Clinical Trial Protocol

	Document Number: c11428532-01
BI Trial No.:	1386-0007
BI Investigational Product:	BI 1467335
Title:	Safety, tolerability, pharmacokinetics and pharmacodynamics of multiple rising oral doses of BI 1467335 in healthy Japanese male volunteers with multiple oral doses at the highest dose in Caucasian for comparison (randomised, double-blind, placebo-controlled trial)
Lay Title:	This study tests BI 1467335 in healthy Japanese and Caucasian men. The study tests how different doses of BI 1467335 are taken up in the body and how well they are tolerated.
Clinical Phase:	I
Trial Clinical Monitor:	Phone: Fax:
Co-ordinating Investigator:	Phone: Fax:
Status:	Final Protocol
Version and Date:	Version: 1.0 Date: 11 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 1467335			
Protocol date: 11 May 2017	**Trial number:** 1386-0007		**Revision date:** Not Applicable

Title of trial:	Safety, tolerability, pharmacokinetics and pharmacodynamics of multiple rising oral doses of BI 1467335 in healthy Japanese male volunteers with multiple oral doses at the highest dose in Caucasian for comparison (randomised, double-blind, placebo-controlled trial)
Co-ordinating Investigator:	
Trial site:	
Clinical phase:	I
Objectives:	To investigate the safety, tolerability, pharmacokinetics and pharmacodynamics following multiple rising oral doses of BI 1467335 in healthy Japanese male volunteers with single dose Caucasian group for comparison
Methodology:	Multiple rising oral doses in Japanese with single dose Caucasian group for comparison, randomised, double-blind, placebo controlled within dose groups, multiple centres.
No. of subjects:	
total entered:	48 (36 Japanese and 12 Caucasian)
each treatment:	12 per dose group /ethnicity (9 on active and 3 on placebo)
Diagnosis:	Not applicable
Main criteria for inclusion:	Healthy male Japanese and Caucasian subjects Age ≥20 and ≤45 years BMI range: ≥18.5 and ≤25 kg/m^2 (Japanese), ≥18.5 and ≤29.9 kg/m^2 (Caucasian)
Test product:	BI 1467335 film-coated tablets
dose:	3, 6 and 10 mg qd (Japanese) and 10 mg qd (Caucasian)
mode of admin.:	Oral administration with 240 mL water after an overnight fast of at least 10 hours
Comparator product:	Placebo
dose:	Not applicable (matching placebo tablets)
mode of admin.:	Oral administration with 240 mL water after an overnight fast of at least 10 hours
Duration of treatment:	28 days with multiple oral doses of BI 1467335 q.d.

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Criteria for pharmacokinetics:	Secondary endpoints: After the first dose: AUC_{0-24} and C_{max} of BI 1467335 After the last dose: $AUC_{0-24,28}$ and $C_{max,28}$ of BI 1467335		
Criteria for pharmacodynamics:			
Criteria for safety:	Primary endpoint: The number [N (%)] of subjects with drug-related AEs		
Statistical methods:	Descriptive statistics will be calculated for all endpoints. Dose proportionality of BI 1467335 will be explored using a regression model; a 95% confidence interval for the slope will be computed.		

FLOW CHART

Visit	Day	Planned time (relative to first drug administration [h:min]	Approximate clock time of actual day [h:min]	Event and comment	Safety laboratory	PK blood [9]			12-lead ECG [8]	Vital signs (BP, PR)	Questioning for AEs and concomitant therapy [6]
1	-28 to -2			Screening (SCR)[1, 5, 12]	x[5]				x	x	
2	-3 to -1[7]	-48:00	09:00	Ambulatory visit	x				x	x	x
	-1	-12:00	21:00	Admission to trial site	x[5]						x
	1	-2:00	07:00	Allocation to treatment[2]	x[2,13]			x[2, 16]	x[2]	x[2]	x[2]
		-0:05	08:55			x[14]	x[10]				
		0:00	09:00	First drug administration			▲				
		0:15	09:15			x	|		x		
		0:30	09:30			x	|		x	x	
		0:45	09:45			x	|		x	x	
		1:00	10:00			x	|		x	x	x
		1:30	10:30			x	|		x		
		2:00	11:00	240 mL fluid intake and light breakfast[3]		x	|		x	x	x
		3:00	12:00			x	|				
		4:00	13:00	240 mL fluid intake, thereafter lunch[3]		x	+		x	x	x
		6:00	15:00			x	|				
		8:00	17:00	Snack (voluntary)[3]		x	+		x	x	x
		10:00	19:00	Dinner[3]		x	|				
		12:00	21:00			x	+		x	x	x
	2	23:55	08:55			x[14]	▼	x[14]	x[2]	x[2]	x[2]
		24:00	09:00	Drug administration[11]							
	3	48:00	09:00	Drug administration[11]	x				x[2]	x[2]	x[2]
	4	71:55	08:55			x[14]					
		72:00	09:00	Drug administration[11]					x[2]	x[2]	x[2]
		72:30	09:30			x					
		73:00	10:00	Discharge from trial site (confirmation of fitness)[4]		x			x	x	x
	7	143:55	08:55	Ambulatory visit		x[14]		x[14]			
		144:00	09:00	Drug administration[11]	x[2]				x[2]	x[2]	x[2]
		144:30	9:30			x					
		145:00	10:00	Discharge		x			x	x	

Visit	Day	Planned time (relative to first drug administration [h:min]	Approximate clock time of actual day [h:min]	Event and comment	Safety laboratory	PK blood [9]			12-lead ECG [8]	Vital signs (BP, PR)	Questioning for AEs and concomitant therapy [6]
2	13	300:00	21:00	Admission to trial site							
	14	310:00	07:00		x[2]				x[2]	x[2]	x[2]
		311:55	08:55			x[14]		x[14]			
		312:00	09:00	Drug administration			▲				
		312:15	09:15			x	|		x		
		312:30	09:30			x	|		x	x	
		312:45	09:45			x	|		x	x	
		313:00	10:00			x	|		x	x	x
		313:30	10:30			x	|		x		
		314:00	11:00	240 mL fluid intake and light breakfast[3]		x	|		x	x	x
		315:00	12:00			x	|				
		316:00	13:00	240 mL fluid intake, thereafter lunch[3]		x	+		x	x	x
		318:00	15:00			x	|				
		320:00	17:00	Snack (voluntary)[3]		x	+		x	x	x
		322:00	19:00	Dinner[3]		x	|				
		324:00	21:00			x	+		x	x	x
	15	335:55	08:55			x[14]	▼				
		336:00	09:00	Drug administration[11]					x[2]	x[2]	x[2]
		336:30	09:30			x					
		337:00	10:00	Discharge		x			x	x	
	21	479:55	08:55	Ambulatory visit		x[14]		x[14]			
		480:00	09:00	Drug administration[11]	x[2]				x[2]	x[2]	x[2]
		480:30	09:30			x					
		481:00	10:00	Discharge		x			x	x	x
	26	599:55	08:55	Admission to trial site		x[14]					
		600:00	09:00	Drug administration[11]					x[2]	x[2]	x[2]
		600:30	09:30			x					
		601:00	10:00			x			x	x	x
		612:00	21:00								
	27	623:55	08:55			x[14]					
		624:00	09:00	Drug administration[11]			▲		x[2]	x[2]	x[2]
		624:30	09:30			x	|				
		625:00	10:00			x	|		x	x	x

Visit	Day	Planned time (relative to first drug administration [h:min]	Approximate clock time of actual day [h:min]	Event and comment	Safety laboratory	PK blood [9]			12-lead ECG [8]	Vital signs (BP, PR)	Questioning for AEs and concomitant therapy [6]
2	28	646:00	7:00		x[2]		┃		x[2]	x[2]	x[2]
		647:55	08:55			x[14, 15]	▼	x[14, 16]			
		648:00	09:00	Last drug administration			▲				
		648:15	09:15			x	┃		x		
		648:30	09:30			x[15]	┃	x	x	x	
		648:45	09:45			x	┃		x	x	
		649:00	10:00			x[15]	┃ ┃	x	x	x	x
		649:30	10:30			x	┃		x		
		650:00	11:00	240 mL fluid intake and light breakfast[3]		x[15]	┃	x	x	x	x
		651:00	12:00			x	┃				
		652:00	13:00	240 mL fluid intake, thereafter lunch[3]		x[15]	┼	x	x	x	x
		654:00	15:00			x[15]	┃	x			
		656:00	17:00	Snack (voluntary)[3]		x[15]	┼		x	x	x
		658:00	19:00	Dinner[3]		x[15]	┃	x			
		660:00	21:00			x[15]	┼	x	x	x	x
	29	672:00	09:00			x[15]	▼	x	x	x	x
		673:00	10:00	Discharge from trial site (confirmation of fitness)[4]							
	30	696:00	09:00	Ambulatory visit[17]	x	x[15]		x	x	x	x
	32+/-1	744:00	09:00	Ambulatory visit[17]		x[15]		x			x
	36+/-2	840:00	09:00	Ambulatory visit[17]		x[15]		x			
	40	936:00	09:00	Ambulatory visit		x[15]		x			
3	42 to 48			End of trial (EOT) examination[4, 12]	x			x	x	x	x

1. Screening includes subject information, informed consent, physical examination, check of vital signs, ECG, safety laboratory (including exclusionary laboratory tests), demographics (including determination of body height and weight, smoking status and alcohol history), relevant medical history, concomitant therapy and review of inclusion/exclusion criteria.
2. 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, body weight, vital signs, ECG, safety laboratory, recording of AEs and concomitant therapies. Confirmation of fitness includes physical examination.
5. Urine drug screening and alcohol breath test will be done at screening and Day -1.
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, ECG, blood pressure assessment and AE questioning to be done and medically evaluated within 3 days prior to first administration of study drug; this visit can be omitted, if the screening examination is performed on Days -3, -2 or -1.
8. The ECG recording has to be performed as triple on Day 1 and Day 2, Day 14 and Day 15, Day 28 and Day 29. All other ECG recordings will be single ECGs.
9. 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 400 mL per subject.

11. Administration under fasting conditions. On the hospitalization days, light breakfast (or snack) 2 h after drug administration
12. Ophthalmological examinations (exclusion of cataract).Slit lamp test can be performed during screening or until Day -1 and from Day 29 to EOT visit.

14. Samples to be drawn immediately (within 30 minutes) prior to drug administration.
15. Additional blood samples for metabolite analysis.

17. If consecutive two-day ambulatory visits take place, subjects can stay at the site.

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ABBREVIATIONS

$\lambda_{z(,N)}$	Terminal rate constant of the analyte in plasma (after the N^{th} dose)
AE	Adverse event
AESI	Adverse events of special interest
ANCOVA	Analysis of covariance
$AUC_{0-24(,N)}$	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 to 24h (after the N^{th} dose)
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
CCl_4	Carbon tetrachloride
CI	Confidence interval
$C_{max(,N)}$	Maximum measured concentration of the analyte in plasma (after the N^{th} dose)
CML	Clinical Monitor Local
CNS	Central nervous system
CRA	Clinical Research Associate
CRF	Case report form
CRO	Clinical Research Organisation
CTCAE	Common Terminology Criteria for Adverse Events
CTP	Clinical trial protocol
CTR	Clinical trial report
CTSU	Clinical Trial Supplies Unit
CV	Arithmetic coefficient of variation
DEDP	Drug exposure during pregnancy
DILI	Drug induced liver injury
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
EDTA	Ethylenediaminetetraacetic acid
ELISA	Enzyme-Linked Immunosorbent Assay
EOT	End of trial
FDA	Food and Drug Administration
FIH	First in human

FOB	Functional observational battery
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
GI	Gastro-intestinal
GLP	Good Laboratory Practice
gMEAN	Geometric mean
HCC	Hepatocellular carcinoma
HR	Heart rate
IB	Investigator's brochure
IEC	Independent Ethics Committee
IPV	Important protocol violations
IRB	Institutional Review Board
ISF	Investigator site file
LLOQ	Lower limit of quantification
MCD	Methionine-Choline deficient Diet
MedDRA	Medical Dictionary for Regulatory Activities
MRD	Multiple-rising dose
NBE	New biological entity
NC	Not calculated
NCE	New chemical entity
NOA	Not analysed
NOAEL	No observed adverse effect level
NOR	No valid result
NOS	No sample available
PD	Pharmacodynamic(s)
PE	Polyethylene
PK	Pharmacokinetic(s)
PKS	Pharmacokinetic parameter analysis set
p.o	per os
PP	Polypropylene
PR	Pulse rate
PTM	Planned time of the measurement
q.d.	*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)
QTcV	heart-rate corrected QT interval using Van de Water's formula
R	Reference treatment

RDC	Remote Data Capture
REP	Residual effect period
SAE	Serious adverse event
SCR	Screening
SOC	System Organ Class
SOP	Standard Operating Procedure
SRD	Single-rising dose
SUSAR	Suspected Unexpected Serious Adverse Reaction
T	Test product or treatment
TDMAP	Trial Data Management and Analysis Plan
TEAE	Treatment-emergent adverse event
TMF	Trial master file
TS	Treated Set
TSAP	Trial statistical analysis plan
TSH	Thyroid stimulating hormone
ULN	Upper limit of normal

2. RATIONALE, OBJECTIVES, AND BENEFIT - RISK ASSESSMENT

2.2 TRIAL OBJECTIVES

The primary objective of the current study is to investigate the safety and tolerability of BI 1467335 in healthy Japanese male subjects following oral administration of multiple rising doses of 3, 6 and 10 mg (for details see Section 5.2).The Caucasian group will receive 10 mg only.

A secondary objective is the exploration of the pharmacokinetics and pharmacodynamics of BI 1467335 in healthy Japanese and Caucasian male subjects.

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.

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

This multiple rising dose trial will be randomised, double-blind, and placebo controlled within dose groups.

A total of 48 volunteers will participate in the trial according to three groups with 12 subjects in dose groups 1 & 2 and 24 subjects in dose group 3. Each of the sequential dose groups has one or two ethnic subgroups and within each of the subgroups 9 subjects will receive the active drug and 3 subjects will receive placebo. One dose is tested within each group.

The dose groups to be evaluated are as outlined in Table 3.1: 1 below.

Table 3.1: 1 Dose groups and subject numbers

Dose group	1	2	3	
Dose	3 mg q.d.	6 mg q.d.	10 mg q.d.	
Ethnicity	Japanese	Japanese	Japanese	Caucasian
No of subjects	12	12	12	12
Subjects receiving placebo	3	3	3	3
Subjects receiving active	9	9	9	9

The different dose groups will be investigated consecutively in ascending order of the doses in Japanese. The decision to proceed to the next dose group will be based upon the safety of the preceding dose group. Preliminary PK assessments as detailed in Section 7.3.4 will be performed at 6 mg dose level before starting with 10 mg dose level.

The investigator is allowed to stop the further dose escalation in case the safety evaluation leads to concerns which would not allow higher dosing.

3.1.1 Administrative structure of the trial

The trial will be conducted at and in
The trial medication will be provided by the Clinical Trial Supplies Unit (CTSU), BI Pharma GmbH & Co. KG, Biberach, Germany.
On-site monitoring will be performed under the responsibility of Clinical Operations in Nippon BI.

Safety laboratory tests will be performed by the local laboratory of the trial site or/and at a CRO designated by the sponsor.

The analyses of BI 1467335 plasma concentrations will be performed at the Department of Drug Metabolism and Pharmacokinetics, BI Pharma GmbH & Co. KG, Biberach, Germany.

A central ECG laboratory will be selected to provide services for ECG evaluation as required for this protocol. The ECG device will be provided by the ECG service vendor. Please refer to Section 5.2.4 for the details.

The trial is sponsored by Boehringer Ingelheim.

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

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

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 will be defined according to BI SOPs. A list of responsible persons and relevant local information (as protocol reference, if applicable) can be found in the ISF (Investigator site file).

Relevant documentation on the participating (Principal) Investigators and other important participants, including their curricula vitae, will be filed in ISF.

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

For multiple 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 as well as pharmacokinetics of BI 1467335.

With the rising dose design, double-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.

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 minimising subject risk by sequentially studying ascending doses. This implicates a confounding factor concerning statistical comparisons between the dose levels.

The resulting group sizes (nine subjects per active treatment group for doses 3mg and 6 mg, nine subjects per active treatment group per ethnicity for 10 mg) are in general considered as sufficient for the exploratory evaluation of pharmacokinetics.

It is standard in trials involving healthy volunteers to include a placebo group as control for the evaluation of safety, tolerability and pharmacokinetic effects. Each dose group consists of 12 subjects per ethnicity with 9 on active treatment, and 3 on placebo. The placebo control group includes all subjects of all dose groups treated with placebo.

3.3 SELECTION OF TRIAL POPULATION

It is planned that 48 healthy male subjects will enter the study. Based on the known safety profile and general applicability to a variety of potential indications that BI 1467335 is pursuing, healthy volunteer are chosen in this phase I study. Healthy subjects as a Phase I trial population are ideal because they provide relatively stable physiological, biochemical, and hormonal conditions. In these subjects there is absence of disease-related variations and concomitant medications. Healthy subjects can be tested under standardised conditions and in an environment that allows repeated testing.

3.3.1 Main diagnosis for study entry

The study will be performed in healthy male subjects.

3.3.2 Inclusion criteria

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

1. Healthy male subjects according to the 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. Japanese ethnicity or Caucasian, according to the following criteria:
   - Japanese; born in Japan, have lived outside of Japan <10 years, and have parents and grandparents who were all born in Japan
   - Caucasian
3. Age of 20 to 45 years (incl.)
4. BMI of 18.5 to 25 kg/m^2 (incl.) for Japanese and 18.5 to 29.9 kg/m^2 (incl.) for Caucasian
5. Signed and dated written informed consent by date of Visit 1 in accordance with GCP and local legislation.
6. Male subjects who agree to minimize the risk of female partners becoming pregnant by fulfilling any of the following criteria starting from at least 30 days before the first administration of trial medication and until 30 days after trial completion:

- Use of adequate contraception, e.g. any of the following methods *plus* condom: combined oral contraceptives, intrauterine device
- Vasectomised (vasectomy at least 1 year prior to enrolment)
- Surgically sterilised (including hysterectomy) female partner

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. Any laboratory value outside the reference range that the investigator considers to be of clinical relevance
3. Any evidence of a concomitant disease judged as clinically relevant by the investigator
4. Gastrointestinal, hepatic, renal, respiratory, cardiovascular, metabolic, immunological or hormonal disorders
5. Surgery of the gastrointestinal tract that could interfere with kinetics of the trial medication (except appendectomy and simple hernia repair)
6. Diseases of the central nervous system (including but not limited to any kind of seizures or stroke), and other relevant neurological or psychiatric disorders
7. History of relevant orthostatic hypotension, fainting spells, or blackouts
8. Chronic or relevant acute infections including HIV, viral hepatitis and (or) tuberculosis or evidence of tuberculosis infection as defined by a positive QuantiFERON TB-Gold (or T-SPOT) test. Subjects with a positive QuantiFERON TB-Gold (or T-SPOT) test will not participate in the study.
9. History of relevant allergy or hypersensitivity (including allergy to the trial medication or its excipients)
10. Intake of biologic agents other than current study medication or drugs considered likely to interfere with the safe conduct of the study
11. Intake of drugs with a long half-life (more than 24 h) within 30 days or less than 10 half-lives of the respective drug prior to administration of trial medication
12. Within 10 days prior to administration of trial medication, use of drugs that might reasonably influence the results of the trial or that might prolong the QT/QTc interval
13. Participation in another trial (including bioequivalence trial) with an investigational drug within 90 days or 5 half-lives (whichever is greater) prior to planned administration of trial medication
14. Smoker (more than 10 cigarettes or 3 cigars or 3 pipes per day)
15. Inability to refrain from smoking on specified trial days
16. Alcohol abuse (consumption of more than 30 g per day)
17. Drug abuse or positive drug screening
18. Blood donation of more than 200 mL within 30 days prior to administration of trial medication or intended donation during the trial

19. Intention to perform excessive physical activities within one week prior to administration of trial medication or during the trial
20. Inability to comply with dietary regimen of trial site
21. 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
22. A history of additional risk factors for Torsades de Pointes (such as heart failure, hypokalemia, or family history of Long QT Syndrome)
23. Have received any live bacterial or live viral vaccination in the 12 weeks prior to the date of screening. Subjects must agree not to receive a live bacterial or live viral vaccination during the study and up to 12 months after the last administration of study drug
24. Have received Bacille Calmette-Guerin (BCG) vaccination in the 12 months prior to the date of screening. Subjects must agree not to receive BCG vaccination during the study and up to 12 months after the last administration of study drug
25. 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
26. Signs of cataract at screening by slit lamp test

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, 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, 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 (BP <90/50 mmHg) or hypertension (BP >180/100 mmHg) or of clinically relevant changes in ECG requiring intervention as well as unexplained liver enzyme elevations at any time during the trial.

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). The only exception to this rule is when the subject had an AESI and/or SAE that the investigator considers related to the screening procedure. 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 EOT examination will be performed if possible and the information will be recorded in the CRFs. 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 in one dose group show drug-related and clinically relevant adverse events of moderate or severe intensity, or if at least one drug-related serious adverse event is reported that is considered to be unacceptable.
2. The sponsor decides to discontinue the further development of the investigational product.
3. Violation of GCP, or the CTP or the contract with BI by a trial site or investigator, disturbing the appropriate conduct of the trial.

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

3.3.5 Replacement of subjects

In case some subjects of an ethnic cohort do not complete the dose level, the trial clinical monitor together with the trial pharmacokineticist and the trial statistician are to decide whether and how many subjects will be replaced. A replacement subject will be assigned a unique study subject number, and will be assigned to the same treatment as the subject he replaces. There will be no replacement for the subjects removed due to safety reason related to the trial drug.

4. TREATMENTS

4.1 TREATMENTS TO BE ADMINISTERED

The investigational product will be provided by BI Pharma GmbH & Co. KG.

4.1.1 Identity of BI investigational product and comparator product

The characteristics of the test product are below.

Substance:	BI 1467335
Pharmaceutical form:	Film-coated Tablet
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Unit Strength:	1, 5 mg
Posology	q.d.
Route of administration:	p.o.
Duration of use:	28 days

The characteristics of the reference product are below.

Substance:	Matching placebo
Pharmaceutical form:	Film-coated Tablet
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Unit Strength:	Not applicable
Posology	q.d.
Route of administration:	p.o.
Duration of use:	28 days

4.1.2 Method of assigning subjects to treatment groups

Prior to start of the study, subjects willing to participate in this study will be recruited to dose groups according to their temporal availability, which can be characterized as a ‘first comes, first chooses’ approach. Recruitment will be done successively for the dose groups, i.e. if the

planned number of subjects for one dose group will be completed the recruitment of the next higher dose group will be started. Therefore, the recruitment of subjects for the dose groups will neither be influenced by the trial personnel nor by any characteristics of the subjects, but only by temporal availability. Subjects who will be included in the study (in regard to the in- and exclusion criteria) will be assigned a sequential subject number according to the original order of recruitment and the subgroup they belong to, i.e. Japanese subjects to Japanese subgroup, Caucasian subjects to Caucasian subgroup.

Subjects will be randomized (to active drug or placebo for each dose group) within each ethnicity on day one of treatment according to the randomization list which will have been provided to the trial site in advance.

4.1.3 Selection of doses in the trial

Three doses are to be investigated in this trial. These three doses will cover potential therapeutic dose ranges. The number of doses will also allow for evaluation of dose proportionality in Japanese subjects.

This trial is designed to evaluate the safety, tolerability and pharmacokinetics of BI 1467335 in Japanese and Caucasian healthy young male volunteers using a safe and tolerable dose achieved in previous trials.

4.1.4 Drug assignment and administration of doses for each subject

The treatments to be evaluated are as outlined in Table 4.1.4: 1 below. The number of units for placebo corresponds to the number of units of the respective dose level.

Table 4.1.4: 1 BI 1467335 and placebo treatments

Treatment	Substance	Formulation	Route of administration	Number of units	Unit strength [mg]	Total dose [mg]
1	BI 1467335	tablet	po	3	1	3
2	BI 1467335	tablet	po	1	1,5	6
3	BI 1467335	tablet	po	2	5	10
1-3*	placebo	tablet	po	1~3	-	-

* Subjects receiving placebo are equally distributed across dose groups, and receive same number of tablets as active.

The trial medication will be administered to the subjects, while in a sitting position, as an oral dose together with about 240 mL of water under supervision of the investigating physician or an authorised designee. Administration will be performed following an overnight fast, which is to start no later than 10 h before the scheduled dosing. The dose should be taken at 22-26 hour interval at home. Subjects will be kept under close medical surveillance from the evening of Day -1 to the morning of Day 4, from the evening of Day 13 to the morning of Day 15, and from the morning of Day 26 to the morning of Day 29. During the first 2 h after drug administration on Days 1, 14 and 28, subjects are not allowed to lie down (i.e. no

declination of the upper body of more than 45 degrees from upright posture except for medical examination), or to sleep.

4.1.5 Blinding and procedures for unblinding

4.1.5.1 Blinding

The trial is designed double-blind with regard to the subjects and the investigators (as well as the research staff at the trial site) in order to eliminate observer or performance bias. This means avoiding systematic differences in assessments regarding the subject's treatment (active or placebo). According to the rising dose design, the current dose level will be known to subjects and investigators. The trial will only be unblinded to the subjects, investigators and trial site staffs after locking of the database.

Sponsor staff that have direct interaction with the investigator and site staff (e.g. CML and CRA) will not be aware of the treatment allocation (i.e. active vs placebo) as well until database lock.

The database of this trial will be handled open-label, i.e., all functions involved in the data cleaning and analysis of the trial (e.g. the trial clinical monitor, the trial pharmacokineticist, the trial bioanalyst, the trial statistician, trial programmer and the trial data manager) will have access to the unblinded data during conduct. In particular, this means the project team may be unblinded in case it is required. This can be done since no bias with regard to data cleaning or safety measures is expected.

Due to the requirements to report Serious Unexpected Suspected Adverse Reactions (SUSARs) by treatment, it may be necessary for a representative from BI's pharmacovigilance group to access the randomization code for individual subjects during study conduct. In such cases, access to the code will only be permitted by authorized pharmacovigilance representatives. Access to the code will be via the master list.

4.1.5.2 Procedures for emergency unblinding

For blinded trials, the investigator will be supplied with a set of sealed envelopes containing the medication codes for each subject according to the randomisation scheme. The envelopes will be kept unopened at the trial site until the end of data collection. An envelope may only be opened in emergency situations when the identity of the trial drug must be known to the investigator in order to provide appropriate medical treatment or to assure safety of trial participants. If the envelope for a subject is opened, the sponsor must be informed immediately. The reason for opening the code break must be documented on the envelope or appropriate CRF page along with the date and the initials of the person who broke the code. At the close-out visit all envelopes are collected.

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 with trial identification.

The clinical trial supply containers are labelled with:

- BI trial number
- Medication number
- Batch number
- Use by date
- Name of product and strengths or identification code
- Pharmaceutical dosage form, quantity of dosage units
- Term 'For Clinical Trial Use' (domestic language)
- Sponsor (or CTA holder's) name and address
- Storage conditions

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

4.1.7 Storage conditions

Study medication supplies will be kept in their original packaging and in a secure limited access storage area. 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, immediately contact the local clinical monitor as provided in the lists of contacts.

It may only be dispensed to trial subjects according to the CTP by authorised personnel.

4.1.8 Drug accountability

The investigator, pharmacist or investigational drug storage manager will receive the investigational drugs delivered by the sponsor when the following requirements are fulfilled:

- Approval of the study protocol by the IRB
- Availability of a signed and dated clinical trial contract between the Sponsor and the head of the investigational site
- 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 trial medication must be returned to the sponsor. All used medication will be disposed locally by trial site upon written authorization by the clinical

monitor. Receipt, usage, return and disposal must be documented on the respective forms in ISF. Account must be given for any discrepancies.

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

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

4.2 CONCOMITANT THERAPY, RESTRICTIONS, AND RESCUE TREATMENT

4.2.1 Rescue medication, emergency procedures, and additional treatments

In principle, no concomitant treatment is planned and/or allowed. 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.

All concomitant or rescue therapies will be recorded (including time of intake on study days) on the appropriate pages of the eCRF.

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

For restrictions on concomitant therapies, see Section 4.2.1 above.

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 during in-house days.

From Day 1 to Day 28, no food is allowed for at least 10 h before and 2 h after administration of the study drug.

From 1 hour before drug intake in the morning of PK profiling days 1, 14 and 28, liquid intake will be restricted to the water administered with the drug and 240 mL of water at 2 hours and 4 hours post-dose (mandatory for all subjects). From lunch until 24 hours post-dose fluid intake is restricted within 3000 mL.

Alcoholic beverages, grapefruits, Seville oranges (sour or bitter oranges) and their juices, and dietary supplements and products including St. John's wort (Hypericum perforatum) are not permitted starting 7 days before the first administration of trial medication until after the last PK sample is collected.

nicotine-containing products (e.g., cigarettes, cigars, chewing tobacco, snuff) should be stopped at least 6 weeks before screening and abstained from using these products until study completion.

Methylxanthine-containing drinks or foods (such as coffee, tea, cola, energy drinks, and chocolate) are not permitted 24 hours preceding the administration of trial medication and until the in-house period at the trial site. On the ambulatory days, it is restricted up to max 200 ml (coffee, tea, cola, energy drinks), or 50 g (chocolate and chocolate products).

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

Direct exposure to the sun or exposure to solarium radiation should be avoided during the entire study.

4.3 TREATMENT COMPLIANCE

Compliance will be assured by administration of trial medication in the study centre under supervision of the investigating physician or a designee on the days of hospitalization and ambulatory visits. On other days when medication will be taken at home, subjects will record the information of the drug administration in the diary and bring it to the study site when they come in for the next visit. 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 1467335 is the number [N (%)] of subjects with drug-related AEs.

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 jeopardize 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.

The following events will be handled as “deemed serious for any other reason”. An AE which possibly leads to disability will be reported as an SAE.

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 in section 5.2.2.2.

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, see Section 5.2.2.2.

The following are considered as AESIs:

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

These lab findings constitute a hepatic injury alert and the subjects showing these lab abnormalities need to be followed up according to the "DILI checklist" via the RDC-system. 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 adverse events should be classified and recorded in the (e) CRF according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03 dated 14 June 2010 [R10-4848] in the (e)CRF.

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

AE Collection

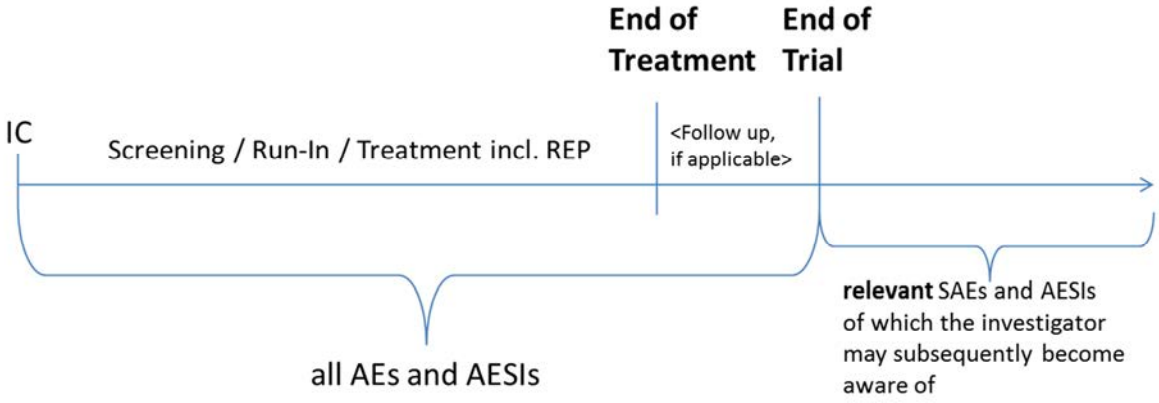
Upon enrolment into a trial, the subject's baseline condition is assessed (for instance, by documentation of medical history/concomitant diagnoses), and relevant changes from baseline are noted subsequently.

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

A 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 eCRF by the investigator:

- From signing the informed consent onwards through the Residual Effect Period (REP), until individual subject's EOT:
  -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 EOT:
  the investigator does not need to actively monitor the subject for AEs but should only report relevant SAEs and relevant AESIs of which the investigator may become aware of.



The REP for BI 1467335, when measurable drug levels or PD effects are still likely to be present after the last administration, is not known at this early stage of development. Therefore, all AEs reported until the trial termination date (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.

1. All SAEs and AESIs must be reported immediately to the head of the trial site.
2. 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 (e)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 eCRF 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 EOT must be followed up until they have resolved, have been sufficiently characterized, or no further information can be obtained.

Pregnancy

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

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

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

5.2.3 Assessment of safety laboratory parameters

A total amount of up to approximately 120 mL blood will be taken per subject during the whole course of the study for safety laboratory parameters. This amount may be exceeded if unscheduled (additional) monitoring including retest of laboratory results is warranted.

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 hours. Overnight fasting is not required at the discretion of the investigator or designate for retests.

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

Manual differential white blood cell count or urine sediment examinations will only be performed if there is an abnormality in the automatic blood cell count or in the urinalysis and it is deemed clinically necessary by the investigator, respectively.

Table 5.2.3: 1 Routine laboratory tests

Functional lab group	Test name
Haematology	Haematocrit Haemoglobin Red blood cell count (RBC) Reticulocyte count White blood cell count (WBC) Platelet count
Automatic WBC differential (relative) [1]	Neutrophils, eosinophils, basophils, monocytes, lymphocytes
Coagulation	Activated partial thromboplastin time (aPTT) Prothrombin time (INR) (ratio) Fibrinogen
Enzymes	Aspartate transaminase (AST/GOT) Alanine transaminase (ALT/GPT) Alkaline phosphatase (ALP) Gamma-glutamyl transferase (GGT/γ-GT) Creatine kinase (CK) CK-MB, only if CK is elevated Lactate dehydrogenase (LDH) Lipase Amylase
Hormones[2]	Thyroid stimulating hormone (TSH)
Substrates	Serum glucose Creatinine Blood Urea Nitrogen (BUN) Total bilirubin Direct bilirubin Total protein Albumin C-Reactive Protein (CRP) Uric acid Total cholesterol Triglycerides
Electrolytes	Sodium Potassium Calcium

Table 5.2.3: 1 Routine laboratory tests (cont.).

Functional lab group	Test name
Urinalysis (strip or dipstick)	Urine nitrite Urine protein Urine glucose Urine ketone Urobilinogen Urine bilirubin Urine erythrocytes Urine leukocytes Urine pH
Urine sediment [3]	Only positive findings will be reported (for instance, the presence of sediment bacteria, casts in sediment, squamous epithelial cells, erythrocytes, leukocytes)

[1] Manual differential white blood cell count will only be performed if there is an abnormality in the automatic blood cell count and it is deemed clinically necessary by the investigator
[2] Only at screening
[3] Only if erythrocytes, leukocytes, nitrite or protein are abnormal in urinalysis and are deemed clinically necessary by the investigator

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.

Table 5.2.3: 2 Exclusionary laboratory tests

Functional lab group	Test name
Drug screening (urine)[1]	Amphetamine/MDA Barbiturates Benzodiazepine Cannabis Cocaine Methadone Methamphetamines/MDMA/XTC Opiates Phencyclidine Tricyclic antidepressants
Infectious serology (blood)[2]	Hepatitis A antibodies (qualitative) Hepatitis B surface antigen (qualitative) Hepatitis B core antibody (qualitative) Hepatitis C antibodies (qualitative) HIV antigen and antibody (qualitative) QuantiFERON TB-Gold (or T-SPOT) Syphilis test (RPR, TP antibody method)
Alcohol test[1]	Breath alcohol test

[1] To encourage compliance with prohibited drug and alcoholic restrictions, urine drug screening and breath alcohol test will be performed at screening and Day -1, and may be repeated at any time during the study at the discretion of an investigator or designee.
[2] At screening only (Visit 1).

Glomerular Filtration Rate

The estimated glomerular filtration rate (eGFR) will be derived from serum creatinine values based on the CKD-EPI formula:

For Japanese:
$eGFR(mL/min/1.73m^2)$
$= 0.813 \times 141 \times \min(SCr/0.9, 1)^{-0.411} \times \max(SCr/0.9, 1)^{-1.209} \times 0.993^{Age}$

For Caucasian:
$eGFR(mL/min/1.73m^2)$
$= 141 \times \min(SCr/0.9, 1)^{-0.411} \times \max(SCr/0.9, 1)^{-1.209} \times 0.993^{Age}$

SCr is serum creatinine in mg/dL, min indicates the minimum of SCr/0.9 or 1, and max indicates the maximum of SCr/0.9 or 1.

The laboratory tests listed in Tables 5.2.3: 1 and 5.2.3: 2 will be performed by the local laboratory of the trial site or/and at a CRO designated by the sponsor.

Laboratory data will be transmitted electronically from the site to the sponsor.

5.2.4 Electrocardiogram

Twelve-lead resting ECGs (I, II, III, aVR, aVL, aVF, V1 - V6) will be recorded using a FDA approved ECG machine 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 ECGSs will be recorded for 10 second 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 to avoid impact of sampling on the ECG quality.

Six limb leads, as specified by Einthoven (I, II and III) and Goldberger (aVR, aVL, aVF), and six pre-cordial leads (V1-V6), according to Wilson, will be used.

Triple sequential ECGs 1 to 3 minutes apart will be recorded on Day 1 and Day 2, Day 14 and Day 15, Day 28 and Day 29. At all other time points single ECGs will be recorded.

ECG data will be collected in two ways: locally printed ECGs and digitally recorded ECGs.

Printed paper traces from ECGs will be collected at clinical sites. All ECGs will be evaluated, signed, dated and commented upon by the investigator and stored locally.

A centralised evaluation (during study and/or post study) of 12-lead ECGs recorded will be performed by an independent ECG laboratory. This analysis will include the determination of cardiac axis (automatically) as well as the intervals RR, PR, QRS and QT measured semi-automatically.

With the exception of the first triple ECG (used as baseline before the first drug administration), only the first of the three replicate ECGs at a single assessment time will be evaluated. The remaining second and third replicate ECGs will be stored for additional analyses if required, e.g. by authorities at a later time point.

All interval measurements in one subject will be performed on the same lead. The intervals will be measured from four waveforms in lead II. If lead II shows a flat T wave or is not measurable for any reason, lead V2 will be used, or if that lead is not measurable, lead I. The lead actually used will be reported. At the ECG laboratory all staff will be blinded with respect to treatment. Within the ECG laboratory, the staff involved with interval measurements and assessments will also be blinded with regard to the recording date and time as well as time points of the ECGs. In case semi-automatic interval measurements will be performed, the interval measurements for a given subject will be performed in random and blinded sequence by a single technician. No more than two different blinded readers will evaluate all ECGs of the study. For quality assurance and control of the measurements, all ECGs of a subject will be subsequently reviewed by the ECG technician supervisor or his/her designee with respect to the overall variance of the measured intervals, in order to detect accidentally switching of leads and/or false subject assignments of the ECGs. After the quality control the fiducial point markings will be reviewed by the cardiologist assigned to the study.

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. If ECGs are repeated for quality reasons, data from ECG with the best quality will be collected. However, all ECGs including the ECGs with poor quality will be kept as documentation to comply with ICH E14 guidance.

ECG measurements will always precede blood sampling to avoid impact of sampling on the ECG results.

Clinically relevant abnormal findings as judged by the investigator will be reported as AEs (during the trial) or baseline conditions (at screening) in the eCRF. 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.

Additional (unscheduled) ECGs can be collected for safety reasons at any time based on the judgement of the investigator. The unscheduled ECGs will not be included into the planned analysis of interval lengths.

5.2.5 Assessment of other safety parameters

5.2.5.1 Vital signs

Systolic and diastolic blood pressures (BP) as well as pulse rate (PR) or heart rate (heart rate is considered to be equal to pulse rate) will be measured by a blood pressure monitor 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 the screening visit, the medical examination will include documentation of subject information, informed consent, demographics including height and body weight, smoking and alcohol history, relevant medical history and concomitant therapy, review of inclusion and exclusion criteria, review of vital signs (BP, PR), 12-lead ECG, laboratory tests, and a physical examination. At the end of trial examination, it will include review of vital signs, 12-lead ECG, laboratory tests, and a physical examination with determination of weight.

5.2.5.3 Ophtalmological examination

A slit lamp examination will be conducted by an ophthalmologist during screening or until Day -1 and from Day 29 to EOT visit to exclude findings suspicious for signs of cataract.

5.4 APPROPRIATENESS OF MEASUREMENTS

All measurements performed during this trial are standard measurements and will be performed in order to monitor subjects' safety and to determine pharmacokinetic parameters in an appropriate way. The scheduled measurements will allow monitoring of changes in vital signs, standard laboratory values, and ECG parameters that might occur as a result of administration of trial medication. The safety assessments are standard, are accepted for evaluation of safety and tolerability of a study 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.

5.5 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

Date and clock time of drug administration and exact time points of blood sampling will be documented in the CRFs by the medical personnel. The actual drug administration times and 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 400 mL. Such changes might be implemented via non-substantial CTP Amendments.

5.5.1 Pharmacokinetic endpoints

The following pharmacokinetic parameters will be determined if feasible:

5.5.1.1 Secondary endpoints

After the first dose (Day 1):

- AUC_{0-24} (area under the concentration-time curve of the analyte in plasma over the time interval from 0 to 24 hours after administration of the first dose)
- C_{max} (maximum measured concentration of the analyte in plasma after administration of the first dose)

After the last dose (Day 28):

- $AUC_{0-24,28}$ (area under the concentration-time curve of the analyte in plasma over the time interval from 0 to 24 hours after administration of Day 28)

- $C_{max,28}$ (maximum measured concentration of the analyte in plasma following administration of Day 28)

5.5.2 Methods of sample collection

5.5.2.1 Plasma sampling for pharmacokinetic analysis

For quantification of BI 1467335 plasma concentrations, approximately mL of blood will be taken from an antecubital or forearm vein into 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.

will be added to all blood samples. Gently invert samples about 10 times to ensure the phenelzine solution is mixed through blood. All blood samples will be centrifuged using a cooled centrifuge at about 2000 x g to 4000 x g and at a temperature of 4 - 8°C for at least 10 minutes (intermittent storage on ice). The obtained EDTA plasma will be transferred into a cryotube (e.g. Nunc tube) which will be frozen immediately and not later than 60 min after blood sampling with interim storage on ice. The aliquots should contain at least mL plasma. Until transfer on dry ice to the analytical laboratory, the plasma samples will be stored frozen and in upright position at about –20°C or below at the clinical site and at the analytical laboratory until analysis.

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

All visits must be performed as specified in Flow Chart. The investigator/sponsor can decide to perform an unscheduled visit if deemed necessary for any valid reasons.

Further details of measurement performed during the study are specified under Section 5.

Time windows are permitted as follows:

- General medical examination: at screening (1 to 21 days prior to Day1) and at the end-of-trial evaluation (within 14 to 20 days after last drug administration).
- BP and PR: ±15 min (0:30, 0:45, 1:00, 2:00) and ±30 min (4:00, 8:00, 12:00) on Day 1, Day 14 and Day 28, ±60 min on other days and up to 3 hours prior to drug administration if indicated "before drug administration"
- ECG: ±15 min (0:15, 0:30, 0:45, 1:00, 1:30, 2:00) and ±30 min (4:00, 8:00, 12:00) on Day 1, Day 14 and Day 28, ±60 min on other days.
  ECGs on Day 1, 2, 14, 15, 28 and 29: for the second and third ECG a time interval of 1-3 min between ECGs should be maintained
- Laboratory/urinalysis: Up to 3 hours prior to drug administration if indicated "before drug administration". Urinalysis test can be done up to 3 hours prior to drug administration at some other time points indicated in the flow chart.
- Pharmacokinetic blood sampling for predose concentration in multiple dose part: ±5 min (has to be done before drug administration)

Other pharmacokinetic blood sampling / urine collection: For planned individual plasma concentration sampling times refer to Flow Chart. While these nominal times should be adhered to as closely as possible, the actual sampling times will be recorded and used for the calculation of pharmacokinetic parameters.

The designation "before" on Day 1 refers to the time period of 3 hours before drug administration (see Flow Chart), i.e., study measurements and assessments scheduled to occur "before" have to be performed and completed within 3 hours prior to drug administration.

Relevant time violations will be identified and their handling discussed no later than at the (B)RPM.

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

6.2.1 Screening

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.

If a subject is eligible but has missed the screening window, or if a subject has been excluded from participation in this trial due to acute conditions which completely resolved, the subject can be re-screened. At re-screening, all procedures listed for Visit 1 in the Flow chart will be repeated.

6.2.2 Treatment period

Each subject will receive one dose of the respective dose strength per day at visit 2. On the morning of the treatment day, study drug will be taken by the subject (under direct supervision of the investigator or designee).

The measurements performed during the treatment period are specified under Flow Chart and. Section 5.2. For time points and instructions for ECG measurements cf. Flow Chart and Section 5.2.4.

For details on time points for collection of plasma PK samples for analysis, cf. Flow Chart.

For details on time points for all other trial procedures, cf. Flow Chart.

6.2.3 End of trial and follow-up period

For AE assessment, laboratory tests, recording of ECG, vital signs and body weight, and physical examination during the EOT 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 EOT 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. All (S)AEs, including those persisting after individual subject's end of trial must be followed up until they have resolved, have been sufficiently characterized, or no further information can be obtained.

In the case of a subject's discontinuation from the trial, the subject will be followed-up until the investigator or sub-investigator is convinced of the subject's safety. When follow-up is not possible or comes to an end, it should be formally completed after discussion with the sponsor. If a subject stops attending trial assessments, the investigator should assess the subject's status as comprehensively as possible and the well-being of the subject should be monitored. However, if the subject withdraws from the trial, it is the subject's choice whether or not to participate; he or she cannot be compelled.

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

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 STATISTICAL DESIGN – MODEL

7.1.1 Objectives

The primary objective of this trial is to investigate the safety and tolerability of BI 1467335 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 1467335. Endpoints as specified in 5.5.1 and 5.6.1 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.

The assessment of dose proportionally will be performed for Japanese subjects only.

7.2 NULL AND ALTERNATIVE HYPOTHESES

Safety and tolerability of 3 different dose groups of BI 1467335 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.

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

7.3 PLANNED ANALYSES

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

7.3.1 Primary analyses

All treated subjects (that is, all subjects who received at least one dose of study drug), will be included in the treated set.

The primary endpoint will be analysed only descriptively on the treated set. For more details see Section 7.3.3.

The secondary endpoints (refer to Section 5.5.1.1) will be calculated according to the BI Standard Operating Procedure (SOP) 'Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics' [001-MCS-36-472].

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

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

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

- the subject experienced emesis that occurred at or before two times median t_{max} of the respective treatment (Median t_{max} is to be determined excluding the subjects experiencing emesis),
- missing samples/concentration data at important phases of PK disposition curve.

The PK parameter analysis set (PKS) includes all subjects in the Treated Set (TS) who provide at least one PK parameter that was not excluded according to the description above. All statistical evaluations of PK parameters will be based on 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.

Assessment of dose proportionality

Dose proportionality will be assessed using the pharmacokinetic endpoints AUC_{0-24}, C_{max}, $AUC_{0-24,28}$ and $C_{max,28}$ as specified in Section 5.5.1.1.

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

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

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

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

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

where

Y_{ij}	logarithm of the pharmacokinetic endpoint for subject j at dose level i; where i = 1, 2, 3, j = 1, 2, …, 12;
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.

Graphical displays

To support the analyses of dose proportionality, linearity
graphical representations of the data might be created. These might include (but are not limited to) individual time-courses of trough and 0.5 h, 1 h post-dose plasma concentrations and the (geometric) mean plasma concentration time profiles.

7.3.3 Safety analyses

Safety will be assessed for the primary endpoint and parameter of interest listed in Section 5.2.1. All treated subjects (that is, all subjects who received at least one dose of study drug), will be included in the safety 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 trial termination date will be assigned to the treatment period. These assignments including the corresponding time intervals will be defined in detail in the TSAP.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Frequency, intensity according to CTCAE grading and causal relationship of AEs will be tabulated by treatment, primary 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 will be flagged. Additionally, differences from baseline will be evaluated.

For vital signs, the differences from baseline will be evaluated.

The derivation of the quantitative and qualitative ECG endpoints and their analyses will be described in the TSAP.

7.3.4 Interim analysis

No formal interim analysis is planned for this trial.

The data will be evaluated as they accumulate in an un-blinded manner. See Section 4.1.5.1 for unbinding procedure.

In addition, although no formal interim clinical trial report will be produced, a limited set of tables and listings may be provided, as basis for regulatory documents. Snapshots of the database may be taken at any time during the study conduct.

Preliminary PK analysis

Preliminary analysis of plasma PK parameters (AUC_{0-24}, $C_{max,}$ $AUC_{0-24,28}$ and $C_{max,28}$) are planned to be performed. Additional preliminary PK analyses may be performed based on the request of the Trial Clinical Monitor, the Investigator, or Trial Clinical Pharmacokineticist if deemed necessary based on the results of available preliminary PK analyses, tolerability and safety of the compound, or changes of dosing schedule (e.g. additional intermediate doses).

After the 6 mg dose group have been treated for 28 days, all plasma samples collected up to 24 hours after drug administration of Day 28 will be analysed, and the data will be used for extrapolation of C_{max} and AUC_{0-24} on days 14 and 28 with higher dose of BI 1467335.

In contrast to the final PK calculations, the preliminary analyses will be based on planned sampling times rather than on actual times. Therefore, minor deviations of preliminary and final results may occur.

The preliminary results will be distributed to the Investigator and the trial team. The PK data together with safety and tolerability results will be used for decisions to continue with treatments as described in Section 2.3. No formal preliminary PK report will be written.

7.3.5 Pharmacokinetic analyses

The pharmacokinetic parameters listed in Section 5.5.1 for drug BI 1467335 will be calculated according to the BI SOP ‘Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics’ [001-MCS-36-472].

Noncompartmental pharmacokinetic parameters will be calculated based on actual sampling times using a validated pharmacokinetic software (e.g. Phoenix® WinNonlin®).

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, pharmacokinetic parameters or other statistical assessment.

Only concentration values within the validated concentration range and actual sampling times will be used for the calculation of pharmacokinetic parameters. Concentrations used in the pharmacokinetic calculations will be in the same format provided in the bioanalytical report.

Descriptive evaluations of PK parameters listed in Section 5.5.1.2 are based on PKS.

The following descriptive statistics will be calculated for analyte concentrations as well as for all pharmacokinetic parameters: N, geometric mean, geometric coefficient of variation, arithmetic mean, arithmetic coefficient of variation, standard deviation, minimum, median, and maximum. Additionally, for PK parameters, the following descriptive statistics will be calculated: 10^{th} percentile, 1^{st} quartile, 3^{rd} quartile and 90^{th} percentile. The data format for descriptive statistics of concentrations will be identical with the data format of the respective concentrations. The descriptive statistics of pharmacokinetic parameters will be calculated using the individual values with the number of decimal places as provided by the evaluation program. Then the individual values as well as the descriptive statistics will be reported with three significant digits in the clinical trial report.

In addition, the PK data from this study may be included in a population PK analysis at the project level. This analysis will not be part of the CTR, but will be reported separately.

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/urine drug concentration - time profile

Handling of missing PK data will be performed according to the relevant SOP of the Sponsor [001-MCS-36-472_RD-01].

If the pre-dose concentration before the first dose is less than or equal to 5% of C_{max} value in that subject, the subject's data without any adjustments can be included in all pharmacokinetic measurements and calculations (i.e. the pre-dose value will not be changed to zero). If the pre-dose value is greater than 5% of C_{max}, the subject should be dropped from all statistical evaluations. The individual pharmacokinetic parameters can be calculated and listed separately.

For tabulation and graphical displays, drug concentration data identified with NOS (no sample available), NOR (no valid result), NOA (not analysed), or BLQ (below the lower limit of quantification) 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).

For the calculation of PK parameters by 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 will be set to zero. All other BLQ 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.

7.4.3 Pharmacokinetic parameters

No imputation of missing PK parameters will be performed.

7.5 RANDOMISATION

Subjects will be randomised within each dose group within each ethnicity in a 3:1 ratio, which reflects the ratio of subjects receiving active drug to placebo.

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

It is planned to include a total of 48 subjects in this trial (i.e., 36 Japanese subjects and 12 Caucasian subjects). The planned sample size is not based on a power calculation. The size of 12 subjects per dose group per ethnicity (9 on active treatment, and 3 on placebo) is commonly used in multiple-rising dose studies of the present type and is in general considered as sufficient for the exploratory evaluation of multiple dose safety and pharmacokinetics [R95-0013].

Additional subjects may be entered to allow testing of additional doses within the planned dose range on the basis of experience gained during trial conduct (e.g. preliminary PK data), i.e. the actual number of subjects entered may exceed 48.

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), relevant BI Standard Operating Procedures (SOPs) and the Japanese GCP regulations (Ministry of Health and Welfare Ordinance No. 28, March 27, 1997).
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 and the Japanese GCP regulations (Ministry of Health and Welfare Ordinance No. 28, March 27, 1997).

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

The certificate of insurance cover is made available to the Investigator and the subjects, and is stored 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) and competent authority (CA) according to Japanese 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 Investigator must give a full explanation to trial subjects by using the subject information form, which is prepared avoiding the use of technical terms and expressions. The subject is given sufficient time to consider participation in the trial. The Investigator obtains written consent of the subject's own free will with the informed consent form after confirming that the subject understands the contents. The Investigator must sign (or place a seal on) and date the informed consent form. If a trial collaborator has given a supplementary explanation, the trial collaborator also signs (or places a seal on) and dates the informed consent.

Re-consenting may become necessary when new relevant information becomes available and should be conducted according to the sponsor's instructions.
The subject must be informed that his personal trial-related data will be used by Boehringer Ingelheim in accordance with the local data protection law. The level of disclosure must also be explained to the subject.

The subject must be informed that his 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 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, 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

Electronic Case Report Forms (eCRFs) for individual subjects will be provided by the sponsor. See Section 4.1.5.2 for rules about emergency code breaks. For drug accountability, refer to Section 4.1.8.

8.3.1 Source documents

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

Data entered in the eCRFs that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained.

The investigator may need to request previous medical records or transfer records, depending on the trial; also current medical records must be available.

For eCRFs all data must be derived from source documents.

8.3.2 Direct access to source data and documents

The investigator / institution will permit trial related monitoring, audits, IRB review and regulatory inspection, providing direct access to all related source data / documents. eCRFs and all source documents, including progress notes 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 (CRA) / on

site monitor and auditor may review all eCRFs, 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 documents and essential documents for a period defined by the Japanese GCP regulation and trial site's contract with the sponsor.

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 given 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.

8.6 COMPLETION OF TRIAL

When the trial is completed, the investigator should inform the head of the trial site of the completion in writing, and the head of the trial site should promptly inform the IRB and sponsor of the completion in writing.

8.7 PROTOCOL VIOLATIONS

The investigator or sub-investigator should record all CTP violations. The investigator should provide and submit the sponsor and the head of the trial site the records of violations infringing the Japanese GCP or violations to eliminate an immediate hazard to trial subjects and for other medically inevitable reasons.

8.8 COMPENSATION AVAILABLE TO THE SUBJECT IN THE EVENT OF TRIAL RELATED INJURY

In the event of health injury associated with this trial, the sponsor is responsible for compensation based on the contract signed by the trial site.

9. REFERENCES

9.1 PUBLISHED REFERENCES

R10-4848 Common terminology criteria for adverse events (CTCAE): version 4.0 (NIH publication no. 09-5410, published: May 28, 2009 (v4.03: June 14, 2010), revised June 2010, reprinted June 2010). http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf; 2010.

P13-02280 Torres DM, Williams CD, Harrison SA. Features, diagnosis, and treatment of nonalcoholic fatty liver disease. Clin Gastroenterol Hepatol. 2012; 10:837-58.

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

R15-1863 Inoue T, Morita M, Tojo T, Nagashima A, Moritomo A, Miyake H. Novel 1H-imidazol-2-amine derivatives as potent and orally active vascular adhesion protein-1 (VAP-1) inhibitors for diabetic macular edema treatment. Bioorg. Med. Chem. 2013; 21:3873-3881.

R15-1868 Foot JS, Deodhar M, Turner CI, et al. The discovery and development of selective 3-fluoro-4-aryloxyallylamine inhibitors of the amine oxidase activity of semicarbazide-sensitive amine oxidase/vascular adhesion protein-1 (SSAO/VAP-1). Bioorg. Med. Chem. Lett. 2012; 22:3935.

R15-2803 Stolen CM, Marttila-Ichihara F, Koskinen K, et al. Absence of the endothelial oxidase AOC3 leads to abnormal leukocyte traffic in vivo. Immunity. 2005; 22:105-115.

R15-5365 Weston CJ, Shepherd EL, Claridge LC et al. Vascular adhesion protein-1promotes liver inflammation and drives hepatic fibrosis. Journal of Clinical Investigation. 2015; 125:501-520.

R15-5652 Bonder CS, Norman MU, Swain MG, et al. Rules of recruitment for Th1 and Th2 lymphocytes in inflamed liver: a role for alpha-4 integrin and vascular adhesion protein-1. Immunity 2005; 23:153-163.

R15-5654 Koskinen K, Vainio PJ, Smith DJ, et al. Granulocyte transmigration through the endothelium is regulated by the oxidase activity of vascular adhesion protein-1 (VAP-1). Blood. 2004; 103: 3388-3395.

R15-6044 Chalasani N, Younossi Z, Lavine JE, et al. The diagnosis and management of non-alcoholic fatty liver disease: practice guideline by the American Association for the Study of Liver Diseases, American College of Gastroenterology, and the American Gastroenterological Association Hepatology. 2012; 55:2005-2023.

R15-6045 Marttila-Ichihara F, Smith DJ, Stolen C, et al. Vascular amine oxidases are needed for leukocyte extravasation into inflamed joints in vivo. Arthritis Rheum. 2006; 54:2852.

R15-6046 Lalor PF, Edwards S, McNab G, et al. Vascular adhesion protein-1 mediates adhesion and transmigration of lymphocytes on human hepatic endothelial cells. J. Immunol. 2002; 169: 983.

R15-6047 Salter-Cid LM, Wang E, O'Rourke AM, et al. Anti-inflammatory effects of inhibiting the amine oxidase activity of semicarbazide-sensitive amine oxidase. J. Pharmacol. Exp. Ther. 2005; 315: 553.

R15-6048 Xu HL, Salter-Cid L, Linnik MD, Wang EY, Paisansathan C and Pelligrino DA. Vascular adhesion protein-1 plays an important role in post ischemic inflammation and neuropathology in diabetic, estrogen-treated ovariectomized female rats subjected to transient forebrain ischemia. J. Pharmacol. Exp. Ther. 2006; 317:19.

R15-6056 O'Rourke AM, Wang EY, Miller A, Podar EM, et al. Anti-inflammatory effects of LJP 1586 [Z-3-fluoro-2-(4-methoxybenzyl)allylamine hydrochloride], an amine-based inhibitor of semicarbazide-sensitive amine oxidase activity. J. Pharmacol. Exp. Ther. 2008; 324: 867.

R15-6057 Murphy SL, Xu J and Kochanek KD. Deaths: final data for 2010. Centers for Disease Control and Prevention website: www.cdc.gov/nchs/data/nvsr/nvsr61/nvsr61_04.pdf (Updated May 8, 2013. Accessed February 6, 2014).

R15-6058 Merinen M, Irjala H, Salmi M, Jaakkola I, Hanninen A, Jalkanen S. Vascular adhesion protein-1 is involved in both acute and chronic inflammation in the mouse. Am J Pathol. 2005;166:793-800.

R15-6059 Lee WY, Salmi M, Kelly MM, Jalkanen S and Kubes P (2013) Therapeutic advantage of anti-VAP-1over anti-α4 integrin antibody in concanavalin Ainduced hepatitis. Hepatology 2013; 58:1413.

R15-6070 Dharel N, Fuchs M. Nonalcoholic Fatty Liver Disease – A Major Public Health Challenge for the 21st Century. JSM Gastroenterology and Hepatology. 2014; 1018.

9.2 UNPUBLISHED REFERENCES

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

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

001-MCG-420 Statistical Methods for Pharmacokinetics. Current version.

c04751792-03 Investigator's Brochure: BI 1467335 in NASH version 3. 05 Dec 2016.

c08854973-03 . Safety, tolerability, pharmacokinetics and pharmacodynamics of multiple rising oral doses of BI 1467335 in healthy male and female subjects.1386.8. 13 Jul 2016.

c09036683-01 Single ascending dose and multiple ascending dose Phase 1 study of PXS-4728A administered orally in healthy adult males. PXS-4728A-101. 13 Nov 2015.

n00247850 A Four-Week Oral Repeat Dose Toxicity and Toxicokinetic Study of PXS-4728A in Beagle Dogs. Pharmaron Study Number 53703-13-825. 04 Apr 2014.

10. APPENDICES

Not applicable

11. DESCRIPTION OF GLOBAL AMENDMENTS

This is original protocol.

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

APPROVAL / SIGNATURE PAGE

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Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Author-Clinical Pharmacokineticist		12 May 2017 03:57 CEST
Author-Trial Clinical Monitor		12 May 2017 04:01 CEST
Author-Trial Statistician		12 May 2017 04:47 CEST
Approval-Therapeutic Area		12 May 2017 06:41 CEST
Approval-Team Member Medicine		12 May 2017 13:53 CEST
Verification-Paper Signature Completion		15 May 2017 02:51 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed