mixed with [C-14]BI 730357 BS
Pharmaceutical formulation:	Oral solution
Source:	
Unit strength:	50 mg BI 730357 • Containing BI 730357 BS (C-14) corresponding to a radioactive dose of 3.7 MBq (100 µCi) • In a solution of 10 mL volume
Posology:	1-0-0
Route of administration:	p.o.
Duration of use:	Single dose

4.1.2 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.

4.1.3 Selection of doses in the trial

The dose of BI 730357 tested in this trial is one single dose of 50 mg.

This dose of 50 mg was already 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.

This dose administered as oral solution will include 3.7 MBq (100.0 µCi) of [^{14}C]-radiolabelled BI 730357. The radioactive dose of 3.7 MBq is required for sufficient analytical sensitivity to enable metabolite quantification in a sufficiently low range. The total effective dose (radiation burden) amounts to 0.14 mSv. This is below the limit of 1.0 mSv, which is considered acceptable for biomedical investigations in small groups of human

volunteers [R18-1905]. Radiation burden calculations are presented in Appendix 10.1. For risk-benefit assessment, see Section 2.3.

4.1.4 Drug assignment and administration of doses for each subject

In the morning of Day 1, following an overnight fast of at least 10 h, all subjects will receive one single dose of the trial drug (BI 730357 BS (C-14) oral solution 5 mg/mL (10 mL; 3.7 MBq)).

The medication will be administered as a single oral dose together with 240 mL of water to a subject in the sitting position under supervision of the investigator or an authorised designee. After administration, will determine for each volunteer the residual amount of [^{14}C]-radioactivity in the syringe used for administration. The amount of administered radiolabelled medication will be calculated based on pre- and post-dose weight of the syringe used for oral administration.

The so-called four-eye principle (two-person rule) should be applied for administration of trial medication.

During the first 4 h after drug administration, subjects are not allowed to lie down (i.e., no declination of the upper body of more than 45 degrees from upright posture) except for medical examination or if necessary for any medical reasons (e.g. adverse events). For restrictions with regard to diet and fluid intake see Section 4.2.2.2.

After drug administration subjects will be kept under close medical surveillance until planned discharge from the unit on Day 15. In case release criteria for radioactivity recovery have not been met on Day 15, subjects will come back to the unit for up to five once-weekly 24 h sampling periods until discharge criteria are met or after the last collection interval Day 49-50 was completed (see Section 3.1).

4.1.5 Blinding and procedures for unblinding

This is an open-label study.

4.1.6 Packaging, labelling, and re-supply

Non-[^{14}C]-labelled and radioactively-labelled drug supplies will be mixed and provided to by the Department of Pharmaceutical Development of Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach, Germany.

Drug product manufacturing is done by . The clinical trial supply consists of containers holding the trial medication which are labelled with trial identification. The final container will be an oral syringe holding the Investigational Drug Products and will be labelled according to GMP Annex 13 / EU GMP guideline and local drug law.

Examples of the labels will be available in the ISF.

No re-supply is planned.

4.1.7 Storage conditions

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

4.1.8 Drug accountability

pharmacy will deliver the investigational drugs to the investigator upon availability of a valid prescription from the investigator.

The investigator will not order the drugs from the pharmacy before the following requirements are fulfilled:

- Approval of the trial protocol by the IRB / ethics committee
- Availability of a signed and dated clinical trial contract between the Sponsor and the Head of Trial Centre
- Approval/notification of the regulatory authority, e.g. competent authority
- Availability of a signed and dated clinical trial protocol or immediately imminent signing of the clinical trial protocol
- Availability of licence for clinical research using radioactive isotopes

Only authorised personnel as documented in the form 'Site Delegation Log' may dispense medication to trial subjects. The trial medication must be administered in the manner specified in the CTP. All unused trial medication must be returned to the Sponsor or disposed locally by the trial site upon written authorisation by the clinical monitor. Appropriate retention samples will be kept at until finalization of the clinical trial report. Receipt, usage and return or disposal must be documented on the respective forms. Account must be given for any discrepancies.

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

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

4.2 OTHER TREATMENTS, EMERGENCY PROCEDURES, RESTRICTIONS

4.2.1 Other treatments and emergency procedures

There are no specific rescue drugs foreseen for the treatment of AEs. There are no special emergency procedures to be followed. No additional treatment is planned. However, in case of adverse events in need of treatment, the investigator can authorise symptomatic therapy. In those cases, subjects will be treated as necessary and, if required, kept under supervision at the trial site or transferred to a hospital until all medical evaluation results have returned to an acceptable level.

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

In principle, no concomitant therapy is allowed throughout the study 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. 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, that are inhibitors or inducers of CYP3A4 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 are restricted from consuming any other foods or drinks than those provided by the staff. On Day 1, standardised meals will be served at the time points described in the Flow Chart. On all other days during in-house confinement, there are no special requirements with the exception of the restrictions with respect to grapefruit (orange)/Seville orange, methylxanthine- and alcohol containing beverages or food. When not fasting, meals and snacks (such as decaffeinated coffee, herbal tea, fruit, and biscuits) will be provided according to standard operating procedures (SOPs). A light supper will be provided on the evening before those days where fasting is required until lunch-time.

Subjects are to be fasted for at least 10 h prior to dosing. No food is allowed for at least 4 h after drug intake. For fasting times before safety laboratory investigations see Section 5.2.3.

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

During the following days of urine collection, subjects will be advised that total fluid intake should be at least 1.5 litres and should not exceed 3.5 litres.

Green tea, grapefruits, Seville oranges (sour or bitter oranges) and their juices, and dietary supplements and products including St. John's wort (Hypericum perforatum) are not permitted starting 7 days before first admission to and during in-house confinement at the trial site.

Poppy-seed containing products should not be consumed within 2 days before screening and starting 2 days before first admission to trial site until last PK sampling of the trial.

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

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

Methylxanthine-containing drinks or foods (such as coffee, tea, cola, energy drinks, and chocolate) are not allowed from 24 h before first admission to 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 first 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.

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 blood and plasma concentrations and excretion in urine and faeces will provide additional confirmation of compliance.

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

5. VARIABLES AND THEIR ASSESSMENT

5.1 EFFICACY - CLINICAL PHARMACOLOGY

5.1.1 Endpoints of efficacy

No efficacy endpoints will be evaluated in this trial.

5.1.2 Assessment of efficacy

Not applicable.

5.2 SAFETY

5.2.1 Endpoints of safety

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

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

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

5.2.2 Assessment of adverse events

5.2.2.1 Definitions of adverse events

Adverse event

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

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

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

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

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

Serious adverse event

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

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

AEs considered 'Always Serious'

Cancers of new histology and exacerbations of existing cancer must be classified as a serious event regardless of the time since discontinuation of the drug and must be reported as described in Section 5.2.2.2, 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.

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 5.2.2.2.

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 (according to RCTC grading)
- 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.

Intensity (severity) of AEs

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

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

Causal relationship of AEs

Medical judgment should be used to determine the relationship, considering all relevant factors, including pattern of reaction, temporal relationship, de-challenge or re-challenge,

confounding factors such as concomitant medication, concomitant diseases and relevant history.

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

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

5.2.2.2 Adverse event collection and reporting

AE collection

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

Subjects will be required to report spontaneously any AEs as well as the time of onset, end, and intensity of these events. In addition, each subject will be regularly assessed by the medical staff throughout the clinical trial and whenever the investigator deems necessary. As a minimum, subjects will be questioned for AEs (and concomitant therapies) at the time points indicated in the Flow Chart. Assessment will be made using non-specific questions

such as 'How do you feel?'. Specific questions will be asked wherever necessary in order to more precisely describe an AE.

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

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

- From signing the informed consent onwards until an individual subject's end of trial:
    - All AEs (serious and non-serious) and all AESIs

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

AE reporting to Sponsor and timelines

The Investigator must report SAEs, AESIs, and non-serious AEs which are relevant for the reported SAE or AESI, on the BI SAE form via fax immediately (within 24 hours) 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 timelines apply as for the initial information.

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.

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.

5.2.3 Assessment of safety laboratory parameters

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

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

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

Table 5.2.3: 1 Routine laboratory tests

Functional lab group	BI test name [comment/abbreviation]	A	B	C	D
Haematology	Haematocrit	X	X	X	X
	Haemoglobin	X	--	X	X
	Red Blood Cell Count/Erythrocytes	X	--	X	X
	Reticulocytes, absol.	X	--	X	X
	White Blood Cells/Leucocytes	X	--	X	X
	Platelet Count/Thrombocytes (quant)	X	--	X	X
Automatic WBC differential, relative	Neutrophils/Leukocytes; Eosinophils/Leukocytes; Basophils/ Leukocytes; Monocytes/Leukocytes; Lymphocytes/Leukocytes	X	--	X	X
Automatic WBC differential, absolute	Neutrophil, absol.; Eosinophils, absol.; Basophils, absol.; Monocytes, absol.; Lymphocytes, absol.	X	--	X	X
Manual differential WBC (if automatic differential WBC is abnormal)	Neut. Poly (segs); Neut. Poly (segs), absol.; Neutrophils Bands; Neutrophils Bands, absol.; Eosinophils/Leukocytes; Eosinophils, absol.; Basophils/ Leukocytes; Basophils, absol.; Monocytes/ Leukocytes; Monocytes, absol.; Lymphocytes/Leukocytes; Lymphocytes, absol.				
Coagulation	Activated Partial Thromboplastin Time	X	--	X	X
	Prothrombin time – INR (International Normalization Ratio)	X	--	X	X
Enzymes	AST [Aspartate transaminase] /GOT, SGOT	X	--	X	X
	ALT [Alanine transaminase] /GPT, SGPT	X	--	X	X
	Alkaline Phosphatase	X	--	--	X
	Gamma-Glutamyl Transferase	X	--	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	X
	Amylase	X	--	X	X
Hormones	Thyroid Stimulating Hormone	X	--	--	--
Substrates	Glucose (Serum)	X	--	X	X
	Creatinine	X	--	X	X
	Bilirubin, Total	X	--	X	X
	Bilirubin, Direct	X	--	X	X
	Protein, Total	X	--	X	X
	Albumin	X	--	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	X
	Potassium	X	--	X	X
	Magnesium	X	--	X	X
	Calcium	X	--	X	X

Table 5.2.3: 1 Routine laboratory tests (cont.)

Functional lab group	BI test name [comment/abbreviation]	A	B	C	D
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) and at Visit 2 on Day -1
B: Parameters to be determined at Visit 2 on Day 1 (at PTM 2:00, 4:00, 12:00) and Day 2 (at PTM 24:00)
C: Parameters to be determined at Visit 2 on Days 1 (PTM -2:00), 8, 15 and 35 (for time points refer to Flow Chart)
D: Parameters to be determined at Visit 3 (end-of-trial examination)

The tests listed in Table 5.2.3: 2 are exclusionary laboratory tests which may be repeated as required. The results will not be entered in the CRF/database and will not be reported in the CTR. 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 of the treatment period, and may be repeated at any time during the study at the discretion of the Investigator or designee. The results will not be included in the CTR.

Table 5.2.3: 2 Exclusionary laboratory tests

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

The laboratory tests listed in Table 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.

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 time points given 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 ECGs for a 10 sec duration 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 (except for blood drawing from an intravenous cannula that is already in place) to avoid compromising ECG quality.

All locally printed ECGs will be evaluated by the Investigator or a designee. ECGs may be repeated for quality reasons for instance due to alternating current artefacts, muscle

movements, or electrode dislocation. The repeat ECGs are assigned to the respective scheduled time point.

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

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

5.2.5 Assessment of other safety parameters

5.2.5.1 Vital signs

Systolic and diastolic blood pressures (BP) as well as pulse rate (PR) or heart rate (heart rate is considered to be equal to pulse rate) will be measured by a blood pressure monitor (Dinamap CareScape VC150, GE Medical Systems) at the times indicated in the Flow Chart, after subjects have rested for at least 5 min in a supine position. All recordings should be made using the same type of blood pressure recording instrument on the same arm if possible.

5.2.5.2 Medical examinations

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

5.4 APPROPRIATENESS OF MEASUREMENTS

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

5.5 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

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

5.5.1 Pharmacokinetic endpoints

5.5.1.1 Primary endpoints

Primary endpoints will be the mass balance recoveries of [^{14}C]-radioactivity in urine and faeces:

- $fe_{urine,\ 0\text{-}t2}$ (fraction of [^{14}C]-radioactivity excreted in urine as percentage of the administered dose over the time interval from 0 to t_2 (where t_2 is the last quantifiable data point across all subjects))
- $fe_{faeces,\ 0\text{-}t2}$ (fraction of [^{14}C]-radioactivity excreted in faeces as percentage of the administered dose over the time interval from 0 to t_2 (where t_2 is the last quantifiable data point across all subjects))

Timeframe: The timeframe for determination of these endpoints depends on excretion/recovery of radioactivity and may vary between 2-7 weeks, inclusive, after drug administration.

5.5.1.2 Secondary endpoints

The following secondary endpoints will be evaluated for [^{14}C]-radioactivity and BI 730357 in plasma:

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

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

5.5.1.3

5.5.2 Methods of sample collection

5.5.2.1 Sampling of whole blood and plasma

Whole blood and plasma will be collected at time points shown in the Flow Chart:

- to determine [^{14}C]-radioactivity concentrations in whole blood and plasma
- to determine concentrations of BI 730357

5.5.2.2 Sampling of whole blood and plasma for [^{14}C]-radioactivity analysis in whole blood and plasma and quantification of BI 730357 in plasma

At each time point listed in the Flow Chart, 4 mL (for time points from 1 h up to 72 h post-dose (inclusive)), or 8 mL (for the pre-dose, at time point 0.5 h and from time point 120 h up to 312 h post-dose) or 6 mL (for time points at ambulatory visits) blood will be taken from a forearm vein using a commercial vacutainer or monovette collection tube with K2-EDTA as anticoagulant. Withdrawal of blood will be done via an indwelling cannula or direct venae puncture.

It is planned that aliquots of all time points are prepared for determination of [^{14}C]-radioactivity in whole blood and plasma.

Aliquots for bioanalysis of BI 730357 in plasma are planned to be prepared for up to 312 h after drug administration.

Premature stopping of blood sampling from 168 h onwards

In case [^{14}C]-radioactivity in plasma samples is not detectable (<LLOQ 10 dpm/mL) at two consecutive time points for a subject, blood sampling can be stopped for this subject. However, all samples until and including the 168 h sample have to be taken.

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

5.5.2.3 Sampling of plasma for metabolic profiling

At each time point listed in the Flow Chart for metabolic profiling sampling, blood will be withdrawn from a forearm vein using a commercial vacutainer or monovette collection tube with K2-EDTA as anticoagulant. Pre-dose 8 mL of blood will be taken and at all time points post-dose the maximum possible volume of blood will be drawn according to what is allowed considering the blood samples taken for all other samples except metabolic profiling.

Approximately 8 mL of blood will be taken at 1 h and 2 h post dosing. Approximately 10 mL, 20 mL, 40 mL, 60 mL, 80 mL and 40 mL will be taken at 4 h, 8 h, 12 h, 24 h, 48 h and 72 h hours, respectively, after drug administration (Table 5.5.2: 3)

Table 5.5.2: 3 Blood volume to be taken for metabolic profiling

Time after dosing (h)	Blood volume (mL)
Pre-dose	8
1	8
2	8
4	10
8	20
12	40
24	60
48	80
72	40
Total	274

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

5.5.2.4

5.5.2.5 Urine sampling

During the trial urine will be collected at time points or in intervals as indicated in the Flow Chart:

- to determine [^{14}C]-radioactivity
- to determine concentrations of BI 730357

A blank sample will be taken within approximately 14 hours prior to drug administration.

For urine collection, addition of Tween 20 resulting in a final concentration of at least 0.05% Tween 20 is required. The weight of the containers has to be determined prior to (empty containers) and at the end of the collection interval. The urine volume (weight will be set equal to volume, i.e. 1 kg = 1 L, without correction for specific gravity of urine) for each collection interval will be documented. Volunteers will empty their bladders at the end of each sampling interval. The exact start and end times of the urine collection intervals will be recorded in the CRF.

All samples after intake of BI 730357 BS (C-14) are planned to be used for determination of [^{14}C]-radioactivity.

Samples until and including the collection interval 312-336 h are planned to be used for analysis of BI 730357.

Samples to be used for metabolic profiling will be selected according to the levels of radioactivity in each urine sample.

For a detailed description of urine sampling, preparation of collection containers, sample storage, sample handling, labelling, and sample shipment refer to the laboratory manual.

5.5.2.6 Faeces sampling

Faeces will be collected for the analysis of [^{14}C]-radioactivity and for metabolic profiling in intervals as indicated in the Flow Chart. A blank sample will be taken within approximately 48 hours prior to drug administration. If several samples are available, the sample closest to drug administration will be used for analyses.

All faeces samples after intake of BI 730357 BS (C-14) are planned to be used for determination of [^{14}C]-radioactivity.

Samples to be used for metabolic profiling will be selected according to the levels of radioactivity in each faeces sample interval.

All stools will be collected quantitatively in portions up to 336 hours after drug administration. The weight of the faeces and the exact times of faeces collection will be recorded in the eCRF.

If subjects are to collect faeces during the ambulatory phase of the study (see Section 3.1 for release criteria), subjects are to collect faeces at home within 24 h intervals before admission to once-weekly in-house collection intervals. Home collection intervals are (if applicable): Days 20-21, 27-28, 34-35, 41-42, and 48-49. If faeces are collected in the subsequent in-house collection interval, faeces collected at home will be discarded. If no faeces is collected in the subsequent in-house collection interval (no defecation), faeces collected at home will be used instead for analysis

For a detailed description of faeces sampling, sample preparation, sample storage, labelling, and sample shipment refer to the laboratory manual.

5.5.2.7 Collection of vomit

If vomiting occurs in a volunteer within 12 h after drug administration, the vomit will be collected for determination of weight and [^{14}C]-radioactivity.

For a detailed description of vomit sampling, sample preparation, sample storage, labelling, and sample shipment refer to the laboratory manual.

5.5.2.8 Further investigations

Back-up and left-over samples (plasma, urine, faeces; see laboratory manual for details) may be used for metabolic profiling if not needed for their primary purpose (bioanalysis and radiokinetic).

After completion of the trial, blood, plasma, urine, faeces samples (and vomit, if applicable) may be used for further methodological investigations, e.g. for stability testing of the drug and/or drug metabolites, assessment of drug metabolites. However, only data related to the analyte and/or its metabolite including anti-drug antibodies (if applicable) will be generated by these additional investigations.

The study samples will be discarded after completion of the additional investigations but not later than 5 years upon the final study report has been signed.

5.5.3 Analytical determinations

5.5.3.1 Analytical determinations of BI 730357 and plasma and BI 730357 urine concentrations

Plasma and urine concentrations of BI 730357 will be determined by a validated LC-MS/MS (liquid chromatography tandem mass spectrometry) assay. All details of the analytical method will be available prior to the start of sample analysis.

Analysis will be performed at:

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

5.5.3.2 Metabolic profiling

Determination of the metabolic pattern of BI 730357 in plasma, urine, and faeces including structure elucidation of the metabolites will be performed at

Metabolic profiling data will be reported separately from CTR.

5.5.3.3 Radiokinetic and Excretion Balance

Determination of [^{14}C]-radioactivity concentrations in plasma, whole blood, urine, and faeces (and vomit, if applicable) will be done by means of validated liquid scintillation counting methods at

The blood, plasma, urine and faeces concentrations of radioactivity will be determined in agreement with relevant Standard Operating Procedures (SOPs).

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

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

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

The acceptable deviation from the scheduled time for vital signs, ECG and laboratory tests will be ± 30 min on Day 1 and ± 90 min from Day 2 onwards in Visit 2.

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

For planned individual plasma/blood concentration sampling times and urine/faeces sampling times or collection intervals refer to the Flow Chart. While these nominal times should be adhered to as closely as possible, the actual sampling times will be recorded and used for determination of pharmacokinetic parameter. If beginning or end of a urine/faeces collection interval and a blood sample are scheduled for the same time point, urine/faeces collection should be done first, with withdrawal of the blood sample as close to the planned time point as possible.

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

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

6.2.1 Screening period

Screening visit is defined as Visit 1.

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

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

6.2.2 Treatment period

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

On Day -1 of the treatment period study participants will be admitted to the trial site and kept under close medical surveillance until discharge from the trial site on Day 15. In the morning of Day 15, the subjects will then be allowed to leave the trial site after formal assessment and confirmation of their fitness.

Thereafter, until release criteria (see Section 3.1) have been reached, subjects will return to the trial site for up to 5 weekly 24-h collection intervals of urine and faeces. For these additional 24 h collection intervals, subjects will be admitted to the trial site on Days 21, 28, 35, 42, and 49. One day later, on Days 22, 29, 36, 43, and 50, respectively, subjects will be discharged from the trial site after formal assessment and confirmation of their fitness.

Within 24 h before each once-weekly in-house collection interval, subjects are to collect faeces at home (beginning of home collections on Days 20, 27, 34, 41, and 48). Faeces collected in these 24 h home-collection intervals will be used for analysis in case no defecation occurs in the subsequent 24 h in-house collection interval. E.g., if no defecation occurs in in-house collection interval Day 21-22, faeces of home-collection interval Day 20-21 will be used for analysis. If, however, faeces are collected in the subsequent 24 h in-house collection interval, faeces collected at home will be discarded. Once release criteria are reached, home collections will be stopped.

Irrespective of whether release criteria have been met or not after collection interval Days 49-50, no further collections are planned.

For details on time points and procedures for collection of blood/plasma/urine/faeces samples for PK analysis and mass balance assessment, refer to Flow Chart and Section 5.5.2.

The safety measurements performed during the treatment period are specified in Section 5.2 of this protocol and in the Flow Chart. AEs and concomitant therapy will be assessed continuously from screening until the end-of-trial examination.

6.2.3 End-of-trial period

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

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

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

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

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 STATISTICAL DESIGN – MODEL

7.1.1 Objectives

The primary objective of this trial is to investigate the basic pharmacokinetics of BI 730357, [^{14}C]-radioactivity, including mass balance, excretion pathways and metabolism following a single oral dose of 50 mg BI 730357 BS (C-14) given to healthy male subjects. The secondary objective of this trial is to determine PK parameters of [^{14}C]-radioactivity, BI 730357 after single oral dose of BI 730357 BS (C-14) and to determine the routes and rates of elimination of BI 730357.

The assessment of safety and tolerability will be an additional objective of this trial, and will be evaluated by descriptive statistics. More details will be provided in the Trial Statistical Analysis Plan.

7.1.2 Endpoints

The basic pharmacokinetics of BI 730357 and [^{14}C]-radioactivity, including mass balance, excretion pathways and metabolism is to be determined on the basis of the primary and secondary pharmacokinetic endpoints (see Section 5.5.1).

Additionally, the PK parameters listed in Section 5.5.1.3 will be calculated and analysed descriptively, if feasible. Safety and tolerability will be determined on the basis of the parameters specified in Section 5.2.1.

7.1.3 Model

No statistical model will be used.

7.2 NULL AND ALTERNATIVE HYPOTHESES

No confirmatory analysis will be conducted for this study. Data will be reported with descriptive statistics only.

7.3 PLANNED ANALYSES

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

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

- a pre-dose concentration >5% of the C_{max} value of that subject
- missing samples/concentration data at important phases of PK disposition curve

The following subject and analysis sets will be defined for this trial:

Treated set (TS):
This subject set includes all subjects who were documented to have received one dose of study drug. This is the full analysis set population in the sense of ICH-E9.

PK analysis set (PKS):
The PK analysis set includes all subjects in the treated set who provide at least one value for primary or secondary PK endpoint and are not excluded according to the description above. Thus, a subject will be included in the PKS, even if he contributes only one PK endpoint value for the statistical assessment.

7.3.1 Primary analyses

The analysis of primary and secondary endpoints will be based on descriptive statistics only: number, arithmetic mean, standard deviation, minimum, median, maximum, arithmetic coefficient of variation, geometric mean, and geometric coefficient of variation. These evaluations will be based on the PKS. See Sections 5.5.1 and 7.3.5 for further definitions of this analysis.

7.3.2 Secondary analyses

Refer to Section 7.3.3 for a description of the analysis of safety.

7.3.3 Safety analyses

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

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

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

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

Therefore, measurements planned or AEs recorded prior to first intake of trial medication will be assigned to 'screening', those between first trial medication intake until end of the residual effect period (see Section 1.2) will be assigned to the treatment period. Events after the residual effect period but prior to end-of-trial examination will be summarized as ‘follow-up’. These assignments including the corresponding time intervals will be defined in detail in the TSAP.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Frequency, severity and causal relationship of AEs will be tabulated by treatment, system organ class and preferred term. SAEs, AESIs (see Section 5.2.2.1) and other significant AEs (according to ICH E3) will be listed separately.

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

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

Relevant ECG findings as judged by the investigator will be reported as AEs.

7.3.4 Interim analyses

No interim analysis is planned.

7.3.5 Pharmacokinetic analyses

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

Subjects who are not included in the PKS (refer to Section 7.3) will be reported with their individual plasma/urine/faeces concentrations and individual pharmacokinetic parameters; however, they will not be included in descriptive statistics for plasma/urine/faeces concentrations, pharmacokinetic parameters or other statistical assessment.

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).

The following descriptive statistics will be calculated for concentration-time data as well as for all pharmacokinetic parameters: number, arithmetic mean, standard deviation, minimum,

median, maximum, arithmetic coefficient of variation, geometric mean, and geometric coefficient of variation. Descriptive statistics of pharmacokinetic parameters will be calculated using the individual values with the number of decimal places as provided by the evaluation program. Then the individual values as well as the descriptive statistics will be reported with three significant digits in the Clinical Trial Report.

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

7.4 HANDLING OF MISSING DATA

7.4.1 Safety

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

7.4.2 Blood/plasma/urine/faeces drug or [^{14}C]-radioactivity concentration - time profiles

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

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

7.4.3 Pharmacokinetic parameters

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

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

7.5 RANDOMISATION

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.

7.6 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.

The sample size of 6 subjects accounts for moderate PK variability, the potential of the drug to induce vomiting and potential drop-outs. For replacement rules, refer to Section 3.3.5.

8. INFORMED CONSENT, DATA PROTECTION, TRIAL RECORDS

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

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

The rights of the Investigator and of the Sponsor with regard to publication of the results of this trial are described in a separate agreement between the Investigator or the trial site and the Sponsor. As a general rule, no trial results should be published prior to finalisation of the CTR.

8.1 STUDY APPROVAL, SUBJECT INFORMATION, AND INFORMED CONSENT

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

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

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

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

8.2 DATA QUALITY ASSURANCE

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

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

8.3 RECORDS

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

8.3.1 Source documents

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

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

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

8.3.2 Direct access to source data and documents

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

8.3.3 Storage period of records

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

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

8.4 EXPEDITED REPORTING OF ADVERSE EVENTS

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

8.5 STATEMENT OF CONFIDENTIALITY

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

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

8.6 COMPLETION OF TRIAL

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

9. REFERENCES

9.1 PUBLISHED REFERENCES

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R15-3219 International Commission on Radiological Protection (ICRP). 2007 Recommendations of the International Commission on Radiological Protection (users edition): abstract. website.icrp.org/publication.asp?id=ICRP%20Publ ication%20103%20(Users%20Editi on) (access date: 24 June 2015) ; (ICRP Publication; 103 (Users Edition)) International Commission on Radiological Protection (ICRP); 2007.

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9.2 UNPUBLISHED REFERENCES

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n00258749-01 Excretion of radioactivity in urine, faeces and bile after oral and intravenous administration of [14C]BI 730357 to rats. A194/16FU. B5718. 03 Nov 2017.

n00260847-01 Quantitative whole-body autoradiography in male pigmented rats after single intravenous or oral administration of [14C]BI 730357. A117/17JS. B6163. 27 Mar 2018.

10. APPENDICES

10.1 RADIO BURDEN CALCULATION

Radiation Burden Calculation Report

Title (provisional)	A phase I, open-label, single-dose trial to investigate metabolism and pharmacokinetics of BI 730357 BS (C-14) administered as oral solution in healthy male volunteers
Sponsor:	Boehringer Ingelheim
Protocol No:	BI1407-0031
PRA Project Id:	BID015EC-180155
Version Date:	05 July 2018

Calculation of Radiation Burden (Dosimetry)

BI 730357 is a new chemical entity Retinoic acid-related Orphan Receptor-γt (RORγt) antagonist, in development for the treatment of patients with psoriasis, psoriatic arthritis, ankylosing spondylitis, asthma, and inflammatory bowel disease. RORγt is a nuclear hormone receptor/transcription factor expressed in distinct subsets of lymphoid cells. Upon cell activation, in response to multiple activation signals including cytokines and T cell receptor engagement, RORγt regulates the transcription of IL-17A, IL-17F, IL-22 genes, and of the IL-23 receptor gene.
Excretion and pharmacokinetic studies using BI 730357 were conducted on rats[1,3], and quantitative tissue distribution studies on pigmented rats[2]. A radiation dose assessment was made based on these studies. In addition, data from the Investigator Brochure[4] were taken into consideration.
The following assumptions, based on the data from these experiments, and taking the worst-case scenario, were made to be able to estimate the effective radiation dose:

- After oral dosing, BI 730357 and possible metabolites are considered to be distributed more or less homogeneously throughout the body, with the exception of higher exposure of the liver, which is calculated separately.
- The major part of the administered amount of ^{14}C-radiolabeled BI 730357 and possible metabolites show reasonably slow, bi- and triphasic elimination from the body, mostly via fecal and for a smaller part via urinary excretion. For this estimation, the longest elimination half-life given for whole blood or plasma was used.
- Using the data of the BI 730357 study in rats a half-life of total ^{14}C-activity of 64 hours is estimated. In humans a terminal phase half-life of BI 730357 of approximately 28 hours is assumed[3]. In the current estimation a half-life of total radioactivity of 64 hours is used.
- The absorbed fraction is assumed to be 1, based on a study on the biliary and intestinal excretion in the rat[3], which gave a number of 94%.
- Based on the excretion study in rats[3] ^{14}C-radiolabeled BI 730357 is found to be excreted both in feces and in urine. For the calculation is assumed: 86% of the administered radioactivity is excreted via the gastrointestinal tract in feces and 14% is excreted via the kidneys in urine.

Based on these assumptions the estimated effective radiation burden after a single oral radioactivity dose of 3.7 MBq ^{14}C-radiolabeled BI 730357 is approximately 0.14 mSv. For biomedical investigations in small groups of human volunteers an effective dose of 0.1 – 1.0 mSv is considered acceptable[5].

References:

1: Excretion of radioactivity in urine, feces and bile after oral and intravenous administration of [14C]-BI 730357 to rats, 03Nov17
2: Quantitative whole-body autoradiography in male pigmented rats after single iv or oral administration of [14C]BI 730357 27Mar18
3. Investigation of intestinal secretion and biliary excretion of radioactivity after iv administration of [14C]BI 730357 to rats 16Feb18
4: Investigator's brochure Version 3 dated 28 June 2017.
5: Recommendations of the International Commission on Radiological Protection. User's ICRP publication 60, Pergamon Press 1992 and update from ICRP 103.

Appendix A1: Radiation burden of the gastrointestinal tract after oral administration of 3.7 MBq ^{14}C BI 730357

Using SEE-values, an organ-specific radiation burden can be estimated. The SEE-value is dependent, among other factors, on the mass of the target organ and the type of radiation.
With these SEE-values and the number of disintegrations U in the target organ, the organ dose equivalent H_t is calculated:
H_t= constant x U x SEE (mSv); using a target organ-related weight factor, the contribution of the organ burden to the body burden is translated as: $H_{wb,t}$ = H_t x weight factor (mSv).

In order to be able to calculate the radiation burden of the GI tract, this has been divided in five sections, i.e., the stomach (st), the small intestines (si), the right part of the large intestines, the left part of the large intestines (lc) and the rectum / sigmoid (rs).
The SEE-values for these organs are:

ST:	1.0 x 10 -5,	(weight factor = 0.12)
SI:	3.2 x 10 -7,	(weight factor = 0.01)
RC:	2.3 x 10 -10,	(weight factor = 0.048)
LC:	2.9 x 10 -10.	(weight factor = 0.045)
RS:	9.2 x 10 -10.	(weight factor = 0.027)

The number of disintegrations U in each target organ depends on the amount of radioactivity excreted, or any metabolites that are eliminated via the gall bladder that is standardised for the various compartments of the GI tract (constant). I_0 = 3.7 MBq; excretion via GI tract: 86% of the dose, excretion via urine: 14% of the dose. These assumptions give:

Hst=	0.0030 mSv
Hsi=	0.0000 mSv
H_{RC}=	0.0000 mSv
H_{LC}=	0.0000 mSv
H_{RS}=	0.0000 mSv
total GI:	0.0030 mSv

The total contribution of the GI tract to the effective dose (body radiation burden) amounts to 0.0030 mSv.

Appendix A2: Radiation burden of the central compartment after oral administration of 3.7 MBq ^{14}C BI 730357

Average body weight = 70 kg; SEE = 7.1905 x 10-7; 88% of the dose administered orally and excreted with a half-life of 64 hours. Total number of disintegrations in the central compartment after oral administration of 3.7 MBq [^{14}C] BI 730357 is 1072 x 10^9 with a tissue weighting factor of 0.96 giving a H_{tw} of 0.1152 mSv.

Appendix A3: Radiation burden of the liver after oral administration of 3.7 MBq ^{14}C BI 730357

For the Liver SEE = 2.72 x 10-5; 12% of the dose administered orally excreted by the liver with a half-life of 53 h. The weighting factor for the liver is 0.04, the contribution to the radiation burden is 0.0211 mSv.

The total effective dose (radiation burden), based on the above-mentioned worst-case scenario amounts to 0.0030 + 0.1152 + 0.0211 = 0.14 mSv.

Name and Date: **Signature:**

05 July 2018

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

Number of global amendment		1
Date of CTP revision		25 September 2018
EudraCT number		2018-001837-41
BI Trial number		1407-0031
BI Investigational Product(s)		BI 730357
Title of protocol		A phase I, open-label, single-dose trial to investigate metabolism and pharmacokinetics of BI 730357 BS (C-14) administered as oral solution in healthy male volunteers
To be implemented only after approval of the IRB / IEC / Competent Authorities		☐
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		☐
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		☒
Section to be changed	3.3.5 5.2.3 5.2.5.1 5.5.2.5	Exclusion Criteria Assessment of safety laboratory parameters Vital signs Urine sampling
Description of change	3.3.5 5.2.3 5.2.5.1 5.5.2.5	Deleted the number before sentence “In addition, the following trial-specific exclusion criteria apply” Deleted the sentence “(please specify which)” and deleted the timepoint Day 1, 1:00 in the footnote for lab set C in table 5.2.3: 1 Changed the type of monitor used for blood pressure measurements Added “at least” in front of “0.05 % Tween 20”
Rationale for change	3.3.5	The incorrect numbering in the list of exclusion criteria was corrected. The exclusion criteria per

Number of global amendment		1
		se were not changed.
	5.2.3	The type of alcohol test is specified in the next paragraph; the deleted sentence was a leftover from protocol drafting process
		Inconsistency in the footnote: Timepoint Day 1, 1:00 for safety lab is not in the Flow Chart since it is not necessary for safety reasons.
	5.2.5.1	Site has changed the equipment since old monitor has become obsolete
	5.5.2.5	The concentration of Tween 20 in the urine container is now allowed to be 0.05% or higher.

APPROVAL / SIGNATURE PAGE

Document Number: c22159106 **Technical Version Number:2.0**

Document Name: clinical-trial-protocol-revision-01

Title: A phase I, open-label, single-dose trial to investigate metabolism and pharmacokinetics of BI 730357 BS (C-14) administered as oral solution in healthy male volunteers

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Author-Trial Clinical Pharmacokineticist		25 Sep 2018 16:56 CEST
Author-Clinical Trial Leader		25 Sep 2018 17:41 CEST
Approval-Team Member Medicine		25 Sep 2018 17:58 CEST
Approval-Therapeutic Area		27 Sep 2018 16:36 CEST
Verification-Paper Signature Completion		28 Sep 2018 13:09 CEST
Author-Trial Statistician		01 Oct 2018 10:05 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed