Clinical Trial Protocol

	Document Number: c11248385-04
EudraCT No.:	2016-003047-11
BI Trial No.:	1407.1
BI Investigational Product:	BI 730357
Title:	A partially randomised, single-blind, placebo-controlled trial to investigate safety, tolerability, pharmacokinetics and pharmacodynamics of single rising doses of BI 730357 administered as oral solution and tablets to healthy subjects, and a randomized, open-label, single-dose, three-way cross-over bioavailability comparison of BI 730357 as tablet versus oral solution and tablet with and without food
Clinical Phase:	I
Trial Clinical Monitor:	[redacted] Phone: [redacted] Fax: [redacted]
Principal Investigator:	[redacted] Phone: [redacted] Fax: [redacted]
Status:	Final Protocol (Revised Protocol based on global amendment 3)
Version and Date:	Version: 4.0 Date: 05 May 2017

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: 13 October 2016	**Trial number:** 1407.1		**Revision date:** 05 May 2017

Title of trial:	A partially randomised, single-blind, placebo-controlled trial to investigate safety, tolerability, pharmacokinetics and pharmacodynamics of single rising doses of BI 730357 administered as oral solution and tablets to healthy subjects, and a randomized, open-label, single-dose, three-way cross-over bioavailability comparison of BI 730357 as tablet versus oral solution and tablet with and without food
Principal Investigator:	[redacted]
Trial site:	[redacted]
Clinical phase:	I
Objectives:	To investigate the safety, tolerability, pharmacokinetics incl. dose proportionality, and pharmacodynamics of BI 730357 (single rising dose [SRD] part), and the relative bioavailability of the tablet formulation versus oral solution as well as the influence of food on the bioavailability of the tablet formulation (bioavailability [BA] part).
Methodology:	SRD part: Single rising dose, partially randomized, single-blind, placebo-controlled, parallel group design. BA part: Single dose, randomised, open-label, intra-individual three-way cross-over comparisons of the relative bioavailability of tablet fasted versus oral solution fasted, and tablet fasted versus tablet fed
No. of subjects:	
total entered:	84[1]
each treatment:	SRD part: 72[1] (6 on active drug and 2 on placebo at each of 10 dose levels) BA part: 12 (all on active drug)
	[1] In dose group (DG) 8 (400 mg BI 730357 or placebo with continental breakfast) and DG 9 (400 mg BI 730357 or placebo with high-fat breakfast) the same subjects will be included for an intra-individual comparison of two different diets
Diagnosis:	Not applicable
Main criteria for inclusion:	Healthy male subjects, age of 18 to 45 years (inclusive), body mass index (BMI) of 18.5 to 29.9 kg/m^2 (inclusive)

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Test products:	SRD part:	BI 730357 as a powder for oral solution (1 mg/mL formulation) or film-coated tablet (25 mg and 50 mg formulations)
	BA part:	BI 730357 as a powder for oral solution (10 mg/ml) in treatment T1 and as film-coated tablet (25 mg) in treatment T2
dose:	SRD part:	2 and 8 mg as powder for oral solution (PfOS) and 25, 50, 100, 200, 400 and 800 mg as film-coated tablet
	BA part:	25 mg[2] as film-coated tablet and PfOS [2]The BA part will only start when at least the 100 mg dose is tested during the SRD part and have been safe and well tolerated.
mode of admin.:	SRD part:	Oral with 240 mL of water in fasted state (doses from 2 mg to 400 mg, inclusive) or in fed state (400 mg dose after continental breakfast, doses of 400 and 800 mg after high-fat breakfast)
	BA part:	Oral with 240 mL of water in fasted and fed state (high-fat breakfast)
Comparator products:	SRD part:	Placebo solution or placebo tablets
	BA part:	BI 730357 as film-coated tablet (25 mg) in treatment R
dose:	SRD part:	Not applicable (matching placebo)
	BA part:	25 mg as film-coated tablet
mode of admin.:	SRD part:	Oral with 240 mL of water in fasted state (matching placebo from 2 mg to 400 mg, inclusive) or in fed state (matching placebo to 400 mg after continental breakfast, matching placebo to 400 and 800 mg after high-fat breakfast)
	BA part:	Oral with 240 mL of water in fasted state
Duration of treatment:	SRD part:	1 single dose
	BA part:	3 single doses separated by a washout period of at least 8 days
Criteria for safety:	Primary endpoint to assess safety and tolerability of BI 730357 is the number [N (%)] of subjects with adverse reactions. Further criteria: AEs including clinically relevant findings from the physical examination, safety laboratory tests, 12-lead electrocardiogram (ECG), continuous ECG monitoring, vital signs (blood pressure [BP], pulse rate [PR])	
Criteria for pharmacokinetics:	Secondary endpoints: $AUC_{0-\infty}$ and C_{max} of BI 730357 [redacted]	

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Protocol date: 13 October 2016	**Trial number:** 1407.1		**Revision date:** 05 May 2017
Criteria for pharmacodynamics:	[redacted]		
Statistical methods:	Descriptive statistics will be calculated for all endpoints. SRD part: Dose proportionality will be explored under fasted conditions using a regression model. A 95% confidence interval for the slope will be computed. BA part: Relative bioavailability will be estimated by the ratios of the geometric means (tablet / PfOS, tablet fed / tablet fasted) for the secondary endpoints. Additionally, their two-sided 90% confidence intervals (CIs) will be provided. Since the main focus is on estimation and not testing, an acceptance range was not specified. The statistical model will be an ANOVA on the logarithmic scale including effects for 'sequence', 'subjects nested within sequences', 'period' and 'treatment'. CIs will be calculated based on the residual error from ANOVA.		

FLOW CHART FOR THE SINGLE RISING DOSE PART

Visit	Day	Planned time (relative to drug administration [h:min]	Approximate clock time of actual day [h:min]	Event and comment	Safety laboratory	PK blood [10, 11]	PK urine [10.12]	Blood sampling for biomarkers [10 13],	12-lead ECG	Continuous ECG monitoring	Vital signs (BP, PR)	Questioning for AEs and concomitant therapy [6]
1	-21 to -1			Screening (SCR)[1]	x				x[14]		x	
2/3*	-3 to -1	-72:00[7]	08:00	Ambulatory visit	x							x
	1	-2:00	06:00	Admission to trial site in visits 2-3, allocation to treatment[2] in visit 2 only	x[2,5]	x[2]	x[2]	x[2]	x[2,9]	x[2]	x[2]	x[2]
		-0:30	07:30	Standard breakfast in dose groups 8-10 [16]								
		0:00	**08:00**	**Drug administration**			▲			▲		
		0:30	08:30			x	|		x[9]	|	x	x
		1:00	09:00			x	|		x[9]	|	x	x
		1:30	09:30			x	|			|		
		2:00	10:00	240 mL fluid intake		x	|	x	x[9]	|	x	x
		2:30	10:30			x	|			|		
		3:00	11:00			x	|		x[9]	|	x	x
		4:00	12:00	240 mL fluid intake, thereafter lunch[3]		x[8]	┼	x	x[9]	|	x	x
		5:00	13:00			x	|		x[9]	|	x	x
		6:00	14:00		x	x	|	x	x[9]	▼	x	x
		8:00	16:00	Snack (voluntary)[3]		x	┼		x[9]		x	x
		10:00	18:00	Dinner[3]		x	|		x[9]		x	x
		12:00	20:00			x	┼		x[9]		x	x
	2	24:00	08:00	Breakfast (voluntary)[3], discharge from trial site	x	x	┼	x	x[9]		x	x
		34:00	18:00	Ambulatory visit		x	|		x[9]		x	x
	3	48:00	08:00	Ambulatory visit		x	▼	x	x[9]		x	x
	4	72:00	08:00	Ambulatory visit	x	x					x	x
	5	96:00	08:00	Ambulatory visit		x		x			x	x
	8	168:00	08:00	Ambulatory visit	x[15]	x		x				x
5	9 to 13			End of trial (EOT) examination [4]	x				x[14]		x	x

* Only one treatment period (Visit 2) for dose groups 1-7 and 10. Two identical treatment periods separated by a wash-out phase of at least 14 days between drug administration for dose group (DG) 8 (Visit 2) and DG 9 (Visit 3). In DGs 8-9 the same subjects will be included.

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

7. Safety laboratory to be taken and to be medically evaluated within 3 days prior to administration of study drug; this ambulatory visit including the safety laboratory can be omitted, if the screening examination is performed on Days -3, -2 or -1.
8. Two blood sample for stability testing will be taken at this time point (refer to Section 5.5.2.4)
9. The ECG recording has to be performed as triple at this time point
10. Sampling times and periods may be adapted based on information obtained during the trial (e.g. preliminary PK data) including addition of samples and visits as long as the total blood volume taken does not exceed 500 mL per subject
11. Including blood sample for metabolite identification (refer to Section 5.5.2.2)
12. A blank urine sample (x) is to be obtained prior to administration of trial medication. Other urine samples are to be collected over the stated post-dose intervals (◄—|—|—►) 0-4, 4-8, 8-12, 12-24 and 24-48 h.
13. Two blood samples should be collected: 4.3 mL in sodium citrate tubes and 4.5 mL in lithium heparin tubes.
14. The ECG will be recorded as single ECG at this time point
15. Only haematology, automatic WBC differential and lymphocytes subtypes (refer to Table 5.2.3: 1) at this time point
16. Standard continental breakfast (see Table 4.1.4: 3) in DG 8 and standard high-fat breakfast (see Table 4.1.4: 4) in DGs 9 and 10

FLOW CHART FOR THE BIOAVAILABILITY PART

Visit	Day	Planned time (relative to drug administration [h:min]	Approximate clock time of actual day [h:min]	Event and comment	Safety laboratory	PK $_{blood}$ [8]	12-lead ECG	Vital signs (BP, PR)	Questioning for AEs and concomitant therapy [6]
1	-21 to -1			Screening (SCR)[1]	x		x[10]	x	
2/3/4*	-3 to -1	-72:00[7]	08:00	Ambulatory visit	x				x
	1	-2:00	06:00	Admission to trial site in visits 2-4, allocation to treatment in visit 2 only[2]	x[2,5]	x[2]	x[10,2]	x[2]	x[2]
		-0:30	07:30	Standard breakfast[9]					
		0:00	**08:00**	**Drug administration**					
		0:30	08:30			x			
		1:00	09:00			x			x
		1:30	09:30			x			
		2:00	10:00	240 mL fluid intake		x	x[10]	x	x
		2:30	10:30			x			
		3:00	11:00			x			
		4:00	12:00	240 mL fluid intake, thereafter lunch[3]		x	x[10]	x	x
		5:00	13:00			x			
		6:00	14:00			x	x[10]	x	x
		8:00	16:00	Snack (voluntary)[3]		x			x
		10:00	18:00	Dinner[3]		x	x[10]	x	
		12:00	20:00			x			x
	2	24:00	08:00	Breakfast (voluntary)[3], discharge from trial site	x	x	x[10]	x	x
		34:00	18:00	Ambulatory visit		x			x
	3	48:00	08:00	Ambulatory visit		x	x[10]	x	x
	4	72:00	08:00	Ambulatory visit		x			x
	5	96:00	08:00	Ambulatory visit		x			x
	8	168:00	08:00	Ambulatory visit	x[11]	x			x
5	9 to 13			End of trial (EOT) examination[4]	x		x[10]	x	x

* Three identical treatment periods separated by wash-out phases of at least 8 days between each drug administration

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

7. Safety laboratory to be taken and to be medically evaluated within 3 days prior to each administration of study drug; this ambulatory visit including the safety laboratory can be omitted, if the screening examination is performed on Days -3, -2 or -1.
8. Sampling times and periods may be adapted based on information obtained during the trial (e.g. preliminary PK data) including addition of samples and visits as long as the total blood volume taken does not exceed 500 mL per subject
9. Standard breakfast only in one treatment period under fed condition
10. The ECG will be recorded as single ECG at this time point. However, the number of ECGs per time point may be increased to three ECGs based on the preliminary ECG results obtained during the SRD part of this trial.
11. Only haematology, automatic WBC differential and lymphocytes subtypes (refer to Table 5.2.3: 1) at this time point.

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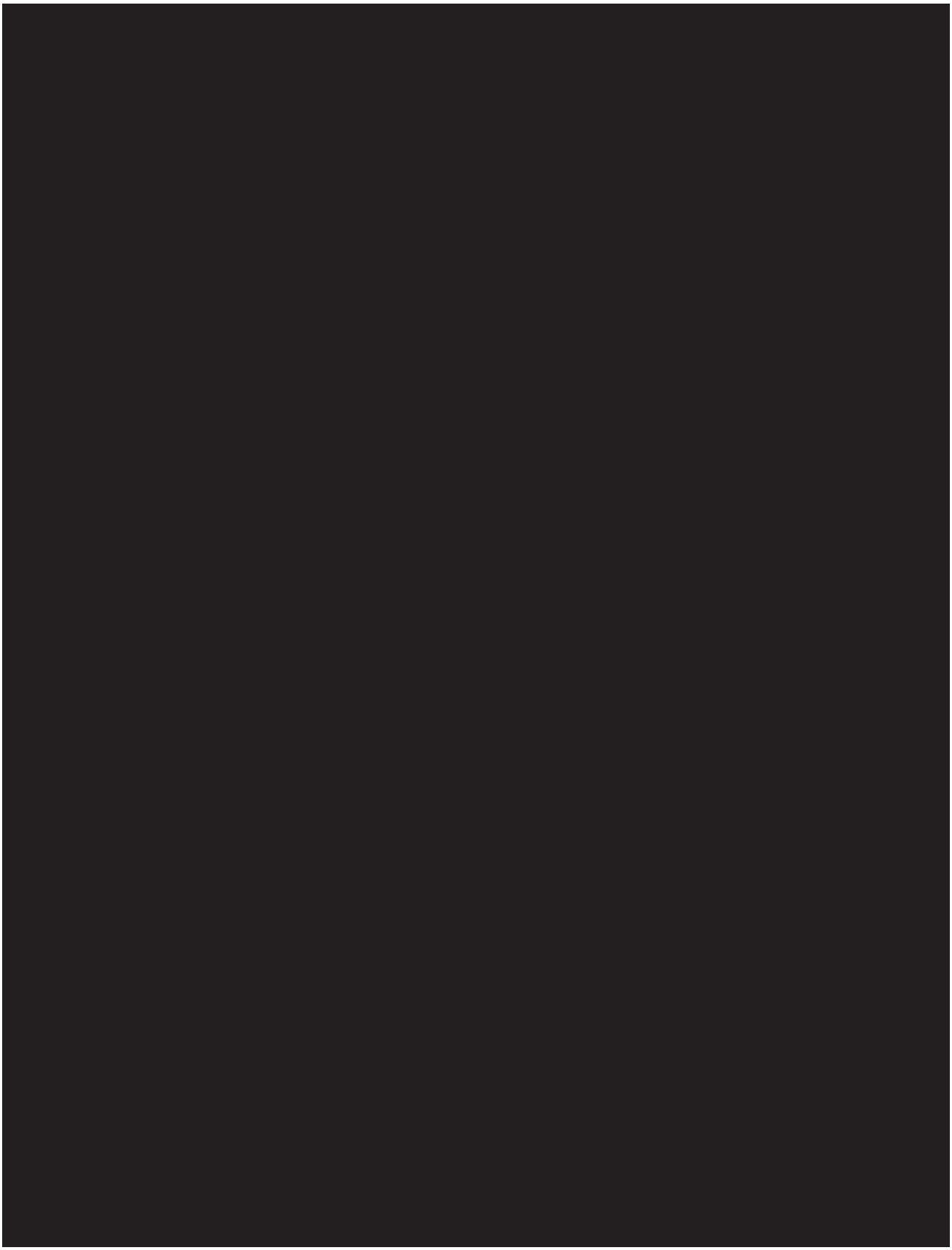
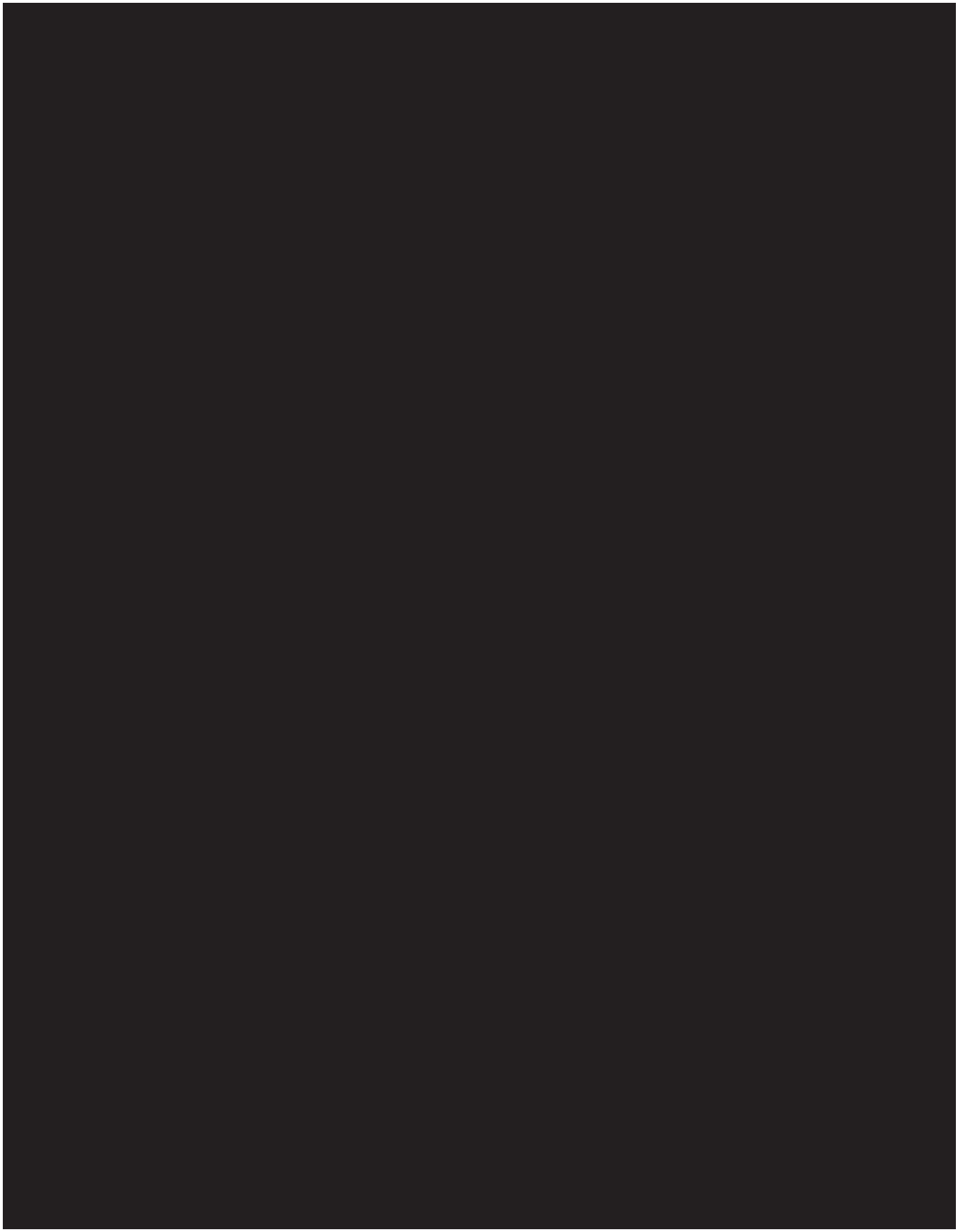
ABBREVIATIONS

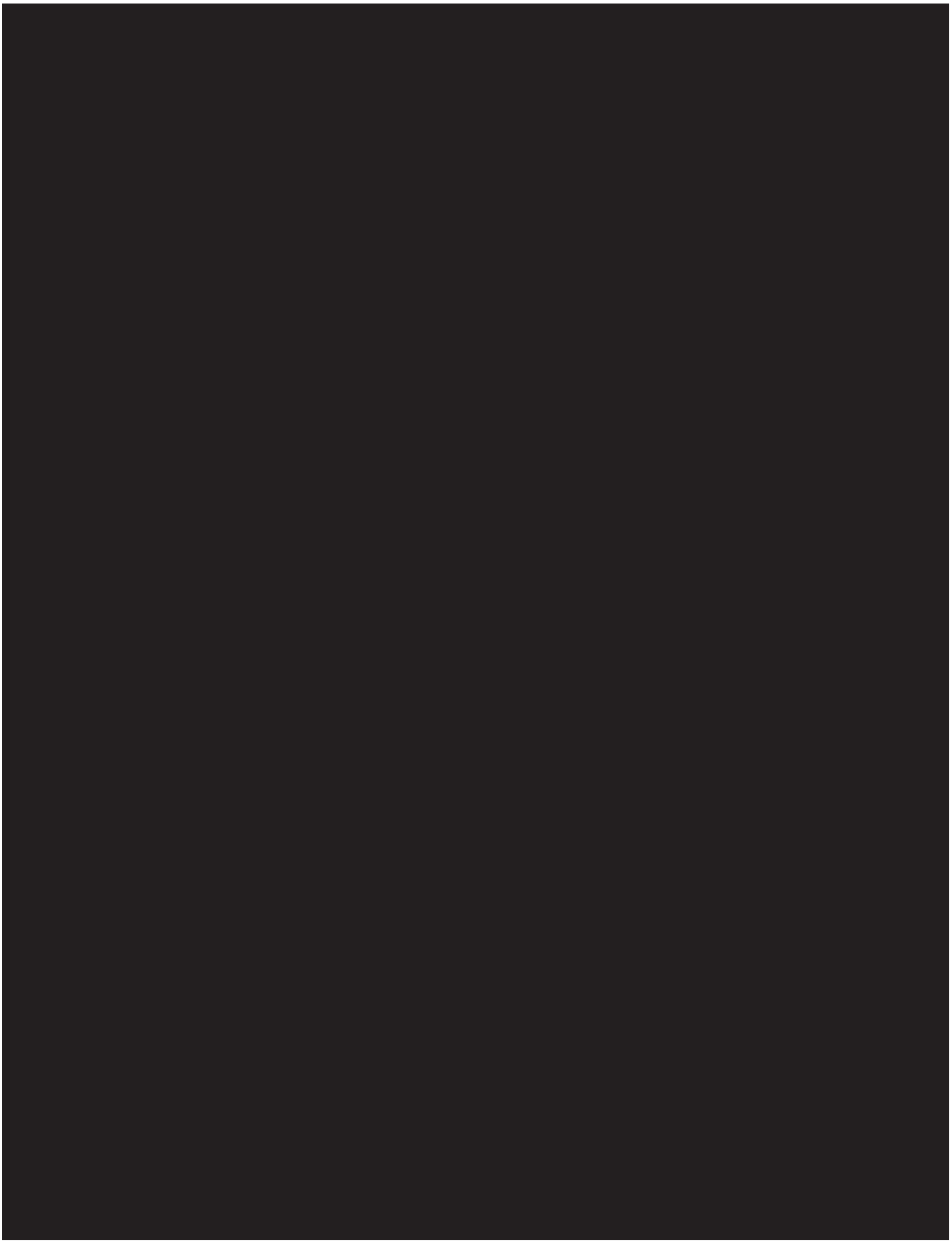
ADME	Absorption, distribution, metabolism, and excretion
AE	Adverse event
AESI	Adverse events of special interest
Ae_{t1-t2}	Amount of analyte eliminated in urine over the time interval t_1 to t_2
ANOVA	Analysis of variance
$AUC_{0-\infty}$	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity
AUC_{0-24}	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 to 24 hours
AUC_{t1-t2}	Area under the concentration-time curve of the analyte in plasma over the time interval t_1 to t_2
AUC_{0-tz}	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 to the last quantifiable data point
BA	Bioavailability
BI	Boehringer Ingelheim
BLQ	Below limit of quantification
BMI	Body mass index (weight divided by height squared)
BP	Blood pressure
CA	Competent authority
CI	Confidence interval
CL/F	Apparent clearance of the analyte in plasma after extravascular administration
$CL_{R,\ t1-t2}$	Renal clearance of the analyte in plasma from the time point $_{t1}$ to $_{t2}$
C_{max}	Maximum measured concentration of the analyte in plasma
C_{min}	Minimum measured concentration of the analyte in plasma
CNS	Central nervous system
CRF	Case report form
CTP	Clinical trial protocol
CTR	Clinical trial report
CYP	Cytochrome P450
DILI	Drug induced liver injury
DG	Dose group
ECG	Electrocardiogram
EDTA	Ethylenediaminetetraacetic acid
EEG	Electroencephalograph
EMG	Electromyogram
EOT	End of trial

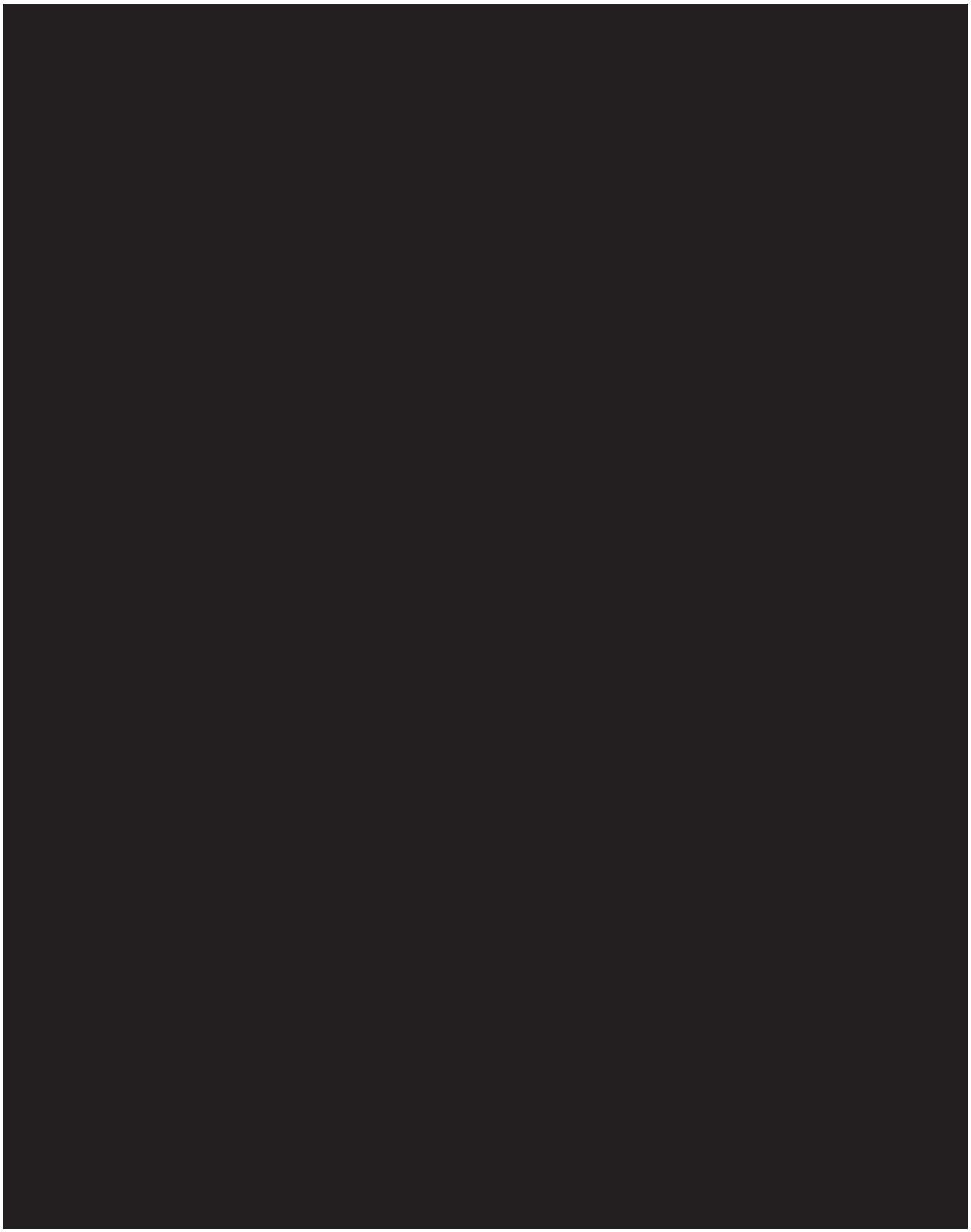
fe_{t1-t2}	Fraction of administered drug excreted unchanged in urine over the time interval from t_1 to t_2
FIM	First-in-man
gCV	Geometric coefficient of variation
hERG	Human-ether-à-go-go related gene
HR	Heart rate
hLXRα	human liver X receptor α
hPXR	human pregnane X receptor
IC_{50}	50% inhibitory concentration
IEC	Independent Ethics Committee
IL	Interleukin
IRB	Institutional Review Board
ISF	Investigator site file
ITE	Indirect target engagement
LC-MS/MS	Liquid chromatography tandem mass spectrometry
λ_z	Terminal rate constant of the analyte in plasma
MACS	Magnetic-activated cell sorting
MedDRA	Medical Dictionary for Regulatory Activities
MIST	Metabolites in Safety Testing
MRT_{po}	Mean residence time of the analyte in the body after oral administration
NC	Not calculated
NOA	Not analysed
NOAEL	No observed adverse effect level
NOP	No peak detectable
NOR	No valid result
NOS	No sample available
PAD	Pharmacologically active dose
PD	Pharmacodynamic(s)
PE	Polyethylene
PEG	Polyethylene glycol
PfOS	Powder for reconstitution of an oral solution
PK	Pharmacokinetic(s)
PKS	Pharmacokinetic set
PP	Polypropylene
PR	Pulse rate
[redacted]	[redacted]
PCR	Polymerase chain reaction
QD	*Quaque die*, once daily

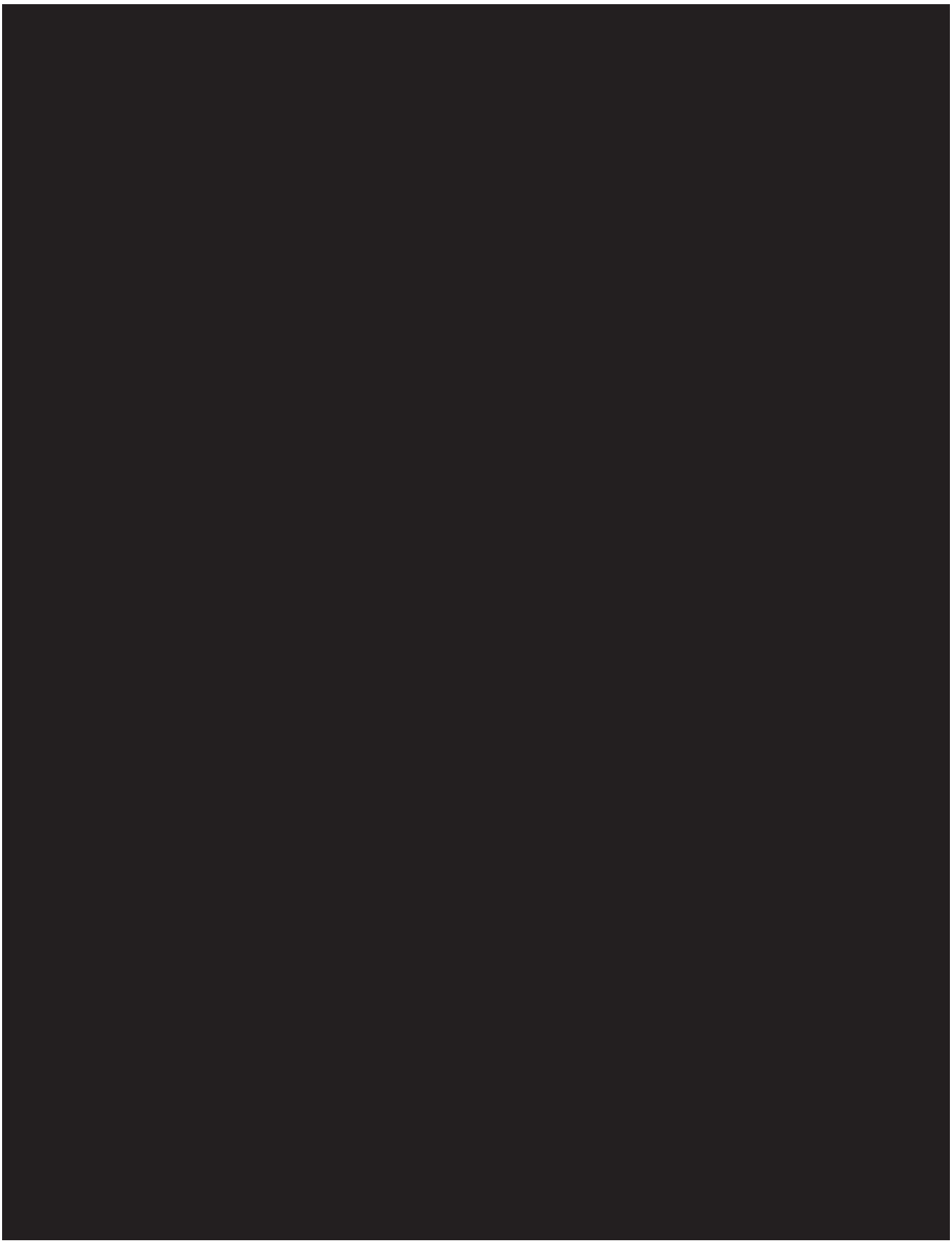
QT	Time between start of the Q-wave and the end of the T-wave in an electrocardiogram
QTc	QT interval corrected for heart rate using the method of Fridericia (QTcF) or Bazett (QTcB)
R	Reference treatment
REP	Residual effect period
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
SAE	Serious adverse event
SCR	Screening
SfOS	Solvent for Oral Solution
SOP(s)	Operating Procedure(s)
SRD	Single-rising dose
SUSAR	Suspected Unexpected Serious Adverse Reaction
T	Test product or treatment
Th	T helper type
TMF	Trial master file
$t_{1/2}$	Terminal half-life of the analyte in plasma
t_{max}	Time from (last) dosing to the maximum measured concentration of the analyte in plasma
t_z	Time of last measurable concentration of the analyte in plasma
TDMAP	Trial Data Management and Analysis Plan
TSAP	Trial statistical analysis plan
ULN	Upper limit of normal
Vd	Volume of distribution
V_z/F	Apparent volume of distribution during the terminal phase after extravascular administration
WOCBP	Women of childbearing potential

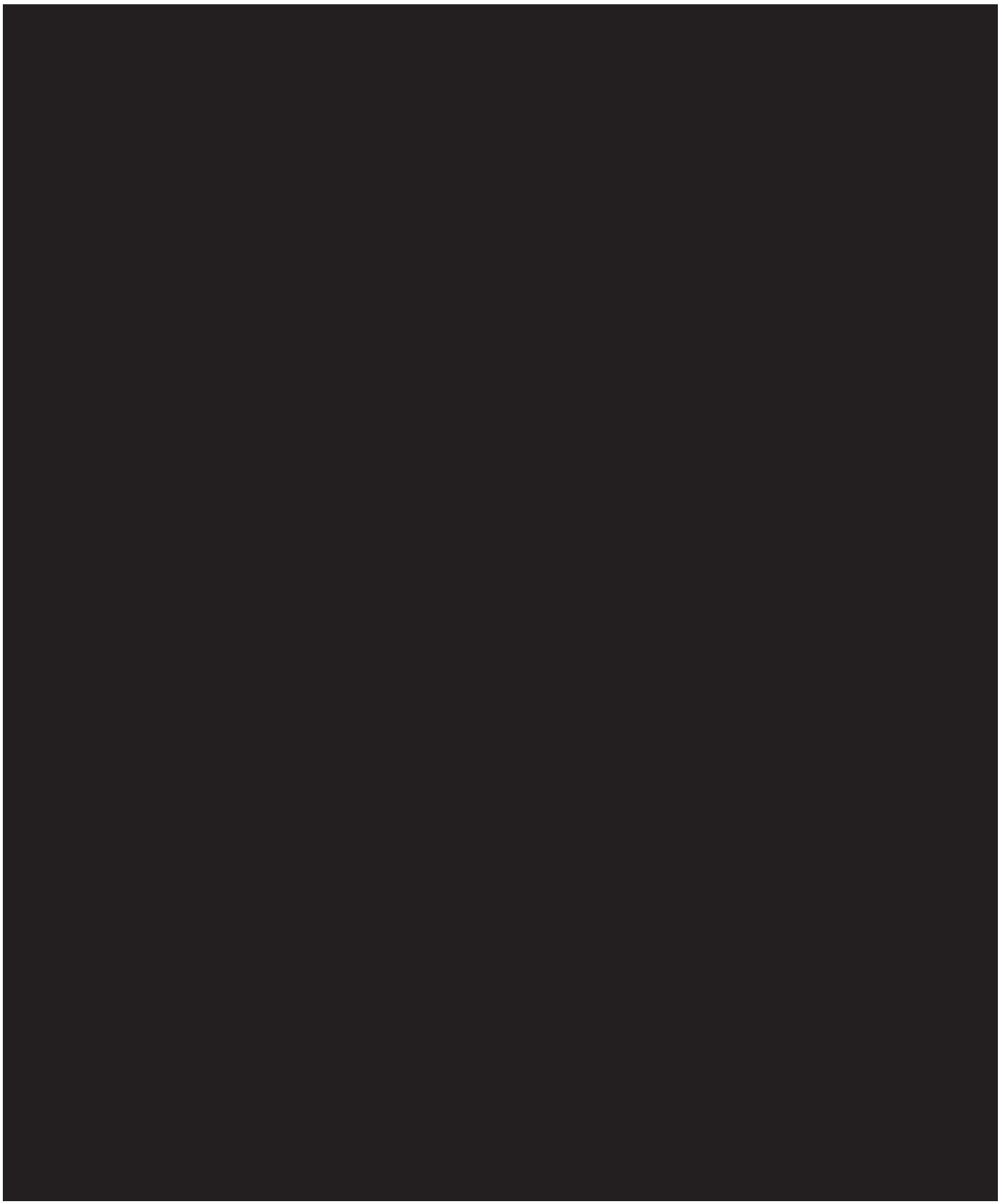


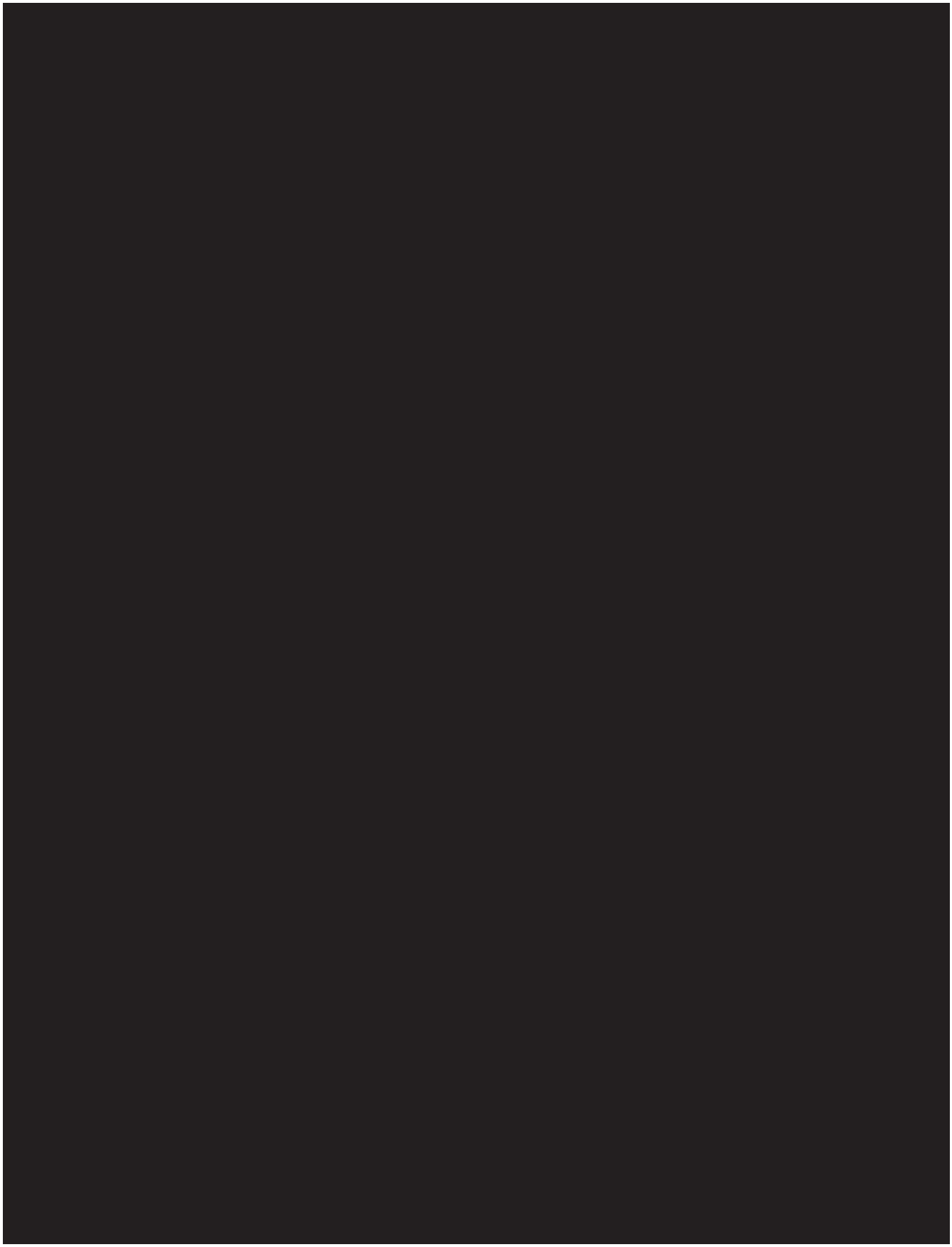


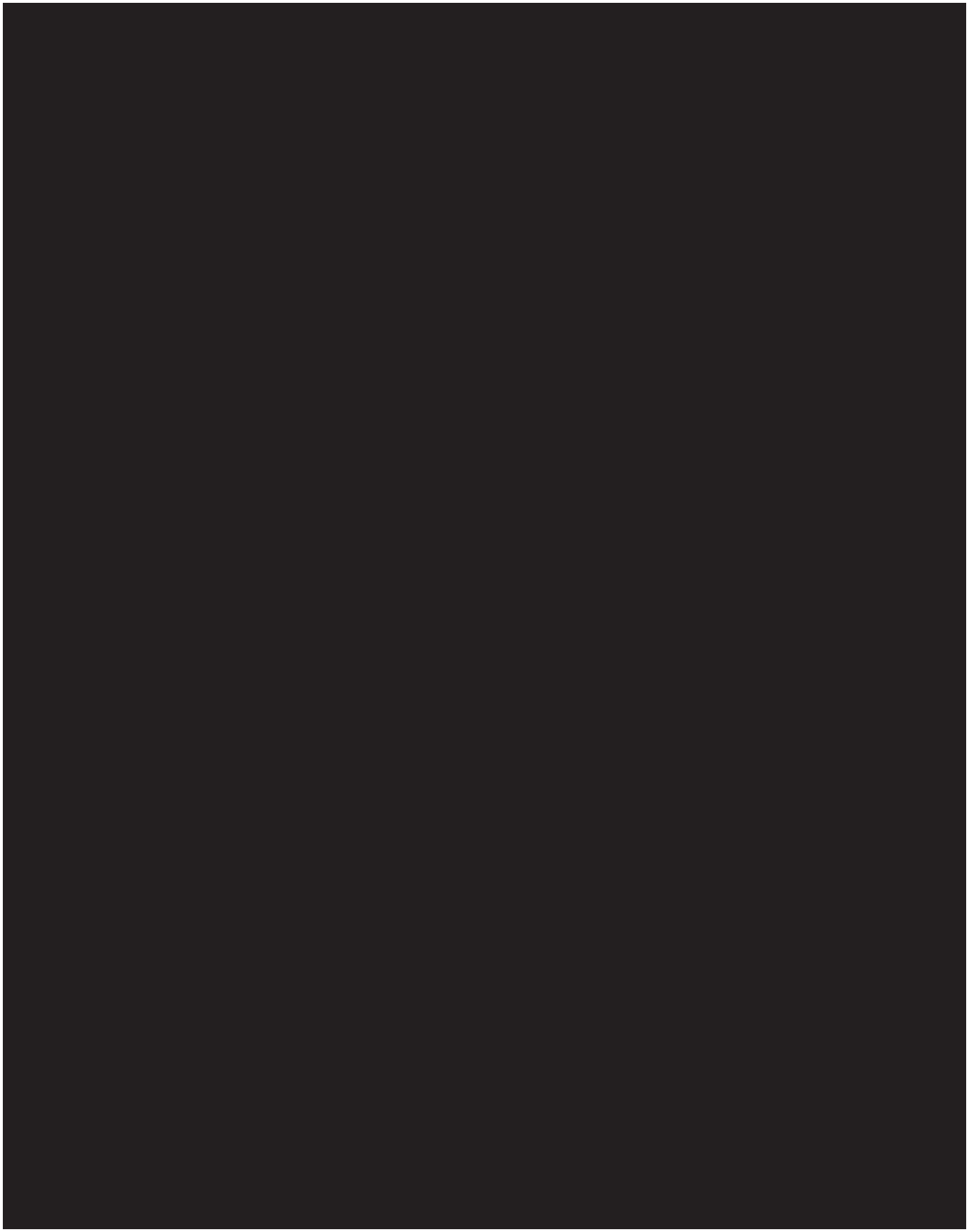




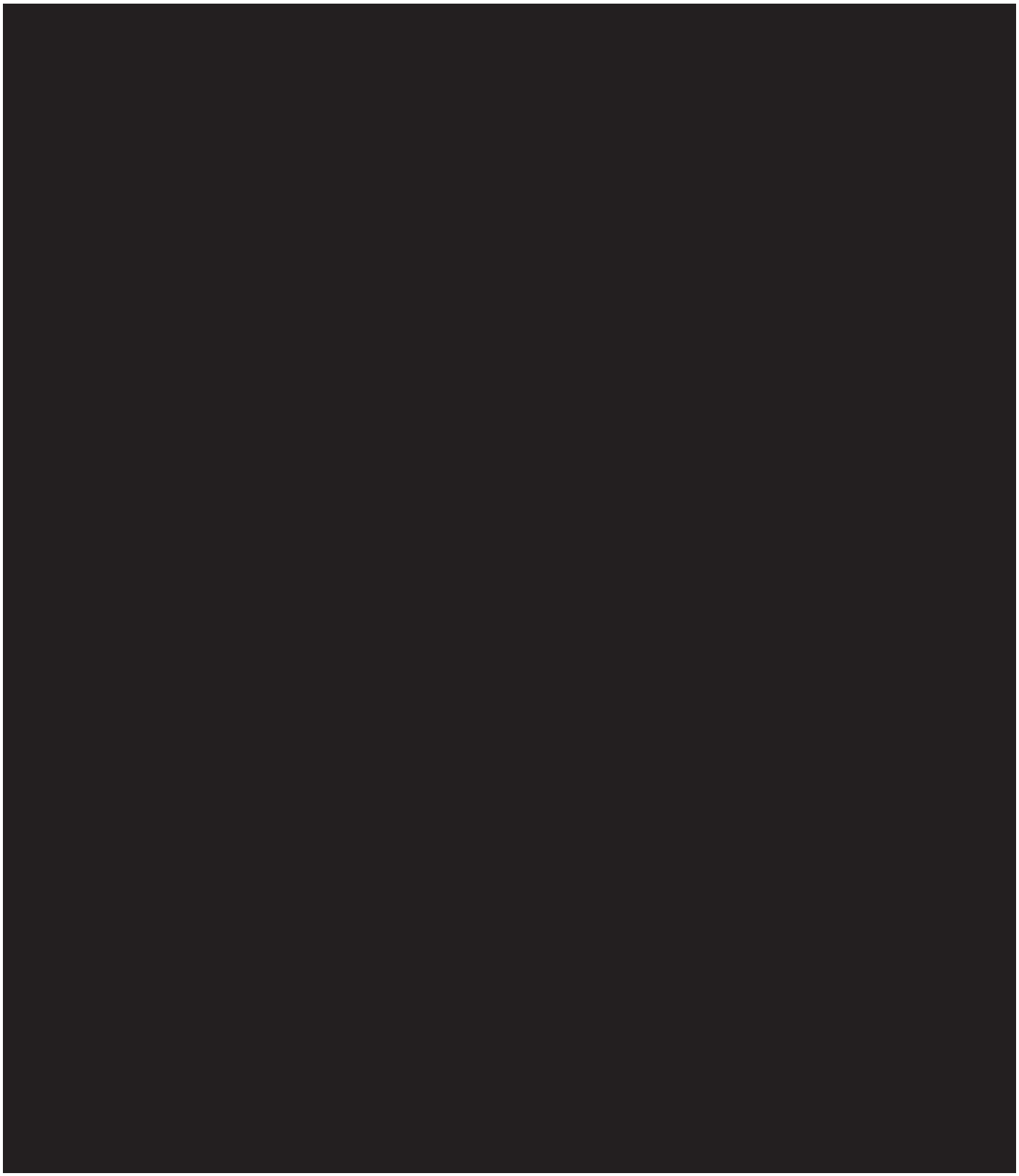


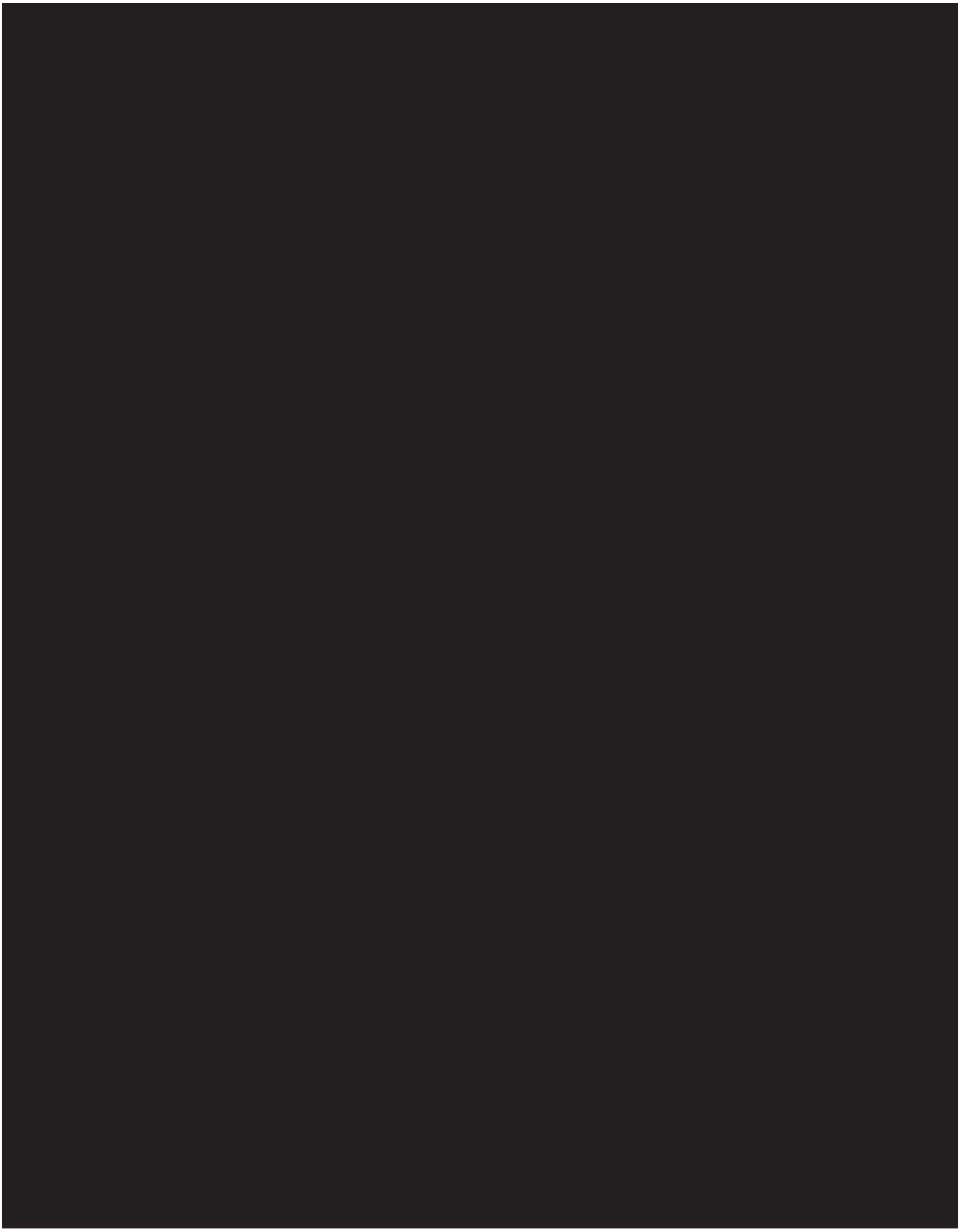


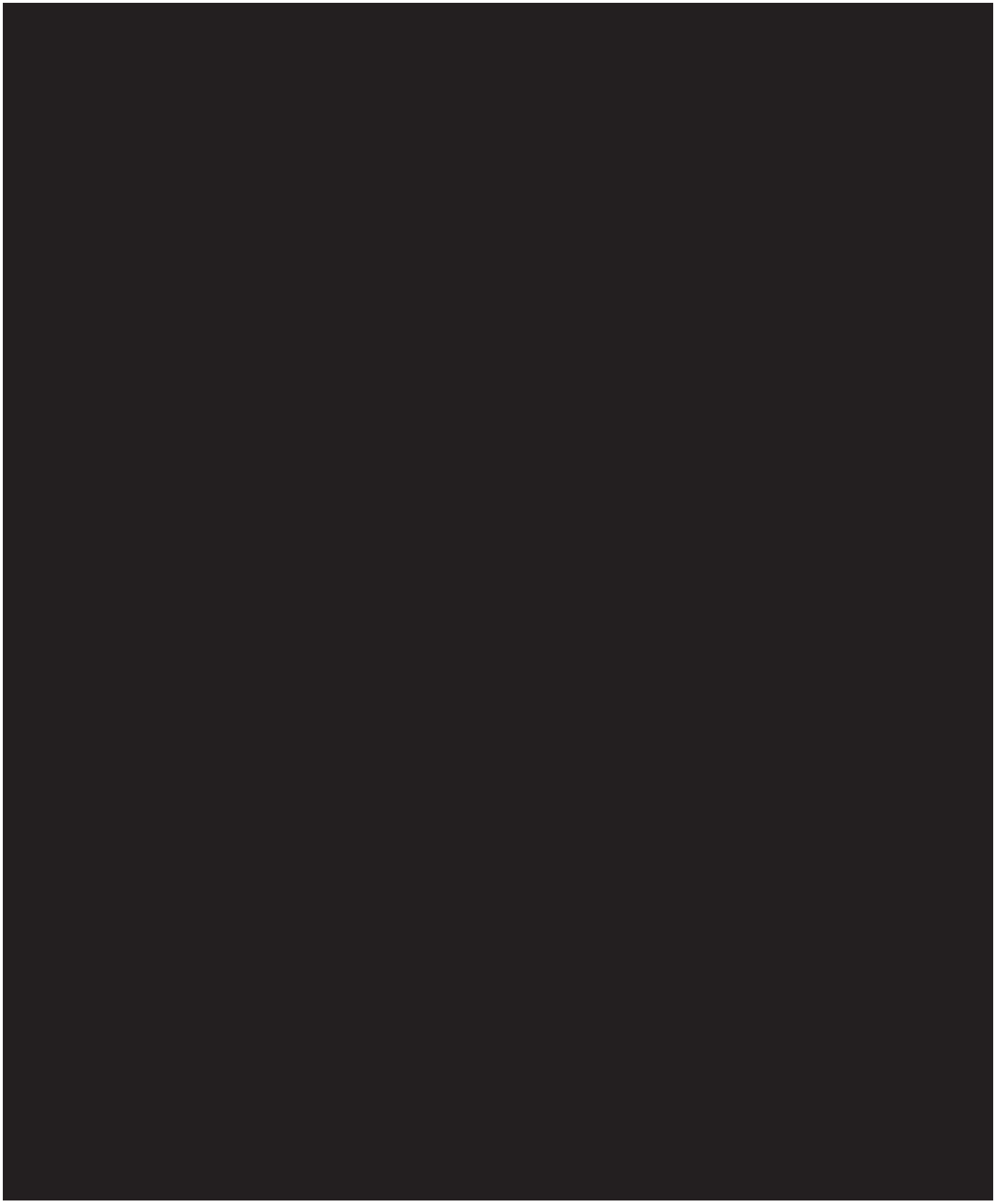




2. RATIONALE, OBJECTIVES, AND BENEFIT - RISK ASSESSMENT







The primary objective of the SRD part (trial part 1) is to investigate the safety and tolerability of BI 730357 in healthy subjects following oral administration of single rising doses after fasting and/or non-fasting conditions. The secondary objective is the exploration of the pharmacokinetics (PK) including dose proportionality, of BI 730357 after single dosing.

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

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

2.3 BENEFIT - RISK ASSESSMENT

Participation in this study is without any (therapeutic) benefit for healthy subjects. Their participation in the study, however, is of major importance to the development of a new orally available drug, which might improve the therapy The subjects are exposed to the risks of the study procedures and the risks related to the exposure to the trial medication.

Procedure-related risks

The use of an indwelling venous catheter for the purpose of blood sampling may be accompanied by mild bruising and also, in rare cases, by transient inflammation of the wall of the vein. In addition, in rare cases a nerve might be injured while inserting the venous catheter, potentially resulting in 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

As the nature of the target and the mechanism of action of BI 730357 are well understood, comparable compounds have been tested by other companies before, and the animal models are believed to be predictive for the effects in humans, BI 730357 is not seen as a high risk compound.

The pharmacological effects of BI 730357 are dose dependent and no evidence for prolonged or irreversible effects has been observed. Single doses up to 400 mg BI 739357 are supported by preclinical safety data.

During this clinical trial each subject will receive not more than 15 ml solvent consisting of PEG 400. PEG 400 is polyethylene glycol with an average molecular weight of 400. Polyethylene glycols are commonly used in a variety of pharmaceutical formulations including parenteral and oral preparations. They are generally regarded as safe, non-toxic, and non-irritant [R99-0697]. PEG 400 was well tolerated, without serious or significant adverse events, with doses up to 15 mL per day for 14 days in healthy volunteers [U02-1602].

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

- Careful dose selection as described in Section 2.1. In addition, dose escalation will be shallow and both, starting dose [redacted]) have ample safety margins with respect to the preclinical findings. Finally, dose selection was based on a sound preclinical package including 4 week toxicological studies (not only 2 weeks).
- Preliminary measurement of BI 730357 plasma concentrations and preliminary determination of PK parameters (C_{max}, AUC_{0-24} see Section 7.3.4). [redacted] Further dose progression would only be allowed after a safety interim analysis and filing and approval of a substantial CTP amendment.
- An extensive safety laboratory will be performed with special focus on full blood exam (see Flow Chart).

- For safety reasons, during the single rising dose part each dose group of 8 subjects (6 on active, 2 on placebo) will be divided into two cohorts of 4 subjects each (3 on active, 1 on placebo). These two cohorts will be separated by at least 48 hours (between 1st subject of each cohort), [redacted]. The first cohort will be dosed in a single blinded, fixed sequence fashion (active - placebo - active - active) and the drug administration will be separated by at least 60 min between the first 3 subjects. This design ensures that between first and second active dose of each dose level there is a time interval of at least 2 hours, which is expected to be sufficient to detect relevant acute effects of BI 730357. If BI 730357 was safe and well tolerated during these initial administrations, the remaining subjects of the respective dose level could be dosed as close as 10 minutes apart.
- A thorough ECG monitoring including continuous ECG measurement over 6 hours post dose to cover the anticipated period of highest drug exposure and additional repeated single 12-lead ECGs over 48 hours following drug administration. Dose escalation would be stopped as soon as at least 2 subjects at one dose level showed relevant QT prolongation (see Section 3.3.4.2 for details).
- The subjects will stay at the trial site (BI Human Pharmacology Centre) for at least 24 hours after study drug administration at each dose level. [redacted]
- During in house-confinement the subjects will be under medical observation and thoroughly monitored for both expected and unexpected adverse events.
- Only if the respective dose of BI 730357 was safe and showed acceptable tolerability and if no stopping criterion was met (refer to Section 3.3.4.2), the next higher dose will be given at least 6 days later (referring to the 1st subject of each dose group).
- Treatments of the BA part (dosing of 25 mg BI 730357) will only start if the 100 mg dose level of the SRD part was safe and showed acceptable tolerability.
- As reproductive toxicity studies have not yet been conducted, women of child-bearing potential will not be enrolled in this study.
- [redacted]

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.

In summary, although not tested in humans to date, BI 730357 has the potential to become an oral treatment for [redacted] Based upon preclinical data for

BI 730357 and clinical information from competitor compounds as well as the implemented safety measures described above, healthy subjects will not be exposed to undue risks in relation to the important information expected from this trial as a basis for further clinical development of this compound. Healthy volunteers are not expected to have any direct benefit from participation in this FIM clinical trial with BI 730357, as is the usual case in such Phase I trials. Considering the medical need of the development of a safer and more effective treatment for [redacted], the Sponsor considers that the benefit outweighs the potential risks and justifies exposure of healthy human volunteers.

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

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

A total of 72 healthy male subjects is planned to participate in 10 sequential groups of 8 subjects each during the SRD part, and in a group of 12 subjects during the BA part. Within each dose group of the SRD part, 6 subjects will receive the active drug and 2 will receive placebo. In the BA part, 12 subjects will receive the active drug. The dose groups to be evaluated are outlined in Table 3.1: 1 below.

Table 3.1: 1 Planned dose groups

Trial part	SRD										BA
Dose Group (DG)	1	2	3	4	5	6	7	8	9	10	
Fasting condition predose	fasted							fed[2]	fed[3]		fasted/ fed
Dose (mg) as oral solution	2	8	--	--	--	--	--	--	--	--	25
Dose (mg) as tablets	--	--	25	50	100	200	400	400	400	800	25
Number of subjects	8	8	8	8	8	8	8	8	8	8	12
Subjects receiving placebo	2	2	2	2	2	2	2	2	2	2	0
Subjects receiving active drug	6	6	6	6	6	6	6	6	6	6	12
Subject number[1]	[redacted]										

1 Respective reserve subject numbers will be provided for dose groups 1-7 and BA part
2 Intake of a standard continental breakfast prior to drug administration
3 Intake of a standard high-fat breakfast prior to drug administration
4 In DG 8 (400 mg/placebo with continental breakfast) and DG 9 (400 mg/placebo with high-fat breakfast) the same subjects will be included and treated with the same treatments (i.e. always with active or with placebo) for an intra-individual comparison of the two different diets (after washout period of at least 14 days)

SRD part

The first part of the trial, the SRD part, is designed as single-blind, partially randomised, and placebo-controlled within parallel dose groups. Only one dose is tested within each dose group. The groups will be treated consecutively in ascending order of doses. Each group is divided into 2 cohorts of 4 subjects each (3 on active drug and 1 on placebo). On the first study day within each dose group, the first cohort will be treated in a single-blind manner in the following order: first subject (active) followed at least 1 h later by the second subject (placebo) followed at least 1 h later by the third subject (active) followed at least 10 min later by the fourth subject (active).

If BI 730357 treatment is safe and showed acceptable tolerability in the first cohort, the subjects in the second cohort will be treated not earlier than 2 days later in a single-blind randomised manner. In the second cohort, a time interval of at least 10 min will be

maintained between each administration of the trial drug to the individual subjects. A time interval of at least 6 days will be maintained between the first drug administration in the previous dose group and the first drug administration of the subsequent dose group. The decision to proceed to the next dose group will be based upon the safety, tolerability, and pharmacokinetic data of the preceding dose groups. The next dose will only be given if, in the opinion of the Investigator, no safety concerns arose in the preceding dose group (i.e. no dose-limiting events occurred) and if none of the pre-specified trial-specific stopping criteria were met (refer to Section 3.3.4.2).

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

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

- AEs in the current and preceding dose groups up to at least 48h post dosing, including clinically relevant findings from ancillary safety testing listed below (Note: AEs may be ongoing at the time of Safety Reviews and AE information may be subject to change prior to Database Lock)
- Results from 12-lead EGG and continuous ECG monitoring in the current and preceding dose groups.
- Vital signs in the current and preceding dose groups
- Clinical laboratory tests in the current and preceding dose groups
- Preliminary PK data as per Section 7.3.4.
- Check of criteria for stopping subject treatment as per Section 3.3.4.1

The decision to escalate the dose will be made jointly by the Principal Investigator (or an authorised deputy) and the trial clinical monitor (or an authorised deputy) after in-depth analysis of all available safety data, especially SAEs (if occurred), AEs and out-of-range laboratory results (if considered clinically significant). Safety Reviews can be conducted face-to-face or by video/telephone conference. The trial clinical monitor is responsible for organization and minutes of the reviews. Minutes will be signed off by the Principal Investigator (or an authorised deputy) and filed in the ISF and TMF.

The Investigator is allowed to alter the scheduled dose levels (e.g. add an intermediate dose level) within the planned and approved dose range or to prolong in-house confinement on the basis of experience gained during the study. In this case, the total number of subjects in this trial might increase. The Investigator and/or the Sponsor should stop dose escalation in case the safety evaluation leads to concerns that would not allow higher dosing.

BA part

The BA part will be performed in a randomised, open-label, single dose, three-way crossover fashion. Subjects will be administered BI 730357 as tablet in a fasting state (reference treatment R), as oral solution (PfOS) in fasted conditions (test treatment T1) and as tablet after a standardised high-fat breakfast (test treatment T2). The three treatments will be separated by a washout period of at least 8 days between study drug administrations. Subjects will be allocated randomly to one of the six treatment sequences: R/T1/T2, R/T2/T1, T1/R/T2, T1/T2/R, T2/R/T1, T2/T1/R.

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

3.1.1 Administrative structure of the trial

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

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

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

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

The trial will be conducted at the Human Pharmacology Centre of BI Pharma GmbH & Co. KG, Biberach, Germany, under the supervision of the Principal Investigator.

Safety laboratory tests will be performed by the local laboratory of the trial site [redacted]

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

The gene expression and protein analysis will be performed by the laboratories of the Translational Medicine & Genomics & Technologies Unit, BI Pharma GmbH & Co. KG, Biberach, Germany.

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

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

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

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

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

For single-rising dose trials, the design described in Section 3.1 is viewed favourable under the provision not to expose the subjects involved to undue risks since the main study objective is to investigate safety and tolerability of BI 730357 and the risk to subjects will be minimized by studying sequentially ascending doses. For safety reasons the first cohort of each dose level will be treated in a fixed treatment sequence (Active-Placebo-Active-Active). The dose level being investigated at any time will be known to subjects, but single-blind conditions regarding each subject's treatment (active or placebo) will be maintained for both cohorts of each dose level.

The disadvantage of this trial design is a possible observer bias with regard to the dose-depending effects as well as time effects, but it has the virtue of minimizing subject risk by sequentially studying ascending doses. As time-effects are expected to be small relative to the differences between the doses in the broad range investigated, unbiased comparisons between treatments can still be expected.

It is standard in trials involving healthy volunteers to include a placebo group as control for the evaluation of safety and tolerability. Each dose group consists of 8 subjects with 6 on active treatment, and 2 on placebo. The placebo control group includes all subjects of all dose groups treated with placebo. 6 subjects per active treatment group are in general considered as sufficient for the exploratory evaluation of pharmacokinetics.

For the BA part comparing bioavailability of BI 730357 following administration as tablet in the fasted state versus oral solution (PfOS) in fasted state as well as tablet in the fasted state versus tablet under fed conditions, the crossover design is viewed favourable due to its efficiency: since each subject serves as his own control, the comparison between the treatments is based on a comparison within subjects rather than between subjects. Thus the inter-subject variability is removed from the comparison between treatments [R94-1529]. Blinding is not possible because the treatments are distinguishable.

3.3 SELECTION OF TRIAL POPULATION

It is planned that 84 healthy male will enter the study. Subjects will be recruited from the volunteers' pool of the trial site.

Only male subjects will be included into the study because hitherto no data on reproductive toxicology are available. With respect to the embryo-fetal risk coming from the treatment of male subjects with BI 730357, where it is theoretically possible that relevant exposure to BI 730357 may be achieved in women of childbearing potential (WOCBP) from exposure to seminal fluid, male contraception (condom or abstinence) should be used in order to avoid exposure of an existing embryo/fetus [R16-0373] (see 3.3.3, exclusion criterion 23).

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

3.3.1 Main diagnosis for study entry

The study will be performed in healthy subjects.

3.3.2 Inclusion criteria

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

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

3.3.3 Exclusion criteria

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

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

14. Inability to refrain from smoking on specified trial days
15. Alcohol abuse (consumption of more 30 g per day for males)
16. Drug abuse or positive drug screening
17. Blood donation of more than 100 mL within 30 days prior to administration of trial medication or intended donation during the trial
18. Intention to perform excessive physical activities within one week prior to administration of trial medication or during the trial
19. Inability to comply with dietary regimen of trial site
20. A marked baseline prolongation of QT/QTc interval (such as QTc intervals that are repeatedly greater than 450 ms) or any other relevant ECG finding at screening
21. A history of additional risk factors for Torsades de Pointes (such as heart failure, hypokalemia, or family history of Long QT Syndrome)
22. Subject is assessed as unsuitable for inclusion by the Investigator, for instance, because considered not able to understand and comply with study requirements, or has a condition that would not allow safe participation in the study

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

23. Male subjects with WOCBP partner who are unwilling to use male contraception (condom or sexual abstinence) from the first administration of trial medication until 30 days after last administration of trial medication

For study restrictions, refer to Section 4.2.2.

3.3.4 Removal of subjects from therapy or assessments

3.3.4.1 Removal of individual subjects

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

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

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

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

If a subject is removed from or withdraws from the trial prior to first administration of trial medication, the data of this subject will not be entered in the case report form (CRF) or trial database and will not be reported in the clinical trial report (CTR). If a subject is removed from or withdraws from the trial after first administration of trial medication, this will be documented and the reason for discontinuation must be recorded in the CRF. In this case, the data will be included in the CRF/trial database and will be reported in the CTR. At the time of discontinuation a complete end of trial examination will be performed if possible and the information will be recorded in the CRFs. If the discontinuation occurs before the end of the REP (see Section 5.2.2.2), the discontinued subject should if possible be questioned for AEs and concomitant therapies at or after the end of the REP in order to ascertain collection of AEs and concomitant therapies throughout the REP, if not contrary to any consent withdrawal of the subject. These discontinuations will be discussed in the CTR.

3.3.4.2 Discontinuation of the trial by the Sponsor

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

1. New toxicological findings or serious adverse events invalidate the earlier positive benefit-risk-assessment. More specifically, the trial will be terminated if more than 50% of the subjects show drug-related and clinically relevant adverse events of moderate or severe intensity, or if at least one drug-related serious adverse event is reported
2. The expected enrolment goals overall or at a particular trial site are not met
3. Violation of GCP, or the CTP by a trial site or Investigator, disturbing the appropriate conduct of the trial
4. The Sponsor decides to discontinue the further development of the investigational product
5. Dose escalation will be stopped as soon as at least 2 subjects at one dose level on active drug showed relevant individual QT prolongation, i.e. a QTc increase of greater 60 ms from baseline in connection with absolute QT or QTc greater than 500 ms, which has been confirmed by a repeat ECG recording
6. Dose escalation will be stopped based on preliminary PK results (plasma) as soon as measured (in at least one subject) or estimated C_{max} / AUC_{0-24} of BI 730357 exceed [redacted] (upper limit of acceptable exposure in this trial, see Section 2.1).

3.3.5 Replacement of subjects

In case that there are less than 4 subjects on active per dose level in DG 1-7 of the SRD part or less than 9 subjects in the BA part, who do not complete the trial, the trial clinical monitor together with the trial pharmacokineticist and the trial statistician are to decide if and how many subjects will be replaced. There is no replacement in the SRD part for DGs 8, 9 and 10. A replacement subject will be assigned a unique study subject number possessing the same treatment, as the subject [redacted] replaces.

4. TREATMENTS

4.1 TREATMENTS TO BE ADMINISTERED

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

4.1.1 Identity of BI investigational product and comparator products

SRD part

The characteristics of the test product for dose groups 1-2 are:

Substance:	BI 730357
Pharmaceutical formulation:	Powder for oral solution
Source:	BI Pharma GmbH & Co. KG
Drug in bottle:	20 mg
Unit strength:	1.0 mg/mL (concentration in prepared solution)
Posology:	1-0-0
Route of administration:	p.o.
Duration of use:	Single dose

Component for reconstitution: The oral solution for dosing will be prepared as detailed in the reconstitution instruction given in Appendix 10.1 using a solvent containing polyethylene glycol (PEG) 400 (Macrogol 400). The solvent will be supplied in separate 60 mL amber glass bottles and will also be used as placebo solution (see Appendix 10.1).

The characteristics of the test product for dose group (DG) 3 are:

Substance:	BI 730357
Pharmaceutical formulation:	Film-coated tablet
Source:	BI Pharma GmbH & Co. KG
Unit strength:	25 mg
Posology:	1-0-0
Route of administration:	p.o.
Duration of use:	Single dose

The characteristics of the test product for dose groups 4-10 are:

Substance:	BI 730357
Pharmaceutical formulation:	Film-coated tablet
Source:	BI Pharma GmbH & Co. KG
Unit strength:	50 mg
Posology:	1-0-0 (DG 4), 2-0-0 (DG 5), 4-0-0 (DG 6), 8-0-0 (DG 7, DG 8 and DG 9) or 16-0-0 (DG 10)
Route of administration:	p.o.

Duration of use:	Single dose

The characteristics of the reference product (placebo) for dose groups 1-2 are:

Substance:	Matching placebo containing PEG 400 (Macrogol 400)
Pharmaceutical formulation:	Oral solution
Source:	BI Pharma GmbH & Co. KG
Unit strength:	Not applicable
Posology:	1-0-0
Route of administration:	p.o.
Duration of use:	Single dose

The placebo solution will be prepared as detailed in the instruction given in Appendix 10.1.

The characteristics of the reference product (placebo) for dose group 3 are:

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

The characteristics of the reference product (placebo) for dose groups 4-10 are:

Substance:	Placebo matching in size and weight to 50 mg tablet
Pharmaceutical formulation:	Film-coated tablets
Source:	BI Pharma GmbH & Co. KG
Unit strength:	Not applicable
Posology:	1-0-0 (DG 4), 2-0-0 (DG 5), 4-0-0 (DG 6), 8-0-0 (DG 7, DG 8 and DG 9) or 16-0-0 (DG 10)
Route of administration:	p.o.
Duration of use:	Single dose

Components for reconstitution: The oral solution for dosing will be prepared as detailed in the reconstitution instruction given in Appendix 10.1 using a solvent containing PEG 400 (Macrogol 400). The solvent will be supplied in separate 60 mL amber glass bottles.

BA part

The characteristics of test product T1 are:

Substance:	BI 730357
Pharmaceutical formulation:	Powder for oral solution
Source:	BI Pharma GmbH & Co. KG, Germany
Drug in bottle:	200 mg
Unit strength:	10.0 mg/mL (concentration in prepared solution)
Posology:	1-0-0
Route of administration:	p.o.
Duration of use:	Single dose

The characteristics of test product T2 and reference product R are:

Substance:	BI 730357
Pharmaceutical formulation:	Film-coated tablet
Source:	BI Pharma GmbH & Co. KG
Unit strength:	25 mg
Posology:	1-0-0
Route of administration:	p.o.
Duration of use:	Single dose

The 25 mg and 50 mg tablets may be used to allow intermediate dose levels if necessary.

4.1.2 Method of assigning subjects to treatment groups

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

The randomisation list with study subject numbers and allocated treatments (SRD part) or treatment sequences (BA part) will be provided to the trial site in advance. In both parts of the trial, the allocation of subjects to study subject numbers will be performed prior to the first administration of trial medication. For this purpose, the subjects will be allocated to a study subject number (= medication number) by drawing lots. Once a subject number has been assigned, it cannot be reassigned to any other subject.

The randomisation procedure is described in Section 7.5.

4.1.3 Selection of doses in the trial

For the SRD part, oral doses in the range of 2 mg to 800 mg have been selected in order to assess the safety and tolerability of BI 730357 in healthy male volunteers, and to investigate the PK of [redacted] The selected doses cover a safe starting dose in the sub-therapeutic range, the estimated therapeutic range and potentially supra-therapeutic doses within the levels determined by toxicological investigations (see Section 1.2).

The intra-individual comparisons of the BA part investigating the relative bioavailability of tablet fasted versus tablet fed and of tablet fasted versus oral solution fasted are planned to be conducted with a dose of 25 mg as it is assumed that this dose covers the therapeutic range and might be used in the subsequent clinical development.

4.1.4 Drug assignment and administration of doses for each subject

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

Table 4.1.4: 1 BI 730357 and placebo treatments for the SRD part

Dose group	Fasting condition predose	Substance	Pharmaceutical form	Unit strength	Number of units /dose volume per administration	Total dose
1	fasted	BI 730357	oral solution	1 mg/mL	2 mL	2 mg
2	fasted	BI 730357	oral solution	1 mg/mL	8 mL	8 mg
3	fasted	BI 730357	film-coated tablet	25 mg	1 tablet	25 mg
4	fasted	BI 730357	Film-coated tablet	50 mg	1 tablet	50 mg
5	fasted	BI 730357	Film-coated tablet	50 mg	2 tablets	100 mg
6	fasted	BI 730357	Film-coated tablet	50 mg	4 tablets	200 mg
7	fasted	BI 730357	Film-coated tablet	50 mg	8 tablets	400 mg
8	fed[1]	BI 730357	Film-coated tablet	50 mg	8 tablets	400 mg
9	fed[2]	BI 730357	Film-coated tablet	50 mg	8 tablets	400 mg
10	fed[2]	BI 730357	Film-coated tablet	50 mg	16 tablets	800 mg
1-2	fasted	Placebo*	oral solution	--	identical to active treatment	--
3-7	fasted	Placebo*	Film-coated tablet	--	identical to active treatment	--
8-10	fed	Placebo*	Film-coated tablet	--	identical to active treatment	--

* Subjects receiving placebo are equally distributed across dose groups
1 Drug administration after a standard continental breakfast
2 Drug administration after a standard high-fat breakfast
3 Identical to active treatment

Table 4.1.4: 2 BI 730357 film-tablets and oral solution for the BA part

Treatment	Substance	Pharmaceutical form	Unit strength	Number of units / dose volume per administration	Total Dose
T1 (oral solution fasted)	BI 730357	oral solution	10 mg/mL	2.5 mL	25 mg
T2 (tablet fed)	BI 730357	Film-coated tablet	25 mg	1 tablet	25 mg
R (tablet fasted)	BI 730357	Film-coated tablet	25 mg	1 tablet	25 mg

The oral solutions for dosing will be prepared according to the reconstitution instruction given in Appendix 10.1 under the responsibility of the Investigator. The Investigator can decide at any time to discontinue dosing or to decrease the dose escalation by adding intermediate doses in case of intolerability or due to safety concerns.

The trial medication will be administered to the subjects, while in a sitting or standing position, as an oral dose together with about 240 mL of water under supervision of the investigating physician or an authorised designee in the morning of Day 1. The so-called four-eye principle (two-person rule) should be applied for administration of trial medication and – if applicable – its preparation (e.g. reconstitution), if correct dosage cannot be ensured otherwise. Administration will be performed following an overnight fast, which is to start no later than 10 h before the scheduled dosing.

In treatment T2 (tablet fed) of the BA part and dose groups 9 (400 mg BI 730357 or placebo) and 10 (800 mg BI 730357 or placebo) of the SRD part, a high-fat, high-calorie breakfast will be served 30 min before drug administration. In dose group 8 (400 mg BI 730357 or placebo) of the SRD part, a standard continental (normal-fat, normal-calorie) breakfast will be served 30 min before drug administration. The test meals must be completely consumed prior to drug administration. The composition of the standard high-fat, high-calorie breakfast will be in compliance with the FDA guidance 'Food-Effect Bioavailability and Fed Bioequivalence Studies' [R03-2269] as detailed in Table 4.1.4: 3. The composition of the standard continental breakfast will be detailed in Table 4.1.4: 4.

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

Ingredients	kcal
[redacted]	
Sum[1]	984

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

Table 4.1.4: 4 Composition of the continental breakfast

Ingredients	kcal
[redacted]	
Sum[1]	458

[1] The total caloric content was supplied approximately as following: 88 kcal as protein, 133 kcal as carbohydrate, and 237 kcal as fat.

Subjects will be kept under close medical surveillance until at least 24 h following drug administration. During the first 6 hours after drug administration subjects of the SRD part will be confined to bed with a bed inclination angle of at least 45 degrees unless lower or supine positioning is required for trial-related measurements (e.g. recording of 12-lead ECG). During the first 4 hours after drug administration subjects of the BA part will only be allowed to lie down if supine positioning is required for trial-related measurements (e.g. recording of 12-lead ECG). For restrictions with regard to diet see Section 4.2.2.2.

4.1.5 Blinding and procedures for unblinding

4.1.5.1 Blinding

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

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

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

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

Within the ECG laboratory, the staff involved with interval measurements and assessments will be blinded with respect to the treatment within each dose level and also with regard to the recording date and time as well as time the points of the ECGs. The interval measurements for a given subject will be performed in a random and blinded sequence by a single technician. No more than two different blinded readers will evaluate the ECGs of the study.

4.1.5.2 Procedures for emergency unblinding

As this trial will be conducted single-blinded (SRD part) or open-label (BA part), the treatment information will be known. Therefore, no emergency envelopes will be provided.

4.1.6 Packaging, labelling, and re-supply

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

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

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

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

No re-supply is planned.

4.1.7 Storage conditions

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

4.1.8 Drug accountability

The Investigator will receive the investigational drugs delivered by the Sponsor when the following requirements are fulfilled:

- Approval of the trial protocol by the IRB / ethics committee

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

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

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

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

4.2 OTHER TREATMENTS, EMERGENCY PROCEDURES, RESTRICTIONS

4.2.1 Other treatments and emergency procedures

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

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

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

4.2.2.2 Restrictions on diet and life style

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

From 1 h before drug intake until lunch, fluid intake (except for the beverages served with the breakfast in the SRD or BA part) is restricted to the water administered with the drug, and an additional 240 mL of water served at 2 h and 4 h post-dose (mandatory for all subjects). From lunch until discharge from the study centre, liquid intake is restricted to additional 3 litres.

During the days of urine collection, subjects will be advised to drink at least 1.5 litres per day.

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

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

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

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

[redacted]

4.3 TREATMENT COMPLIANCE

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

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

5. VARIABLES AND THEIR ASSESSMENT

5.1 EFFICACY - CLINICAL PHARMACOLOGY

5.1.1 Endpoints of efficacy

No efficacy endpoints will be evaluated in this trial.

5.1.2 Assessment of efficacy

Not applicable.

5.2 SAFETY

5.2.1 Endpoints of safety

Primary endpoint to assess safety and tolerability of BI 730357 is the number [N (%)] of subjects with adverse reactions.

5.2.2 Assessment of adverse events

5.2.2.1 Definitions of adverse events

Adverse event

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

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

Adverse reaction

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

Serious adverse event

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

- results in death,
- is life-threatening, this refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if more severe,
- requires inpatient hospitalisation or prolongation of existing hospitalisation,
- results in persistent or significant disability or incapacity,
- is a congenital anomaly/birth defect,

  or
- is to be deemed serious for any other reason if it is an important medical event when based upon appropriate medical judgment which may jeopardise the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions.

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

AEs considered 'Always Serious'

In accordance with the European Medicines Agency initiative on Important Medical Events, 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 given above.

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

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

Adverse events of special interest (AESIs)

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

The following are considered as AESIs in this trial:

- Hepatic injury, as defined by the following alterations of hepatic laboratory parameters:
  - o 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
  - o marked peak aminotransferase (ALT, and/or AST) elevations ≥10 fold ULN

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

Intensity of AEs

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

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

Causal relationship of AEs

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

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

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

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

- An indication of dose-response (i.e. greater effect size if the dose is increased, smaller effect size if dose is diminished).

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

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

5.2.2.2 Adverse event collection and reporting

AEs collection

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

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

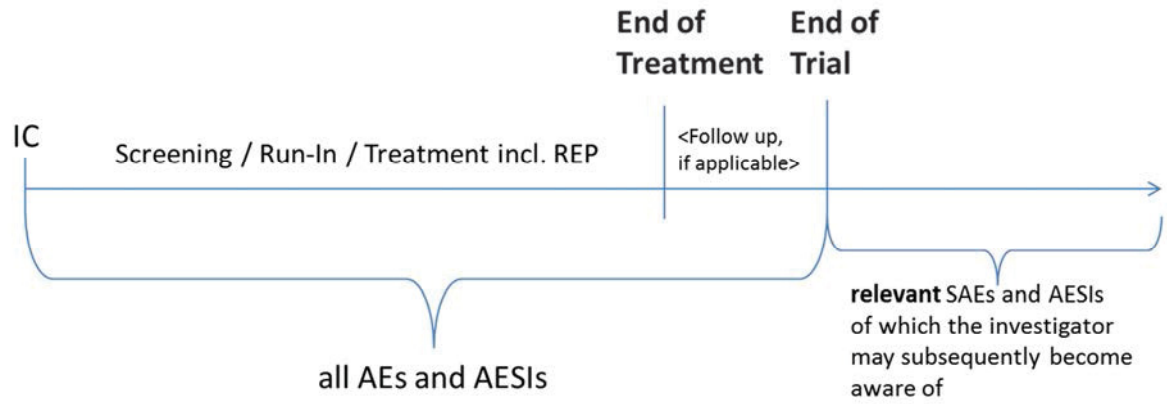
A careful written record of all AEs shall be kept by the Investigator in charge of the trial. Records of AEs shall include data on the time of onset, end time, and intensity of the event as well as any treatment or action required for the event and its outcome.

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

- From signing the informed consent onwards through the residual effect period (REP), until an individual subject's end of trial:
    - All AEs (serious and non-serious) and all AESIs.
    - The only exception to this rule are AEs (serious and non-serious) and AESIs in Phase I trials in healthy volunteers, when subjects discontinue from the trial due to screening failures prior to administration of any trial medication. In

these cases, the subjects' data must be collected at trial site but will not be entered in the CRF or trial database and will not be reported in the CTR.

- After the individual subject's end of trial:
  - The Investigator does not need to actively monitor the subject for AEs but should only report relevant SAEs and relevant AESIs of which [redacted] may become aware of.



The REP for BI 730357, when measurable drug levels or PD effects are still likely to be present after the last administration, is not known for this first-in-human trial. Therefore, all AEs reported until the end of trial examination (last per protocol contact) will be considered on treatment; please see Section 7.3.3.

AE reporting to Sponsor and timelines

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

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

Information required

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

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

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

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

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

5.2.3 Assessment of safety laboratory parameters

For the assessment of laboratory parameters, blood and urine samples will be collected by the trial site at the time points indicated in the Flow Chart after the subjects have fasted for at least 10 h (excluding 6-hour post-dose sample). Overnight fasting is not required at the discretion of the Investigator or designee for retests.

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

Table 5.2.3: 1 Routine laboratory tests

Functional lab group	**Test name**	A[1]	B[2]	C[3]	D[4]	E[5]
Haematology	Haematocrit	X	X	X	X	X
	Haemoglobin	X	X	X	X	X
	Red blood cells (RBC)	X	X	X	X	X
	White blood cells (WBC)	X	X	X	X	X
	Platelets	X	X	X	X	X
	Reticulocyte count	X	X	X	X	X
Automatic WBC differential (relative and absolute)	Neutrophils	X	X	X	X	X
	Eosinophils	X	X	X	X	X
	Basophils	X	X	X	X	X
	Monocytes	X	X	X	X	X
	Lymphocytes	X	X	X	X	X
[redacted]	[redacted]		X		X	
Manual differential WBC (if automatic differential WBC is abnormal)	Polymorphnuclear neutrophils (segs), band neutrophils (stabs), eosinophils, basophils, monocytes, lymphocytes					
Coagulation	Activated partial thromboplastin time (aPTT)	X	X	X	--	X
	Prothrombin Time (Quick and INR)	X	X	X	--	X

[1] **A: parameters to be determined at visit 1 (screening examination)**
[2] B: parameters to be determined at visits 2-4 on Days -3 to -1 (for time point, refer to Flow Chart)
[3] C: parameters to be determined at visits 2-4 on Days 1 to 4 (for time points, refer to Flow Chart)
[4] D: parameters to be determined at visits 2-4 on Day 8 (for time point, refer to Flow Chart)
[5] E: parameters to be determined at visit 5 (end of trial examination)

Table 5.2.3: 1 Routine laboratory tests (cont.)

Functional lab group	**Test name**	A[1]	B[2]	C[3]	D[4]	E[5]
Enzymes	Aspartate aminotransferase (AST/GOT)	X	X	X	--	X
	Alanine aminotransferase (ALT/GPT)	X	X	X	--	X
	Alkaline phosphatase (AP)	X	X	X	--	X
	Gammaglutamyl transferase (GGT)	X	X	X	--	X
	Lactate dehydrogenase	X	X	X	--	X
	Lipase	X	--	--	--	X
Substrates	Plasma glucose	X	X	X	--	X
	Creatinine	X	X	X	--	X
	Total bilirubin	X	X	X	--	X
	Direct bilirubin	X	X	X	--	X
	Total protein	X	X	X	--	X
	C-Reactive Protein (CRP)	X	X	X	--	X
	Urea in serum	X	X	X	--	X
	Phosphate in serum	X	X	X	--	X
	Total cholesterol	X	X	X	--	X
	Triglycerides	X	--	--	--	X
*Electrolytes	Calcium	X	X	X	--	X
	Sodium	X	X	X	--	X
	Potassium	X	X	X	--	X
Hormones	Thyroid stimulating hormone (TSH)	X	--	--	--	--
Urinalysis (Stix)	Urine nitrite	X	X	X	--	X
	Urine protein	X	X	X	--	X
	Urine glucose	X	X	X	--	X
	Urine ketone	X	X	X	--	X
	Urobilinogen	X	X	X	--	X
	Urine bilirubin	X	X	X	--	X
	Urine RBC	X	X	X	--	X
	Urine WBC	X	X	X	--	X
	Urine pH	X	X	X	--	X
Urine sediment (microscopic examination if erythrocytes, leukocytes nitrite or protein are abnormal in urine)	Only positive findings will be reported (e.g. presence of sediment bacteria, casts in sediment, squamous epithelial cells, erythrocytes, leukocytes)				--	

[1] A: parameters to be determined at visit 1 (screening examination)
[2] B: parameters to be determined at visits 2-4 on Days -3 to -1 (for time point, refer to Flow Chart)
[3] C: parameters to be determined at visits 2-4 on Days 1 to 4 (for time points, refer to Flow Chart)
[4] D: parameters to be determined at visits 2-4 on Day 8 (for time point, refer to Flow Chart)
[5] E: parameters to be determined at visit 5 (end of trial examination)

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.

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 prior to each administration of trial medication on Day 1 (for time points refer to Flow Chart).

Table 5.2.3: 2 Exclusionary laboratory tests

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

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

The laboratory tests listed in Table 5.2.3: 1 and 5.2.3: 2 will be performed at [redacted] with the exception of the drug screening tests. These tests will be performed at the trial site using e.g. MAHSAN® -–Kombi/DOA10 rapid test.

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

5.2.4 Electrocardiogram

5.2.4.1 12-lead resting ECG

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

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

All ECGs will be stored electronically on the Muse CV Cardiology System (GE Medical Systems, Freiburg, Germany). Electrode placement will be performed according to the method of Wilson, Goldberger and Einthoven modified by Mason and Likar (hips and shoulders instead of ankles and wrists). Precise electrode placement will be marked with an indelible mark on the skin to allow reproducible placement throughout the study.

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

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

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

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

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

Abnormal findings will be reported as AEs (during the trial) or baseline conditions (at screening) if judged clinically relevant by the Investigator. Any ECG abnormalities will be monitored carefully and, if necessary, the subject will be removed from the trial and will receive the appropriate medical treatment.

For blinding arrangements see Section 4.1.5.

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

5.2.4.2 Continuous ECG monitoring

Cardiac rhythm (including heart rate) will be monitored during the SRD part by means of continuous 3-lead ECG recording for at least 15 min before (for baseline assessment) and 6 h following drug administration using patient monitors (e.g. Carescape B450, GE Healthcare GmbH, Freiburg, Germany). Abnormal findings will be recorded as AEs if judged clinically relevant by the Investigator but no other data will be transferred to the database.

5.2.5 Assessment of other safety parameters

5.2.5.1 Vital signs

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

5.2.5.2 Medical examinations

At screening, the medical examination will include demographics including height and body weight, smoking and alcohol history, relevant medical history and concomitant therapy, review of inclusion and exclusion criteria, review of vital signs (BP, PR), 12-lead ECG (including rhythm strip of at least 15 minutes), laboratory tests, and a physical examination. At the end of trial examination, it will include review of vital signs, 12-lead ECG, laboratory tests, and a physical examination.

5.3 OTHER

5.3.1 Pharmacogenomic evaluation

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

DNA will be extracted from the blood sample in order to sequence genes coding for proteins that are involved in the absorption, distribution, metabolism, and excretion (ADME) of drugs. The gene sequences to be determined include known and likely functional variations of key ADME genes and incorporate more than 90% of ADME-related genetic markers identified by the PharmaADME group (weblink.pharmaadme.org). It is not intended to include the pharmacogenomic data in the final report. However, the data may be part of the report if necessary.

5.4 APPROPRIATENESS OF MEASUREMENTS

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

5.5 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

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

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

5.5.1 Pharmacokinetic endpoints

The following pharmacokinetic endpoints will be determined if feasible:

5.5.1.1 Secondary endpoints

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

[redacted]

[redacted]

5.5.2 Methods of sample collection

5.5.2.1 Plasma sampling for pharmacokinetic analysis

For quantification of BI 730357 plasma concentrations, 2.7 mL of blood will be taken from an antecubital or forearm vein into an K_3-EDTA (tripotassium ethylenediaminetetraacetic acid)-anticoagulant blood drawing tube at the times indicated in the Flow Chart. Blood will be withdrawn by means of either an indwelling venous catheter or by venipuncture with a metal needle.

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

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

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

5.5.2.2 Plasma sampling for metabolism analysis

Additional K_3-EDTA plasma samples for the identification of drug metabolites will be investigated in the 25 mg dose group. Based on the knowledge gained during the trial conduct, e.g. from preliminary PK results, the dose group may be changed. The change will be implemented via a non-substantial CTP Amendment.

The blood samples will be drawn in parallel to PK samples on Days 1 to 5 of the SRD part (see Flow Chart). At each of these time points, 2.7 ml blood will be needed for metabolite analysis. Apart from the storage temperature (see below) the blood samples will be processed in the same way as the PK samples described in Section 5.5.2.1.

Two plasma aliquots will be obtained and stored in polypropylene cryotubes. The first aliquot (labelled as MIST-1 samples), should contain at least 0.5 mL of plasma. The remaining plasma will be the second aliquot (labelled as MIST-2 samples). The process from blood collection to the transfer of plasma aliquots into the freezer should be completed within 90 min, with interim storage of blood samples on crashed ice between blood collection and centrifugation. Until transfer on dry ice to the metabolism laboratory, the aliquots will be stored at the trial site. Samples will be positioned upright and will be frozen at approximately -70°C. The second aliquot will be shipped to the metabolism laboratory after the metabolism scientist has acknowledged safe arrival of the first aliquot. At the metabolism laboratory, the plasma samples will be stored at about -70°C until analysis.

At a minimum, the sample tube labels should list the following information: BI trial number, subject number, visit, planned sampling time and ‘MIST-1 or ‘MIST-2’. Further information such as matrix and analyte may also be provided.

Plasma samples dedicated to metabolism investigation are transferred to:

[redacted]
Department of Drug Metabolism & Pharmacokinetics
Boehringer Ingelheim Pharmaceuticals, Inc
Pharmaceuticals, Inc.
175 Briar Ridge Road
Room R&D 1515
Ridgefield, CT 06810, USA.
Phone: [redacted]

Only data related to the parent compound and its metabolites will be acquired. Evaluation of the drug metabolism will be reported separately but not included in the CTR of this trial. The study samples will be discarded after completion of the experiments but not later than 5 years after the final study report has been signed.

[redacted]

[redacted]

5.5.3 Analytical determinations

5.5.3.1 Analytical determination of analyte plasma concentration

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

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

[redacted]

[redacted]

[redacted]

5.7 PHARMACOKINETIC - PHARMACODYNAMIC RELATIONSHIP

[redacted]

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

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

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

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

The acceptable deviation from the scheduled time for vital signs, ECG and laboratory tests will be ± 15 min for the first 6 h after trial drug administration and ± 30 min thereafter. Starting from 72 h post administration a deviation from the scheduled time for vital signs, ECG and laboratory tests of ±70 min is acceptable.

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

For planned individual plasma concentration sampling times and urine 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 a subject misses an appointment, it will be rescheduled if possible. The relevance of measurements outside the permitted time windows will be assessed no later than at the Blinded Report Planning Meeting.

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

6.2.1 Screening period

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

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

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

6.2.2 Treatment periods

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

For DGs 1-7 and 10 of the SRD part, each subject will receive one dose of the respective trial medication (BI 730357 or placebo) at visit 2. In DGs 8 and 9 of the SRD part, the same subjects will be included and each subject will be treated with the same trial medication (either always active or always placebo), i.e. they will receive the respective trial medication at first in DG 8 (Visit 2) following a standard continental breakfast and in DG 9 (Visit 3) following a high-fat breakfast. The treatments of DG 8 and DG 9 are separated by a wash-out phase of at least 14 days between each drug administration.

The participants of the BA part will receive the respective trial medication (BI 730357) at visit 2, 3 and 4. Details on treatments and procedures of administration are described in Section 4.1.4.

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

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

6.2.3 End of trial period

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

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

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

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

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 STATISTICAL DESIGN – MODEL

7.1.1 Objectives

SRD Part:

The primary objective of the first (SRD) part of this trial is to investigate the safety and tolerability of BI 730357 by using descriptive statistics for all endpoints comparing active dose groups to placebo. The primary endpoint is defined in Section 5.2.1. Inferential statistics is not planned (as explained in Section 7.2).

The secondary objective is the exploration of the pharmacokinetics (PK) of BI 730357. Endpoints as specified in 5.5.1 will be analysed by descriptive statistics. Secondary endpoints as defined in Section 5.5.1.1 will be subjected to analysis of dose proportionality by use of the power model.

BA Part:

The primary objective of the second part of the study is to investigate relative bioavailability of 25 mg BI 730357 as oral solution (Test 1, T1) and 25 mg BI 730357 given as tablet after a standardised high-fat breakfast (Test 2, T2), each compared to 25 mg BI 730357 as tablet in a fasting state (Reference, R)
The secondary objective is the evaluation and comparison of several PK parameters between the treatments. The secondary objectives will be assessed by descriptive statistics.

7.1.2 Endpoints

The primary endpoint to describe safety and tolerability of BI 730357 will be the number (% subjects) with drug-related AEs. The collection of parameters pertaining to these investigations is described in detail in Section 5.2.1.

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

7.1.3 Model

SRD part:

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

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

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

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

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

where

Y_{ij}	logarithm of the pharmacokinetic endpoint for subject j at dose level i; where i = 1, 2, …, 7, j = 1, 2, …, 8;
α	intercept parameter;
β	slope parameter;
X_i	logarithm of dose i;
ε_{ij}	random error associated with subject j at dose level i (assumed to be independent and identically normally distributed).

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

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

BA part: Investigation of relative bioavailability

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

The statistical model used for the analysis of $AUC_{0-\infty}$ and C_{max} will be an ANOVA (analysis of variance) model on the logarithmic scale. This model will include effects accounting for the following sources of variation: ‘sequence’, ‘subjects within sequences’, ‘period’ and ‘treatment’. The effect ‘subjects within sequences’ will be considered as random, whereas the other effects will be considered as fixed. For tests on subject, period, and treatment effects, the denominator sum of squares will be the sum of squares for error; while for tests on sequence effects, the denominator will be the sum of squares for subjects. The model is described by the following equation

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

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

μ = the overall mean,

ζ_i = the ith sequence effect, i = 1, 2, …, 6

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

π_j = the jth period effect, j = 1, 2, 3

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

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

The difference between the expected means for test treatments and reference treatment log(T_i)-log(R), i=1,2, will be estimated by the difference in the corresponding Least Square Means (point estimate) and two-sided 90% confidence intervals based on the t-distribution will be computed. These quantities will then be back-transformed to the original scale to give the point estimator (geometric mean) and interval estimates for the ratio between response under test and response under reference.

Pairwise comparisons will be done for:

- Oral solution (PfOS) fasted (Test 1/T1) vs tablet fasted (Reference)
- Tablet fed (Test 2/T2) vs tablet fasted (Reference)

7.2 NULL AND ALTERNATIVE HYPOTHESES

Safety and tolerability of different dose groups of BI 730357 are to be determined on the basis of the investigated parameters in comparison to placebo. It is not planned to test any statistical hypotheses with regard to these variables in a confirmatory sense. Instead, they will be described in their entirety and evaluated by descriptive statistical methods.

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

The relative bioavailability of BI 730357 will be estimated by the ratios of the geometric means (test/reference) for the secondary PK endpoints. Additionally, their two-sided 90% CIs will be provided. This method corresponds to the two one-sided t-tests procedure, each at the 5% significance level. Since the main focus is on estimation and not on testing, an acceptance range was not specified, that is, no hypothesis will be tested.

7.3 PLANNED ANALYSES

7.3.1 Primary analyses

Analysis of safety and tolerability is described in Section 7.3.3.

7.3.2 Secondary analyses

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

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

Reasons for exclusion of single pharmacokinetic parameters may be:

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

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

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

SRD Part: Assessment of dose proportionality

Dose proportionality of the secondary pharmacokinetic endpoints under fasting conditions will be explored based on the regression model described in Section 7.1.3. Based on the estimate for slope parameter (β), a 2-sided 95% CI for the slope will be computed. Perfect dose proportionality would correspond to a slope of 1. The assumption of a linear relationship between the log-transformed pharmacokinetic endpoint and the log-transformed dose will be checked.

If dose proportionality over the entire dose range under fasting conditions investigated cannot be shown, an attempt will be made to identify dose ranges, where dose proportionality can be assumed.

BA Part: Assessment of relative bioavailability

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

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

7.3.3 Safety analyses

Safety analyses will be performed in accordance with BI standards.

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

Treatments will be compared in a descriptive way. The placebo control group in the safety evaluation will consist of all placebo treated subjects, regardless of the dose group in which they were treated. The active treatment groups will be compared to the placebo group in a descriptive way. Tabulations of frequencies/proportions will be used for the evaluation of categorical (qualitative) data, and tabulations of descriptive statistics will be used to analyse continuous (quantitative) data.

The analyses will be done by ‘treatment at onset’.

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

Additionally, further treatment intervals (analysing treatments) may be defined in order to provide summary statistics for time intervals, such as combined treatments, on-treatment totals or periods without treatment effects (such as screening and post-study intervals).

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

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

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

A centralised evaluation of all 12-lead ECGs recordings (see Section 5.2.4) will be the basis for the derivation of further ECG parameters based on the ECG variables [redacted]. The baseline value of an ECG variable is defined as the mean of the triple ECG measurements prior to drug administration. The derivation of the quantitative and qualitative ECG endpoints and their analyses will be described in the TSAP.

7.3.4 Preliminary PK analyses

A preliminary analysis of PK parameters (AUC_{0-24} and C_{max} of BI 730357) provided as individual values and geometric means of at least the first cohort per dose level, will be performed for

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

(Note: Data from the first cohorts of the above mentioned dose levels will be sufficient as long as the data from at least 2 subjects on active were available)

A preliminary analysis of pharmacodynamic biomarkers is not planned.

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

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

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

7.3.5 Pharmacokinetic analyses

The pharmacokinetic parameters listed in Section 5.5.1 for drug BI 730357 will be calculated according to the BI SOP ‘Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics’ (001-MCS-36-472).

Subjects who are not included in the PKS (refer to Section 7.3.1.) will be reported with their individual plasma / urine concentrations and individual pharmacokinetic parameters; however, they will not be included in descriptive statistics for plasma / urine concentrations, pharmacokinetic parameters.

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

If a predose concentration value is greater than 5% of C_{max}, the subject’s pharmacokinetic data will be not included in any statistical evaluations, in accordance with international guidances. The individual pharmacokinetic parameters of such a subject will be calculated and listed separately. If a predose concentration is above BLQ, but less than or equal to 5% of

the subject's C_{max} value, the subject's data without any adjustments will be included in all pharmacokinetic measurements and calculations.

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

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

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

7.3.6 Biomarker analysis

7.3.6.1 Analysis of target engagement biomarkers

[redacted]

7.4 HANDLING OF MISSING DATA

7.4.1 Safety

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

7.4.2 Plasma drug concentration - time profiles

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

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

7.4.3 Pharmacokinetic parameters

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

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

7.5 RANDOMISATION

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

BA part: Subjects will be randomized to one of the six treatment sequences R/T1/T2, R/T2/T1, T1/T2/R, T1/R/T2, T2/T1/R, T2/R/T1 in a 1:1:1 ratio.

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

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

7.6 DETERMINATION OF SAMPLE SIZE

SRD part

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

BA part

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

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

Table 7.6.1 Expected two-sided 90% confidence intervals for different gCVs and ratios T/R (N=12)

gCV[%]	Ratio[1] [%]	Precision (upper CI limit/lower CI limit)	90% CI [%]
20	80	0.175	(67.17, 95.28)
	100	0.175	(83.97, 119.10)
	125	0.175	(104.96, 148.87)
	150	0.175	(125.95, 178.64)
	200	0.175	(167.93, 238.19)
25	80	0.217	(64.38, 99.41)
	100	0.217	(80.47, 124.27)
	125	0.217	(100.59, 155.33)
	150	0.217	(120.71, 186.40)
	200	0.217	(160.94, 248.53)
30	80	0.259	(61.74, 103.65)
	100	0.259	(77.18, 129.57)
	125	0.259	(96.47, 161.96)
	150	0.259	(115.77, 194.35)
	200	0.259	(154.36, 259.14)

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

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

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

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

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

8. INFORMED CONSENT, DATA PROTECTION, TRIAL RECORDS

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

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

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

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

8.1 STUDY APPROVAL, SUBJECT INFORMATION, AND INFORMED CONSENT

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

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

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

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

8.2 DATA QUALITY ASSURANCE

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

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

8.3 RECORDS

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

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

8.3.1 Source documents

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

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

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

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

8.3.2 Direct access to source data and documents

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

8.3.3 Storage period of records

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

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

8.4 EXPEDITED REPORTING OF ADVERSE EVENTS

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

8.5 STATEMENT OF CONFIDENTIALITY

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

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

8.6 COMPLETION OF TRIAL

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

9. REFERENCES

9.1 PUBLISHED REFERENCES

R03-2269 Guidance for industry: food-effect bioavailability and fed bioequivalence studies. In: U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER); 2002. p. 1-9.

R05-2311 ICH E14: the clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs (ICH harmonised tripartite guideline, recommended for adoption at step 4 of the ICH process on 12 May 2005 by the ICH Steering Committee). www.emea.eu.int; 2005. p. 1-14.

R09-1400 European Medicines Agency (EMEA). ICH topic M3 (R2) non-clinical safety studies for the conduct of human clinical trials and marketing authorization for pharmaceuticals: step 4: note for guidance on non-clinical safety studies for the conduct of human clinical trials and marketing authorization for pharmaceuticals (June 2009, CPMP/ICH/286/95). http://www.emea.europa.eu; 2009.

R09-4830 Brown BD, Badilini F. HL7 aECG implementation guide (March 21, 2005). 2005.

R12-0972 Kupper LL, Hafner KB. How appropriate are popular sample size formulas? Am Stat 1989;43(2):101-105.

R13-0801 Guidance for industry: E14 clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs: questions and answers (R1) (ICH, October 2012). http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guida nces/ucm073161.pdf (access date: 22 February 2013) ; U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER); 2012.

R13-4095 European Medicines Agency (EMA). Committee for Medicinal Products for Human Use (CHMP): ICH guideline E14 - questions and answers: step 5 (May 2012, EMA/CHMP/ICH/310133/2008). http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/0 9/WC500002878.pdf (access date: 13 September 2013) ; London: European Medicines Agency (EMA); 2012.

R13-5279 Elmore SA. Enhanced histopathology of the thymus. Toxicol Pathol 2006;34(5): 656-665.

R16-0373 Recommendations related to contraception and pregnancy testing in clinical trials (final version - 2014-09-15). http://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2014_09_HMA_CTFG_Contraception.pdf (access date: 2 February 2016) ; Clinical Trial Facilitation Group (CTFG), Head of Medicine Agencies (HMA); 2014.

R16-2630 Ueda E, Kurebayashi S, Sakaue M, Backlund M, Koller B, Jetten AM. High incidence of T-cell lymphomas in mice deficient in the retinoid-related orphan receptor RORgamma. Cancer Res 2002;62(3):901-909.

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

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

R99-0697 Ma TY, Hollander D, Krugliak P, Katz K. PEG 400, a hydrophilic molecular probe for measuring intestinal permeability. Gastroenterology 1990;98(1):39-46.

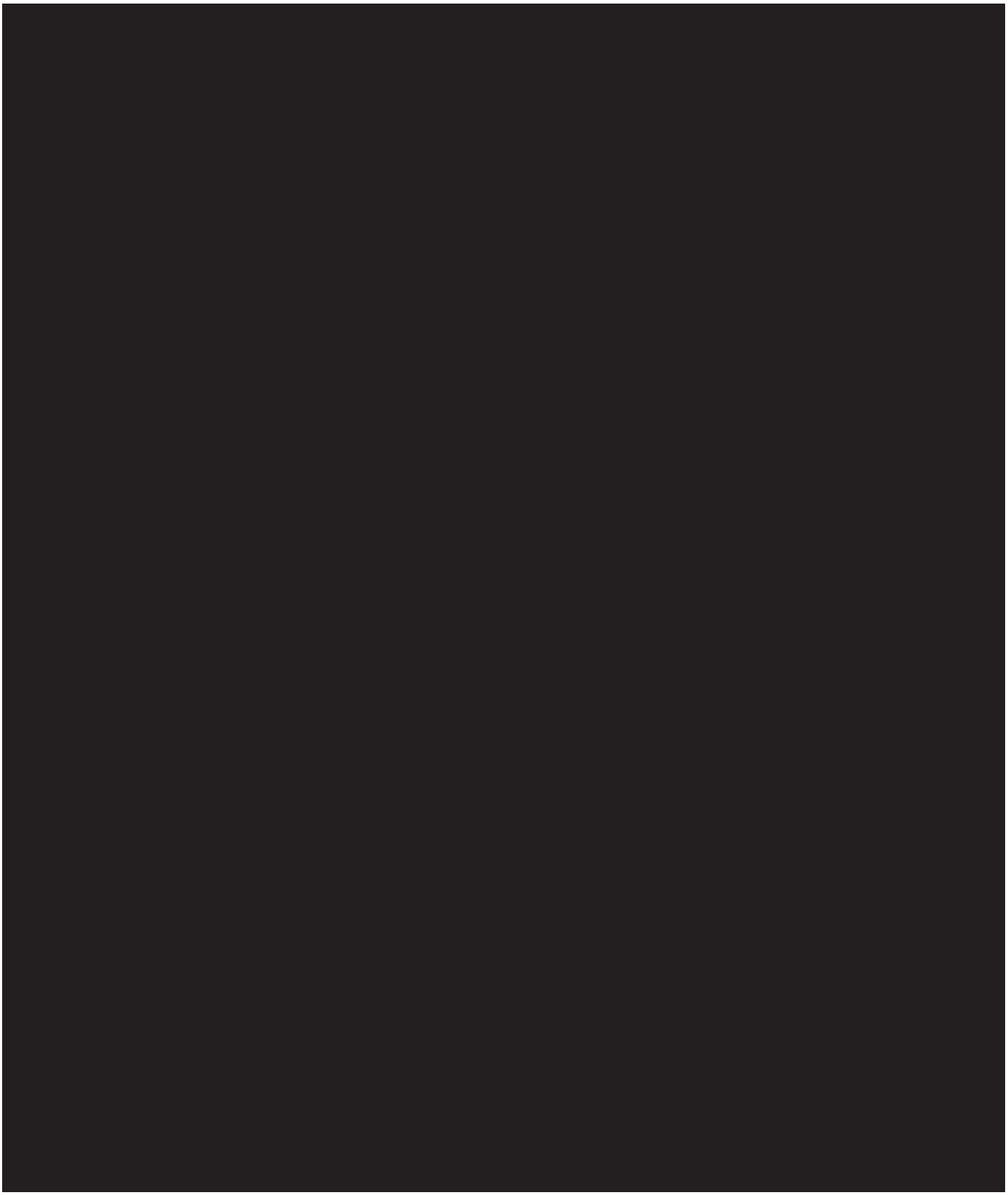
9.2 UNPUBLISHED REFERENCES

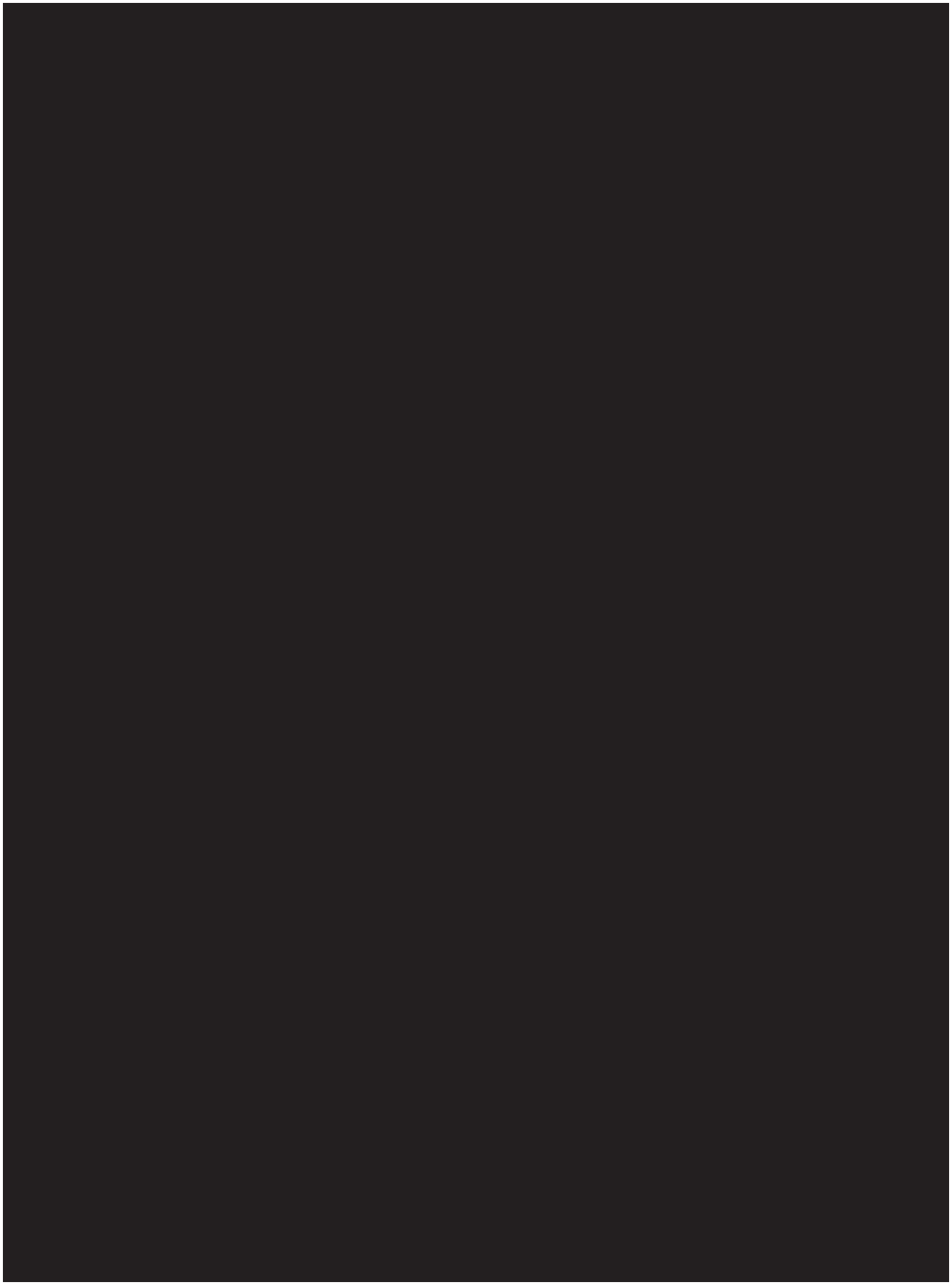
001-MCS-36-472 Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics. Current version

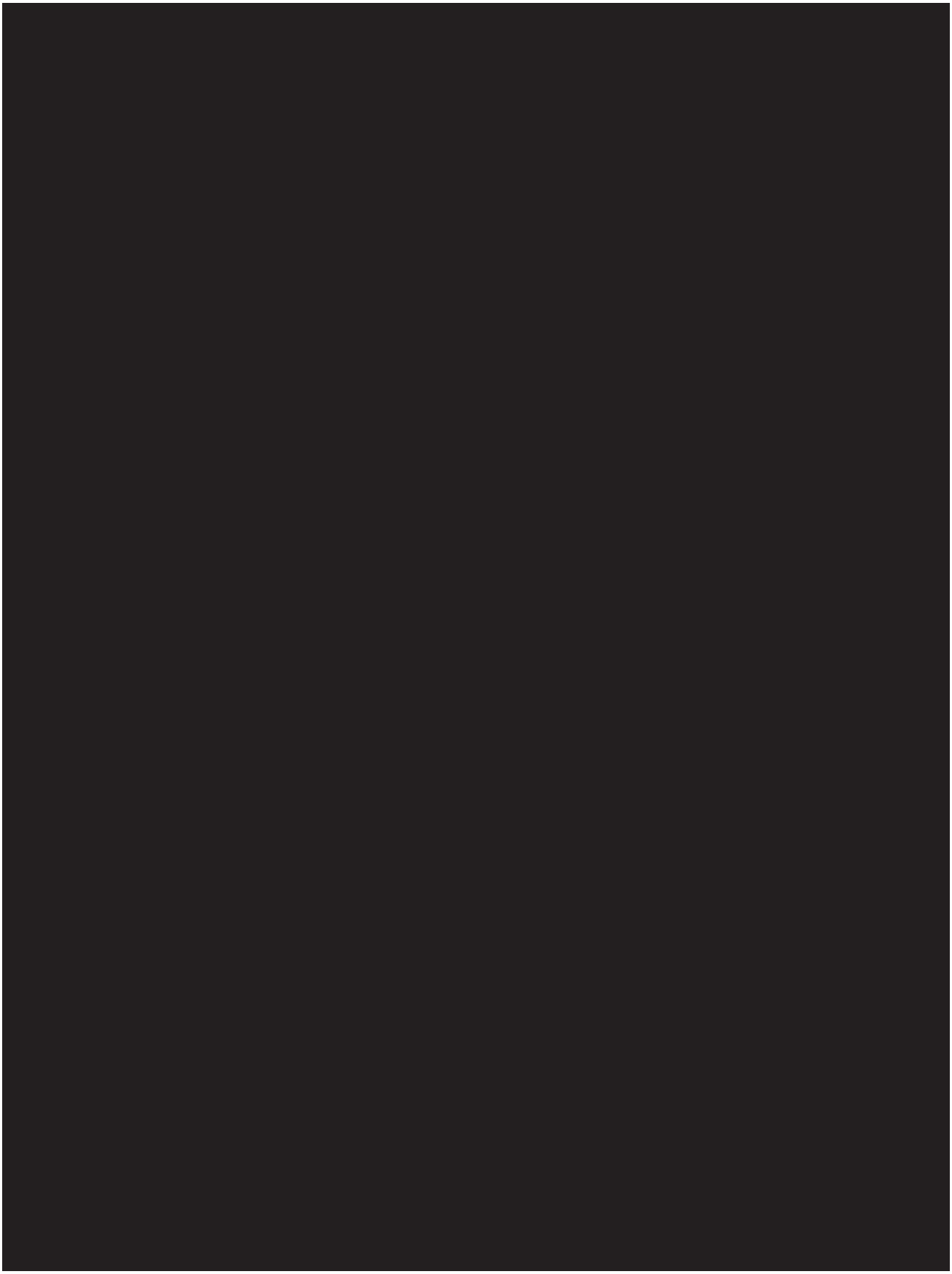
c09228382-01 [redacted] Investigator's Brochure: BI 730357 Psoriasis (ankylosing spondylitis, psoriatic arthritis, asthma, inflammatory bowel disease) 1407.P1 (P2, P3, P4, P5) 29-Sep-2016.

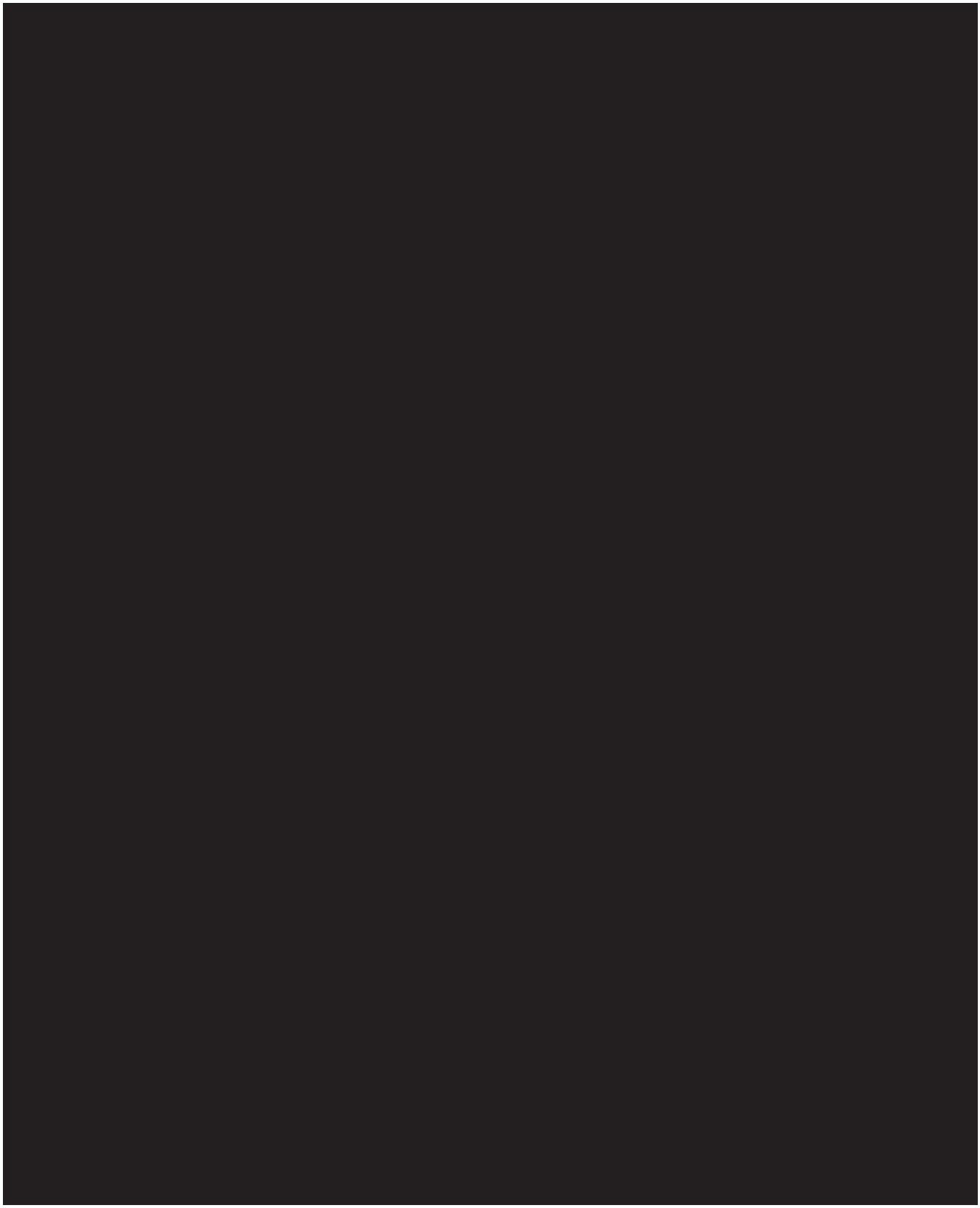
U02-1602 [redacted]. Safety of total daily doses of 5, 10, 15 and 20 mL PEG 400 administered orally to healthy male human subjects once (QD) or twice (BID) for 14 days. A single center, multiple rising dose study, placebo controlled, double-blinded at each dose level. IKP Trial No. 071/01-02.PEG. 13-Sep-2002.

10. APPENDICES









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11. DESCRIPTION OF GLOBAL AMENDMENT(S)

Number of global amendment		1
Date of CTP revision		01 December 2016
EudraCT number		2016-003047-11
BI Trial number		1407.1
BI Investigational Product(s)		BI 730357
Title of protocol		A partially randomised, single-blind, placebo-controlled trial to investigate safety, tolerability, pharmacokinetics and pharmacodynamics of single rising doses of BI 730357 administered as oral solution and tablets to healthy subjects, and a randomized, open-label, single-dose, three-way cross-over bioavailability comparison of BI 730357 as tablet versus oral solution and tablet with and without food
To be implemented only after approval of the IRB / IEC / Competent Authorities		☐
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		☐
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		☒
Section to be changed		1. Synopsis, pages 25, 26, 35, 36, 37 2. Synopsis, pages 49, 58 3. Page 30
Description of change		1. Deletion of “50 mg Dose” in the BA part 2. Minor editorial changes 3. Change of upper age to 45 years (incl)
Rationale for change		1. To address request by the EC 2. Corrections 3. To address request by the CA

Number of global amendment		2
Date of CTP revision		19 January 2017
EudraCT number		2016-003047-11
BI Trial number		1407.1
BI Investigational Product(s)		BI 730357
Title of protocol		A partially randomised, single-blind, placebo-controlled trial to investigate safety, tolerability, pharmacokinetics and pharmacodynamics of single rising doses of BI 730357 administered as oral solution and tablets to healthy subjects, and a randomized, open-label, single-dose, three-way cross-over bioavailability comparison of BI 730357 as tablet versus oral solution and tablet with and without food
To be implemented only after approval of the IRB / IEC / Competent Authorities		☒
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		☐
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		☐
Section to be changed		1. Section 2.1, last paragraph on page 22, line 6 2. Section 2.1, last paragraph on page 22, line 7 3. Section 2.1, last paragraph on page 22, line 11 4. Section 2.3, paragraph 5 on page 24, line 4 5. Section 3.3.4.2, last paragraph, last line
Description of change		1. ‘132,000’ corrected into ‘1,320,000’ 2.-5. ‘13,200’ corrected into ‘132,000’
Rationale for change		1. Correction of AUC_{0-24} value for male dog at 60 mg/kg/day (from 132,000 to 1,320,000 nM*h) according to Investigator’s Brochure for BI 730357 (Table 5.3:2, page 42, column 4). 2.-5. Correction of AUC_{0-24} values for the maximum acceptable human exposure (from 13,200 to 132,000 nM*h).

Number of global amendment		3
Date of CTP revision		05 May 2017
EudraCT number		2016-003047-11
BI Trial number		1407.1
BI Investigational Product(s)		BI 730357
Title of protocol		A partially randomised, single-blind, placebo-controlled trial to investigate safety, tolerability, pharmacokinetics and pharmacodynamics of single rising doses of BI 730357 administered as oral solution and tablets to healthy subjects, and a randomized, open-label, single-dose, three-way cross-over bioavailability comparison of BI 730357 as tablet versus oral solution and tablet with and without food
To be implemented only after approval of the IRB / IEC / Competent Authorities		☒
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		☐
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		☐
Section to be changed		1. Synopsis, pages 2-3 2. Flow chart for the SRD part, pages 5-6 3. Section 1.2.5, pages 20-24 4. Section 2.1, pages 25, 27, 28 5. Section 2.2, page 28 6. Section 2.3, page 31 7. Section 3.1, page 32 8. Section 3.3, page 35 9. Section 3.3.5, page 40 10. Section 4.1, pages 41-45 11. Section 6.2.2, page 66 12. Section 7.1.3, page 68 13. Section 7.3.2, page 71 14. Section 7.6, page 74

Number of global amendment		3
Description of change		1. Number of subjects in the SRD part increased by 16, administration of 400 mg and 800 mg BI 730357 or placebo under fed conditions added, option for additional subjects removed 2. Visit 3 and standard breakfast added 3. Preliminary clinical data on safety, tolerability and PK from the SRD and BA part presented 4. 800 mg dose added, paragraph to 'maximum dose and dose escalation' amended 5. Fasting conditions specified for SRD part 6. Update on observed half-life 7. Number of subjects increased, option for additional subjects removed, 3 additional dose groups (DGs) added in Table 3.3:1 8. No replacement for DGs 8, 9 and 10 9. Number of subjects increased, option for additional subjects removed 10. DGs 8-10 added; maximum dose and number of dose cohorts adapted, DGs 8-10 added in Table 4.1.4: 1, high-fat breakfast and continental breakfast added in the SRD part, composition of standard continental breakfast added (Table 4.1.4:4) 11. Treatments periods of DGs 8-9 described 12. Investigation of dose proportionality under fasting conditions only 13. Investigation of dose proportionality under fasting conditions only 14. Number of subjects in the SRD part increased
Rationale for change		The highest exposures observed in this trial after the 400 mg dose under fasting conditions (C_{max} of 755 nM, AUC_{0-24} of 9,453 nM*h) are significantly below the predicted exposures at 400 mg (C_{max} of 2,547 nM and AUC_{0-24} of 42,458 nM*h) and the acceptable exposure limit of this trial (C_{max} of 5,920 nM, and AUC_{0-24} of 132,400 nM*h). Since we observed a 36% increase in exposure in the fed versus fasted condition, it is planned to investigate 3 additional DGs in the fed condition to further evaluate safety and PK of higher BI 730357 exposures, including the influence of food (normal and high-fat diet) on higher doses. The results will support the testing of higher exposures during the planned multiple-rising dose trial and further clinical development.

APPROVAL / SIGNATURE PAGE

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Document Name: clinical-trial-protocol-revision-03

Title: A partially randomised, single-blind, placebo-controlled trial to investigate safety, tolerability, pharmacokinetics and pharmacodynamics of single rising doses of BI 730357 administered as oral solution and tablets to healthy subjects, and a randomized, open-label, single-dose, three-way cross-over bioavailability ...

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Author-Trial Statistician	[redacted]	05 May 2017 14:49 CEST
Author-Trial Clinical Monitor		05 May 2017 15:01 CEST
Author-Trial Clinical Pharmacokineticist		05 May 2017 15:07 CEST
Verification-Paper Signature Completion		05 May 2017 15:21 CEST
Approval-Therapeutic Area [redacted]		06 May 2017 01:21 CEST
Approval-Team Member Medicine		08 May 2017 04:42 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed