Clinical Trial Protocol

	Document Number: c19596566-03
EudraCT No.:	2017-003853-41
BI Trial No.:	1386-0019
BI Investigational Product:	BI 1467335
Title:	A phase I, open-label, single-arm multiple dose trial to investigate pharmacokinetics and absolute bioavailability of BI 1467335 administered as an oral dose simultaneously with an intravenous microtracer dose of [C-14] BI 1467335 after single and multiple oral doses in healthy male volunteers
Lay Title:	This study in healthy men tests how the body takes up BI 1467335
Clinical Phase:	I
Trial Clinical Monitor:	Phone: Fax:
Principal Investigator:	Phone: Fax:
Status:	Final Protocol (Revised Protocol (based on global amendment 2))
Version and Date:	Version: 3.0 Date: 24 April 2018

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: 16 February 2018	**Trial number:** 1386-0019		**Revision date:** 24 April 2018

Title of trial:	A phase I, open-label, single-arm multiple dose trial to investigate pharmacokinetics and absolute bioavailability of BI 1467335 administered as an oral dose simultaneously with an intravenous microtracer dose of [C-14] BI 1467335 after single and multiple oral doses in healthy male volunteers
Principal Investigator:	
Trial site:	
Clinical phase:	I
Objectives:	To investigate the pharmacokinetics and absolute bioavailability of BI 1467335 with an intravenous formulation containing labelled [C-14] BI 1467335 and an unlabelled oral tablet formulation of BI 1467335 in healthy male subjects
Methodology:	Non-randomised, open-label, single arm multiple dose design
No. of subjects:	
total entered:	12
each treatment:	At least 10 enrolled subjects, maximum 12 enrolled subjects
Diagnosis:	Not applicable
Main criteria for inclusion:	Healthy male subjects, age of 18 to 65 years, body mass index (BMI) of 18.5 to 29.9 kg/m^2
Test product 1 (T1):	BI 1467335 film-coated tablet formulation
dose:	10 mg of free base (2 x 5 mg) QD
mode of admin.:	Oral with 240 mL of water

Name of company: Boehringer Ingelheim		**Tabulated Trial Protocol**	
Name of finished product: Not applicable			
Name of active ingredient: BI 1467335			
Protocol date: 16 February 2018	**Trial number:** 1386-0019		**Revision date:** 24 April 2018

Test product 2 (T2):	Unlabelled BI 1467335 mixed with Carbon 14 labelled BI 1467335 [BI 1467335 (C-14)] as an intravenous infusion
dose:	– On Day 1 50 µg infusion consisting of 41.15 µg unlabelled BI 1467335 free base (= 46.50 µg salt) mixed with 8.85 µg [C-14] BI 1467335 free base (=10 µg salt) in 10 mL solution (5 µg BI 1467335 (C-14) free base /mL) – On Day 28 50 µg infusion consisting of 45 µg unlabelled BI 1467335 free base (=50,85 µg salt) mixed with 5 µg [C-14] BI 1467335 free base (=5,65 µg salt) in 10 mL solution (5 µg BI 1467335 (C-14) free base /mL) The radioactive dose per infusion has been selected to not exceed 2.7 µCi=0.1 MBq.
mode of admin.:	Intravenous infusion
Comparator product:	Not applicable
Duration of treatment:	Intravenous dose (reference): A single15 minutes intravenous infusion of the microtracer on Day 1 and Day 28. Oral dose (test): Non-radiolabelled film-coated tablets once a day from Day 1 to Day 28 (treatment duration 28 days)
Criteria for pharmacokinetics:	*Primary endpoints:* After the first dose: C_{max} and $AUC_{0-\infty}$ of BI 1467335 (after intravenous and oral administration) on Day 1 After multiple doses: $C_{max,\,28}$ and $AUC_{0-24,\,28}$ of BI 1467335 (after oral administration) on Day 28; $C_{max,\,28}$ and $AUC_{0-\infty,\,28}$ of BI 1467335 (after intravenous administration) on Day 28. *Secondary endpoints:* Assessment of the oral pharmacokinetics following intravenous treatment with a microtracer of [C-14] BI 1467335 and a treatment with BI 1467335film-coated tablets in plasma: Oral: t_{max}, $t_{max,28}$, $t_{1/2}$ IV: CL, CL_{28}, V_z, $V_{z,28}$, t_{max}, $t_{max,28}$, $t_{1/2}$, $t_{1/2,28}$ Further pharmacokinetic assessments will be included as appropriate based on emerging data.

Name of company: Boehringer Ingelheim		**Tabulated Trial Protocol**	
Name of finished product: Not applicable			
Name of active ingredient: BI 1467335			
Protocol date: 16 February 2018	**Trial number:** 1386-0019		**Revision date:** 24 April 2018
Criteria for safety:	Adverse events (AEs) including clinically relevant findings from the physical examination, safety laboratory tests, 12-lead electrocardiogram (ECG), vital signs (blood pressure [BP], pulse rate [PR])		
Statistical methods:	Absolute bioavailability (F) will be estimated by the ratio of the geometric means (tablet/infusion) for the dose normalized primary endpoints separately for Day 1 and Day 28. Additionally, its two-sided 90% confidence interval (CI) will be provided. This method corresponds to the two one sided t-tests procedure, each at the 5% significance level. Since the main focus is on estimation and not testing, an acceptance range was not specified. The statistical model will be an ANOVA on the logarithmic scale including the fixed effect for 'formulation' and 'subject' as a random effect. CIs will be calculated based on the residual error from ANOVA. In addition, the absolute bioavailability factor F will be calculated for each subject on Day 1 and Day 28. Descriptive statistics will be calculated for all endpoints.		

FLOW CHART

Visit	Day	Planned time (relative to first oral drug administration [h:min]	Approximate clock time of actual day [h:min]	Event and comment	Safety laboratory	PK_{plasma}	PK_{plasma} [C-14]BI1467335	12-lead ECG	Vital signs (BP, PR)	Questioning for AEs and concomitant therapy
1	-21 to -2			Screening (SCR)[1]	x			x	x	
2	-1	-18:00	14:00	Admission to trial site	x[5]					↕
	1	-2:00	06:00		x[2, 4]	x[2, 8]	x[2]	x[2]	x[2]	
		0:00	08:00	Drug administration (film coated tablet of BI 1467335)						
		0:15	08:15			x				
		0:30	08:30			x				
		0:45	08:45			x				
		1:00	09:00	Start of 10 mL 50 µg infusion consisting of 41.15 µg unlabelled BI 1467335 and 8.85 µg [C-14] BI 1467335						
		1:05	09:05			x	x			
		1:15	09:15	End of infusion			x			
		1:25	09:25			x	x			
		1:35	09:35				x			
		1:45	09:45				x			
		2:00	10:00	240 mL water intake		x	x	x		
		2:15	10:15				x			
		2:45	10:45				x			
		3:00	11:00			x				
		3:15	11:15				x			
		3:45	11:45				x			
		4:00	12:00	Lunch, 240 mL water intake[3]		x				
		4:15	12:15				x			
		4:45	12:45				x			
		5:15	13:15				x			
		6:00	14:00			x				
		6:15	14:15				x			
		7:15	15:15				x[10]			
		8:00	16:00			x				
		8:15	16:15				x[10]			
		9:15	17:15				x[10]			
		10:00	18:00	Dinner[3]						
		13:00	21:00				x[10]			
	2	24:00	08:00	Dispense of study medication				x	x	
		25:00	09:00	Discharge from trial site[7]			x[10]			↕

Visit	Day	Planned time (relative to first oral drug administration [h:min]	Approximate clock time of actual day [h:min]	Event and comment	Safety laboratory	PK_{plasma}	PK_{plasma} [C-14]BI1467335	12-lead ECG	Vital signs (BP, PR)	Questioning for AEs and concomitant therapy
2	6	132:00	20:00	Admission to trial site	x[5]					↑
	7	144:00	08:00	Dispense of study medication, discharge[7]		x[2]		x[2]	x[2]	
	13	300:00	20:00	Admission to trial site	x[5]					
	14	312:00	08:00	Dispense of study medication, discharge[7]	x[2]	x[2]		x[2]	x[2]	
	20	468:00	20:00	Admission to trial site	x[5]					
	21	480:00	08:00	Dispense of study medication, discharge[7]		x[2]		x[2]	x[2]	
	25	582:00	14:00	Admission to trial site[11]	x[5]				x	
	26	600:00	08:00	Drug administration (film coated, of BI 1467335)						
	27	624:00	08:00	Drug administration (film coated, of BI 1467335)						
	28	646:00	06:00		x[2, 4]			x[2]	x[2]	
		647:55	07:55			x	x			
		648:00	08:00	Drug administration (film coated, of BI 1467335)						
		648:15	08:15			x				
		648:30	08:30			x				
		648:45	08:45			x				
		649:00	09:00	Start of 10 mL 50 µg infusion consisting of 45 µg unlabelled BI 1467335 and 5 µg [C-14] BI 1467335						
		649:05	09:05			x	x			
		649:15	09:15	End of infusion			x			
		649:25	09:25			x	x			
		649:35	09:35				x			
		649:45	09:45				x			
		650:00	10:00	240 mL water intake		x	x			
		650:15	10:15				x			
		650:45	10:45				x			
		651:00	11:00			x				
		651:15	11:15				x			
		651:45	11:45				x			
		652:00	12:00	Lunch, 240 mL water intake[3]		x				
		652:15	12:15				x			
		652:45	12:45				x			
		653:15	13:15				x			
		654:00	14:00			x				
		655:15	15:15				x			
		656:00	16:00			x				
		657:15	17:15				x			
		658:00	18:00	Dinner[3]		x				↓

Visit	Day	Planned time (relative to first oral drug administration [h:min]	Approximate clock time of actual day [h:min]	Event and comment	Safety laboratory	PK_{plasma}	PK_{plasma} [C-14]BI1467335	12-lead ECG	Vital signs (BP, PR)	Questioning for AEs and concomitant therapy
2	28	660:00	20:00			x		x	x	↕
		661:00	21:00				x			
	29	672:00	08:00			x				
		673:00	09:00				x			
	30	697:00	09:00		x		x	x	x	
	32	745:00	09:00	Discharge from trial site			x			
3	33-40			End of trial (EOT) examination[6, 9]	x			x	x	x

1. Screening includes subject information, informed consent, physical examination, check of vital signs, ECG, safety laboratory (including drug and virus screening), demographics (including determination of body height and weight, BMI, smoking status and alcohol history), relevant medical history, concomitant therapy and review of inclusion/exclusion criteria.
2. The time is approximate; the procedure is to be performed within a time window of 3 h prior to drug administration. After start of treatment, further PK blood sampling (trough level) within 30 minutes before next scheduled dosing.
3. If several actions are indicated at the same time point, the intake of meals will be the last action.
4. Subjects are to be fasted for at least 10 h before sample is taken.
5. Only urine drug and alcohol screening will be done at this time point.
6. End-of-trial (EOT) examination to be performed on Day 34-41, EOT examination includes physical examination, vital signs, ECG, safety laboratory, recording of AEs and concomitant therapies.
7. On Days 3 to 6, 8 to 13, 15 to 20 and 22 to 25, subjects are allowed to take their study medication at home if deemed appropriate by the investigator. Compliance of medication intake will be monitored by subject diary and daily phone contact between subject and site. The scheduled time for drug intake throughout the study is 08:00 (applies for intake at home and at the trial site).
8. Pharmacogenomic sample.
9. For definition of the individual subject's end of trial see Section 6.2.3.
10. Samples for an individual subject beyond 5 h after end of infusion will be only analyzed if for this subject the plasma level of [C-14]BI 1467335 at this time point (i.e., 6:15) is still above LOQ.
11. Subjects will be hospitalized from admission on Day 25 to Day 32.

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ABBREVIATIONS

ADME	Absorption, Distribution, Metabolism and Excretion
AE	Adverse event
AESI	Adverse events of special interest
ALT	Alanine amino transferase
AMS	Accelerator mass spectrometry
ANOVA	Analysis of variance
AST	Aspartate amino transferase
$AUC_{0-\infty}$	Area under the concentration-time curve of the analyte over the time interval from 0 extrapolated to infinity
AUC_{0-24h}	Area under the concentration-time curve of the analyte over the time interval from 0 to 24
AUC_{0-tz}	Area under the concentration-time curve of the analyte over the time interval from 0 to the last quantifiable data point
AUC_{t1-t2}	Area under the concentration-time curve of the analyte in plasma over the time interval from time point t1 to t2
$\%AUC_{tz-\infty}$	Percentage of $AUC_{0-\infty}$ obtained by extrapolation
AUC_{τ}	Area under the concentration-time curve of the analyte over the time interval from 0 to interval tau
BI	Boehringer Ingelheim
BLQ	Below limit of quantification
BMI	Body mass index (weight divided by height squared)
BP	Blood pressure
[C-14]BI 1467335	[14C]-labelled BI 1467335
CA	Competent authority
CI	Confidence interval
CL/F	Apparent clearance of the analyte after extravascular administration
C_{max}	Maximum measured concentration of the analyte
CML	Clinical Monitor Local
CRA	Clinical Research Associate
CRF	Case report form
CRO	Clinical Research Organization
CTCAE	Common Terminology Criteria for Adverse Events
CTP	Clinical trial protocol
CTR	Clinical trial report
CTSU	Clinical Trial Supplies Unit
DILI	Drug-induced liver injury

DNA	Deoxyribonucleic acid
EC	Ethics committee
ECG	Electrocardiogram
EDTA	Ethylenediaminetetraacetic acid
EOT	End of trial
EU	European Union
F	Absolute bioavailability factor
FDA	Food and Drug Administration
GCP	Good Clinical Practice
gCV	Geometric coefficient of variation
GLP	Good Laboratory Practice
gMean	Geometric Mean
GMP	Good Manufacturing Practice
IB	Investigator's brochure
ICH	International Conference of Harmonization
ICRP	International Commission on Radiological Protection
IEC	Independent Ethics Committee
ILD	Interstitial lung disease
IRB	Institutional Review Board
ISF	Investigator site file
iv	Intravenous
λ_z	Terminal rate constant
LC-MS/MS	Liquid chromatography tandem mass spectrometry
MAT	Mean absorption time
MedDRA	Medical Dictionary for Regulatory Activities
M(R)D	Multiple (rising) dose
MRT_{ex}	Mean residence time of the analyte in the body after oral administration
NOA	Not analysed
NOAEL	No observed adverse effect level
NOR	No valid result
NOS	No sample available
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PKS	Pharmacokinetic analysis set
PR	Pulse rate

qd/QD	*Quaque die*, once daily
QT	Time between start of the Q-wave and the end of the T-wave in an electrocardiogram
QTc	Heart rate-corrected QT interval
QTcF	Heart rate-corrected QT interval following the formula of Fridericia
RDC	Remote Data Capture
REP	Residual effect period
RPM	Report planning meeting
SAE	Serious adverse event
SCR	Screening
SOP	Standard Operating Procedure
S(R)D	Single (rising) dose
SSAO	Semi-carbazide-sensitive amine oxidase
SUSAR	Suspected Unexpected Serious Adverse Reaction
$t_{1/2}$	Terminal half-life of the analyte
TDMAP	Trial Data Management and Analysis Plan
t_{max}	Time from dosing to the maximum measured concentration of the analyte
TMF	Trial master file
TS	Treated set
TSAP	Trial statistical analysis plan
ULN	Upper Limit of Normal
US	United States
V_d	Apparent volume of distribution
V_z/F	Apparent volume of distribution during the terminal phase after extravascular administration

2. RATIONALE, OBJECTIVES, AND BENEFIT - RISK ASSESSMENT

2.1 RATIONALE FOR PERFORMING THE TRIAL

This trial is intended to examine the absolute oral bioavailability of BI 1467335 using an iv [C-14] microtracer approach. The data are considered necessary to further support the understanding of the pharmacokinetics of BI 1467335. Due to the time dependent non-linear kinetics of BI 1467335, systemic exposures on Day 28 cannot be predicted from Day 1 kinetics, (IB [c04751792]).Therefore absolute oral bioavailability using an iv [C-14] microtracer dose will be determined on Day 1 and on Day 28 following a single (Day 1) and multiple dose treatment (Day 1 to 28) with an oral unlabelled dose of 10 mg of BI 1467335 q.d.

2.2 TRIAL OBJECTIVES

The primary objective of this trial is to investigate the absolute bioavailability of BI 1467335 with an intravenous microdose formulation containing labelled [C-14] BI 1467335 and an unlabelled oral tablet formulation of BI 1467335 in healthy male subjects.

The secondary objective is the evaluation of additional pharmacokinetic parameters following the two treatments.

The assessment of safety and tolerability will be an additional objective of this trial.

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

2.3 BENEFIT - RISK ASSESSMENT

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

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

The study will be performed as an open-label, non-randomised, single arm, multiple dose trial in healthy male subjects to define from the systemic exposure from the oral dose (T1, film coated tablet) and that following the iv infusion (T2, microtracer infusion). The resulting data, per subject, will be dose normalised then the absolute oral bioavailability (%) of the 10 mg tablet on Days 1 and 28 will be calculated. For Day 1, $(AUC_{0-\infty}/Dose)_{oral}/((AUC_{0-\infty}/Dose)_{iv}*100$ and for Day 28 $(AUC_{\tau}/Dose)_{oral}/((AUC_{0-\infty,28}/Dose)_{iv}*100$.

The treatments will be a 10 mL intravenous infusion of 50 µg BI 1467335 free base (T2); using on Day 1 a mixture of 41.15 µg unlabelled BI 1467335 and 8.85 µg [C-14] BI 1467335 (corresponding to 46.50 µg and 10 µg of salt respectively) and on Day 28 a mixture of 45 µg unlabelled BI 1467335 and 5 µg [C-14] BI 1467335 free base (corresponding to 50.85 µg and 5.65 µg of salt respectively). The oral treatment (T1) will consist of two 5 mg film-coated tablets (dose strength based on free base) administered once daily for 28 days. On Day 1 and Day 28, both treatments are given in fasted state. For details refer to Section 4.1.

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

3.1.1 Administrative structure of the trial

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

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

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

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

The radiolabelled trial medication will be provided by
.

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

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

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

Accelerator mass spectrometry (AMS) analysis will be conducted

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

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

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

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

Due to the time dependent non-linear kinetics of BI 1467335, systemic exposures on Day 28 cannot be predicted from Day 1 kinetics, (IB [c04751792]).Therefore the absolute oral bioavailability will be determined on two occasions following single (Day 1) and multiple oral dose treatment (Day 28) following 10 mg of BI 1467335 qd (2 film-coated tablets of 5 mg dose strength), the maximum therapeutic dose used in ongoing phase II studies.

The same subject will receive a ^{14}C labelled microtracer infusion on Day 1 after a single oral dose and on Day 28 after multiple oral doses. Thus, the oral bioavailability on Day 1 and 28 will be calculated for each subject on each day. As the iv infusion is given at the geometric mean t_{max} of the oral dose, this accounts for the observed non-proportionality in systemic exposure observed between Days 1 and 28.

[C-14] BI 1467335 is unlikely to exhibit any detectable isotope effects (see Section 2.3).

The open-label treatment is not expected to bias results, since the primary study endpoints are derived from quantitative measurements of plasma concentrations of the analyte following oral and iv dosing.

3.3 SELECTION OF TRIAL POPULATION

It is planned that at least 10 healthy male subjects will enter the study (maximum number of n=12 subjects) to have at least 8 evaluable subjects. They will be recruited from the volunteers' pool of the trial site or, if necessary, via advertisement.

The current trial is designed to investigate the absolute oral bioavailability of BI 1467335 following 10 mg oral dosing. Healthy male subjects are an ideal population for the objectives of this trial, since they provide relatively stable physiological, biochemical and hormonal conditions, i.e. the absence of disease-related variations and relevant concomitant medications.

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

3.3.1 Main diagnosis for study entry

The study will be performed in healthy subjects.

3.3.2 Inclusion criteria

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. Age of 18 to 65 years (incl.)

3. BMI of 18.5 to 29.9 kg/m^2 (incl.)

4. Signed and dated written informed consent prior to admission to the study in accordance with GCP and local legislation

5. Subjects who are sexually active must use, with their partner, highly effective contraception from the time of administration of trial medication until 4 months after administration of trial medication. Adequate methods are:
   - Condoms *plus* use of hormonal contraception by the female partner that started at least 2 months prior to administration of trial medication (e.g., implants, injectables, combined oral or vaginal contraceptives, intrauterine device) *or*
   - Condoms plus surgical sterilization (vasectomy at least 1 year prior to enrolment) or
   - Condoms plus surgically sterilised partner (including hysterectomy) or
   - Condoms plus intrauterine device or
   - Condoms plus partner of non-childbearing potential (including homosexual men)

Subjects are required to use condoms to prevent unintended exposure of the partner to the study drug via seminal fluid.

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

3.3.3 Exclusion criteria

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

1. Any finding in the medical examination (including BP, PR or ECG) is deviating from normal and judged as clinically relevant by the investigator
2. 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. Clinically significant gastrointestinal, hepatic, renal, respiratory (including but not limited to interstitial lung disease), cardiovascular, metabolic, immunological or hormonal disorders
5. Cholecystectomy and/or surgery of the gastrointestinal tract that could interfere with the pharmacokinetics 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
9. History of relevant allergy or hypersensitivity (including allergy to the trial medication or its excipients)
10. Within 30 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
11. Participation in another trial where an investigational drug has been administered within 60 days prior to planned administration of trial medication, or current participation in another trial involving administration of investigational drug
12. Smoker (more than 5 cigarettes or 1 cigar or 1 pipe per day)
13. Inability to refrain from smoking on specified trial days
14. Average intake of more than 24 units of alcohol per week (1 unit of alcohol equals approximately 250 mL of beer, 100 mL of wine or 35 mL of spirits)
15. Drug abuse or positive drug screening
16. Blood donation of more than 100 mL within 30 days prior to administration of trial medication or intended donation during the trial
17. Inability to comply with dietary regimen of trial site
18. A marked baseline prolongation of QT/QTc interval (such as QTcF intervals that are repeatedly greater than 450 ms) or any other relevant ECG finding at screening
19. A history of additional risk factors for Torsades de Pointes (such as heart failure, hypokalemia, or family history of Long QT Syndrome)
20. Subject is assessed as unsuitable for inclusion by the investigator, for instance, because considered not able to understand and comply with study requirements, or has a condition that would not allow safe participation in the study

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

21. Exposure to radiation for diagnostic reasons (except dental X-rays and plain X-rays of thorax and bony skeleton (excluding spinal column) in the period of 1 year prior to screening

For study restrictions, refer to Section 4.2.2.

3.3.4 Removal of subjects from therapy or assessments

3.3.4.1 Removal of individual subjects

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

1. The subject withdraws consent for trial treatment or trial participation, without the need to justify the decision
2. The subject needs to take concomitant drugs that interfere with the investigational product or other trial medication
3. The subject is no longer able to participate for other medical reasons (such as surgery, adverse events, or diseases)
4. The subject shows an elevation of AST and/or ALT ≥3-fold ULN combined with an elevation of total bilirubin ≥2-fold ULN (measured in the same blood sample) and/or needs to be followed up according to the 'DILI checklist' provided in the ISF.
5. A subject can also be removed from the trial if eligibility criteria are being violated or if the subject fails to comply with the protocol (for instance, by non-adherence to dietary rules, or non-attendance at study assessments).

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

3.3.4.2 Discontinuation of the trial by the sponsor

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

1. New toxicological findings or serious adverse events invalidate the earlier positive benefit-risk-assessment. More specifically, the trial will be terminated if at least one drug-related serious adverse event is reported that is considered to be unacceptable. In this case, collection of pharmacokinetic samples and other scheduled activities should continue, if possible without undue risk to already dosed volunteers, but no further administrations of investigational drug will be done.
2. The expected enrolment goals overall are not met
3. Violation of GCP, or the CTP, or the contract with BI by a trial site or investigator, disturbing the appropriate conduct of the trial

4. The sponsor decides to discontinue the further development of the investigational product.

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

4. TREATMENTS

4.1 TREATMENTS TO BE ADMINISTERED

BI 1467335 doses are calculated as a free base. 10 mg BI 1467335 free base equals to 11.3 mg BI 1467335 HCl salt.

Radiolabelled BI 1467335 (C-14) (test product 2) is administered as an intravenous solution. The powder used for intravenous solution contains [C-14] BI 1467335 and unlabelled BI 1467335 both manufactured by BI Pharma GmbH & Co. KG. The mixture of [C-14] BI 1467335 and unlabelled BI 1467335 and the solution from this mixture are made by

Unlabelled film coated tablets (test product 1) have been manufactured by BI Pharma GmbH & Co. KG.

4.1.1 Identity of BI investigational product and comparator product

The characteristics of the test products are given below:

Test product 1

Substance:	BI 1467335
Pharmaceutical formulation:	Film-coated tablet
Source:	BI Pharma GmbH & Co. KG, Germany
Unit strength:	5 mg
Posology:	2-0-0
Route of administration:	p.o.
Duration of use:	28 days

Test product 2

Name:	BI 1467335 (C-14) intravenous solution
Substance:	BI 1467335 mixed with [C-14] BI 1467335
Pharmaceutical formulation:	Intravenous solution
Source:	
Unit strength:	50 µg BI 1467335 (C-14) - Containing 8.85 µg [C-14] BI 1467335 free base and 41.15 µg BI 1467335 free base (Day 1) (corresponding to 10 µg and 46.50 µg salt, respectively) or containing 5 µg [C-14] BI 1467335 free base and 45 µg BI 1467335 free base (Day 28) (corresponding to 5.65 µg and 50.85 µg, respectively)

	- In a saline solution of 10 mL volume (concentration of BI 1467335 (C-14): 5 µg free base/mL)
Posology:	1-0-0
Route of administration:	i.v.
Duration of use:	Two single infusions (Day 1 and Day 28), infused over 15 minutes

4.1.2 Method of assigning subjects to treatment groups

This is an open-label, single arm Phase I, single- and multiple dose study. All subjects receive the same dose. Each subject will be assigned a subject number prior to dosing on Day 1 of Visit 2.

Subject numbers will be for the maximum number of twelve planned subjects and in case subject replacement is necessary (see Section 3.3.5).

Once a subject number has been assigned, it cannot be reassigned to any other subject.

The randomisation procedure is described in Section 7.5.

4.1.3 Selection of doses in the trial

The oral dose of 10 mg BI 1467335 (calculated as free base) is below the already tested highest oral dose of 20 mg of BI 1467335 for 4 weeks in healthy subjects. In healthy volunteers, this dose was safe and well-tolerated (Section 1.2).

An oral dose of 10 mg, administered either as single or multiple dose, is considered adequate for the objectives of the current trial.

The iv dose on Day 1 and Day 28 administered as infusion will include ^{14}C radiolabelled BI 1467335. The radiolabelled dose has been selected to provide sufficient analytical sensitivity, (Accelerator Mass Spectrometry), in this microtracer study while not exceeding the threshold of negligible radioactive burden, see Section 2.3.

4.1.4 Drug assignment and administration of doses for each subject

All subjects will receive the same treatment. Treatment with non-radiolabelled oral compound (film-coated tablets) will consist of 10 mg q.d. from Day 1 to Day 28. On Day 1 and Day 28 the non-radiolabelled medication will be administered to a subject in the sitting position under supervision of the investigator or an authorised designee. Volunteer will drink 240 mL of non-sparkling water.

In principal, the so-called four-eye principle (two-person rule) should be applied for administration of trial medication at the study site, while intake under ambulatory conditions will be monitored by phone contacts between study site and subject.

On Day 1 and Day 28 lunch will be given 4 h postdose. During the first 4 h after drug administration (only on Day 1 and Day 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 examinations (in particular for the microtracer infusion) or if necessary for any medical reasons (e.g., adverse events). For restrictions with regard to diet and fluid intake during the investigational period see Section 4.2.2.2.

Start and time of the infusion will be recorded.

For administration of the microtracer infusion on Day 1 and Day 28 (duration of infusion: 15 minutes), an intravenous indwelling catheter is placed into an arm vein of the subject and will be kept patent with a saline infusion. A second indwelling catheter used for collection of blood samples will be placed on the contralateral arm.

4.1.5 Blinding and procedures for unblinding

No blinding will be performed because the treatments are distinguishable from each other. This Phase I trial will be handled in an open fashion throughout (that is, during the conduct, including data cleaning and preparation of the analysis). This is considered acceptable because the potential for bias seems to be low and does not outweigh practical considerations.

Emergency envelopes will not be provided, since it is an open-label trial.

4.1.6 Packaging, labelling, and re-supply

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

Radiolabelled drug product manufacturing is provided by .

The clinical trial supply consists of containers holding the trial medication which are labelled with trial identification. Investigational Drug Products will be labelled according to GMP Annex 13 / EU GMP Guideline and local drug law.

Examples of the labels will be available in the ISF.

No re-supply is planned.

4.1.7 Storage conditions

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

4.1.8 Drug accountability

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

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

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

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

4.2 OTHER TREATMENTS, EMERGENCY PROCEDURES, RESTRICTIONS

4.2.1 Other treatments and emergency procedures

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

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

No concomitant therapy is allowed. All concomitant or rescue therapies will be recorded (including time of intake on study days) on the appropriate pages of the CRF. Limited amounts of paracetamol are allowed when prescribed by a physician.

In the case of AEs the volunteers will be treated as necessary and kept under constant supervision at the trial centre or transferred to hospital until such time that all the results of the evaluations have returned to a medically acceptable level.

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. In addition, subjects are required to refrain from smoking while hospitalized.

On Day 1 and Day 28 starting from 1 hour before drug administration until 2 h after drug intake fluid intake is not allowed except from the 240 mL water administered with the drug intake and an additional 240 mL of water served on Day 1 and Day 28 at 2 h post-dose (mandatory for all subjects). From 2 hours until 22 hours post-dose fluid intake should be within about 1000 to 3000 mL.

On Day 1 and Day 28 subjects will receive a 15 minutes microtracer infusion 1 h after intake of film-coated tablets (i.e., t_{max} for oral dose). The handling instructions will be filed in the ISF.

Poppy-seed containing products should not be consumed starting 2 days before first trial drug administration until last PK sampling of the trial.

For fasting times before drug administration see Section 4.1.4. For fasting times before safety laboratory investigations see Section 5.2.3.

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.

Alcoholic beverages are not allowed 48 hours before administration of the compound, before each admission and during the clinic period. During ambulatory phases alcohol consumption is restricted to 24 units a week.

Methylxanthine-containing drinks or foods (such as coffee, tea, cola, energy drinks, and chocolate) are not allowed at days of inhouse confinement.

Subjects should be advised to avoid foods containing a very large amount of tyramine (especially found in fermented food) while taking BI 1467335. These include for example aged cheese, aged meats, soybean products (soy sauce), red wine, tap (draft) beer, St John’s Wort, pickled herring, sauerkraut (fermented cabbage), and tryptophan supplements.

Excessive physical activity (such as competitive sport) should be avoided starting 4 days before the first administration of trial medication until the end of trial examination.

4.3 TREATMENT COMPLIANCE

Compliance will be monitored by either administration of all trial medication in the study centre under supervision of the investigating physician or a designee or during ambulatory period subjects confirm drug intake by phone contact with the study site.

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

5. VARIABLES AND THEIR ASSESSMENT

5.1 EFFICACY - CLINICAL PHARMACOLOGY

5.1.1 Endpoints of efficacy

No efficacy endpoints will be evaluated in this trial.

5.1.2 Assessment of efficacy

Not applicable.

5.2 SAFETY

5.2.1 Endpoints of safety

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

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

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

5.2.2 Assessment of adverse events

5.2.2.1 Definitions of adverse events

Adverse event

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

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

Serious adverse event

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

- results in death,
- is life-threatening, which refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if more severe,

- requires inpatient hospitalisation or
- requires prolongation of existing hospitalisation,
- results in persistent or significant disability or incapacity, or
- is a congenital anomaly/birth defect,

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

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation or development of dependency or abuse.

AEs considered 'Always Serious'

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

Cancers of new histology and exacerbations of existing cancer must be classified as a serious event regardless of the duration between discontinuation of the drug and must be reported as described in 5.2.2.2, subsections 'AE collection' and 'AE reporting to sponsor and timelines'.

The latest list of 'Always Serious AEs' can be found in the RDC system. These events should always be reported as SAEs as described above.

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. AESIs need to be reported to the sponsor's Pharmacovigilance Department within the same timeframe that applies to SAE, please see Section 5.2.2.2.

The following are considered as AESIs in this trial:

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

  These lab findings constitute a hepatic injury alert and the subjects showing these lab abnormalities need to be followed up according to the 'DILI checklist' provided in the ISF. In case of clinical symptoms of hepatic injury (icterus, unexplained encephalopathy, unexplained coagulopathy, right upper quadrant abdominal pain,

etc.) without lab results (ALT, AST, total bilirubin) available, the Investigator should make sure 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 (severity) of AEs

The intensity (severity) 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

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 trial treatment continues or remains unchanged.

5.2.2.2 Adverse event collection and reporting

AE collection

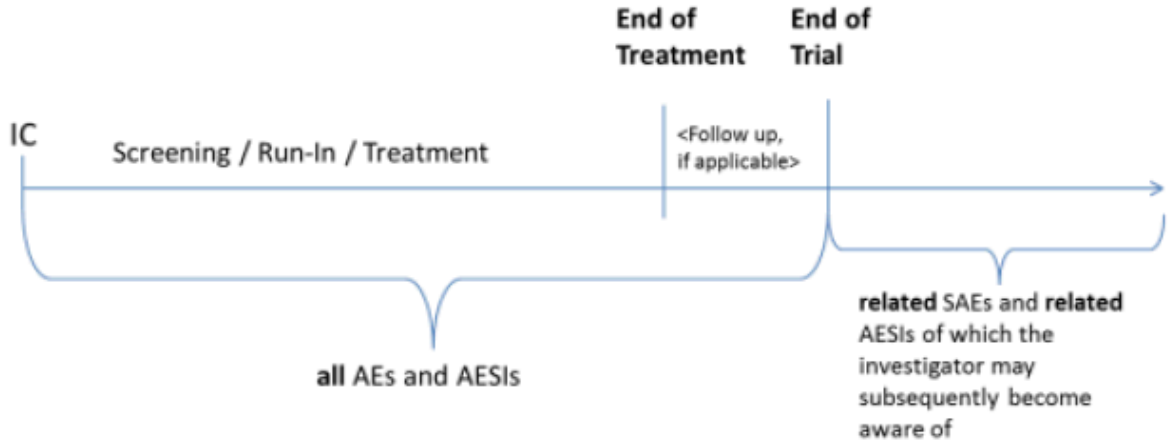
Upon enrolment into a trial, the subject's baseline condition is assessed (for instance, by documentation of medical history/concomitant diagnoses), and relevant changes from baseline are noted subsequently.

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 CRF(s) by the investigator:

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



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 for this clinical trial. Therefore, all AEs reported until the end of trial examination (last per protocol contact) will be considered on treatment (please see Section 7.3.3).

AE reporting to sponsor and timelines

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

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

Information required

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

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

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

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

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

5.2.3 Assessment of safety laboratory parameters

For the assessment of laboratory parameters, blood and urine samples will be collected by the trial site at the time points indicated in the Flow Chart after the subjects have fasted for at least 10 h. Subjects do not have to be fasted for drug screening and for infectious serology at the discretion of the investigator or designee. Fasting is not required at the discretion of the investigator or designee for retests.

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

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

Table 5.2.3: 1 Routine laboratory tests

Functional lab group	Test name
Haematology	Haematocrit Haemoglobin Red blood cell count (RBC) Reticulocyte count White blood cell count (WBC) Platelet count
Automatic WBC differential (relative and absolute)	Neutrophils, eosinophils, basophils, monocytes, lymphocytes
Manual differential WBC (if automatic differential WBC is abnormal)	Polymorphnuclear neutrophils (segs), band neutrophils (stabs), eosinophils, basophils, monocytes, lymphocytes
Coagulation	Activated partial thromboplastin time (aPTT) Prothrombin time (Quick's test and INR)
Enzymes	Aspartate transaminase (AST/GOT) Alanine transaminase (ALT/GPT) Alkaline phosphatase (AP) Gamma-glutamyl transferase (GGT) Creatine kinase (CK) CK-MB, only if CK is elevated Lactate dehydrogenase (LDH) Lipase Amylase (total)
Hormones[1]	Thyroid stimulating hormone (TSH)
Substrates	Serum glucose Creatinine Total bilirubin Direct bilirubin Total protein Albumin Alpha glycoprotein acid C-Reactive Protein (CRP) Uric acid Urea Total cholesterol Triglycerides
Electrolytes	Sodium Potassium Magnesium Calcium

[1] Hormones only at screening and end of trial.

Table 5.2.3: 1 Routine laboratory tests (cont).

Functional lab group	Test name
Urinalysis (Stix)	Urine nitrite Urine protein Urine glucose Urine ketone Urobilinogen Urine bilirubin Urine haemoglobin Urine leukocytes Urine pH
Urine sediment (microscopic examination if haemoglobin, leukocytes nitrite or protein are abnormal in urine)	Only positive findings will be reported (for instance, the presence of sediment bacteria, casts in sediment, squamous epithelial cells, erythrocytes, leukocytes)

[1] Hormones only at screening and end of trial.

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

Table 5.2.3: 2 Exclusionary laboratory tests

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

The laboratory tests listed in Table 5.2.3: 1 and 5.2.3: 2 will be performed at the safety laboratory of ,

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5.2.4 Electrocardiogram

Twelve-lead ECGs (I, II, III, aVR, aVL, aVF, V1 - V6) will be recorded using a computerised electrocardiograph (Mortara ELI 250 Rx) at the time points given in the Flow Chart.

All ECGs will be recorded for a 10-sec duration after the subjects have rested for at least 5 min in a supine position. ECG assessment will always precede all other study procedures of the same time point (except blood drawing from an intravenous cannula which is already in place) to avoid impact of sampling on the ECG quality.

All ECGs will be stored electronically. Electrode placement will be performed according to the method of Wilson, Goldberger and Einthoven.

All locally printed ECGs will be evaluated by the investigator or a designee. ECGs may be repeated for quality reasons (like alternating current artefacts, muscle movements, electrode dislocation) and the repeated ECG will be used for analysis. Additional (unscheduled) ECGs may be collected by the investigator for safety reasons.

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

5.2.5 Assessment of other safety parameters

5.2.5.1 Vital signs

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

5.2.5.2 Medical examinations

At 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.

5.4 APPROPRIATENESS OF MEASUREMENTS

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

5.5 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

Date and clock time of drug administration and pharmacokinetic sampling will be recorded in the eCRF. For drug intake at home the entries from subject's diary will be transferred to the eCRF.

5.5.1 Pharmacokinetic endpoints

5.5.1.1 Primary endpoints

The following primary endpoints will be evaluated for BI 1467335 in plasma after the first dose on Day 1:

- C_{max} (maximum measured concentration of the analyte after oral administration)
- $AUC_{0-\infty}$ (area under the concentration-time curve of the analyte over the time interval from 0 to infinity after oral administration)
- C_{max} (maximum measured concentration of the analyte after intravenous administration)
- $AUC_{0-\infty}$ (area under the concentration-time curve of the analyte over the time interval from 0 to infinity after intravenous administration)

The following primary endpoints will be evaluated for BI 1467335 in plasma in the repeated doses treatment group after repeated dosing (Day 28):

- $C_{max, 28}$ (maximum measured concentration of the analyte after oral administration on Day 28)
- $AUC_{0–24, 28}$ (area under the concentration-time curve of the analyte over the time interval from 0 to 24 h after oral administration on Day 28)
- $C_{max, 28}$ (maximum measured concentration of the analyte from 0 to infinity after intravenous administration on Day 28)
- $AUC_{0–\infty, 28}$ (area under the concentration-time curve of the analyte from 0 to infinity after intravenous administration on Day 28)

Further assessments will include:

5.5.1.2 Secondary endpoint

The following secondary endpoints will be evaluated for BI 1467335 in plasma:

For (C-14) BI 1467335 and for BI 1467335 after SD and MD

- t_{max}, $t_{max,28}$ (time from dosing to the maximum measured concentration of the analyte)
- $t_{1/2,}$ (observed terminal half-life of the analyte) for the oral dose on Day 1
- $t_{1/2,}$ $t_{1/2,28}$ following the iv dose

For (C-14) BI 1467335 after SD and MD

- CL, CL_{28} (clearance of the analyte)
- $V_{z,}$ $V_{z,28}$ (volume of distribution of the analyte on Day 1 and on Day 28)

For BI 1467335 after SD and MD

- F (absolute bioavailability) at day 1 and at day 28

Day 1 $(AUC_{0-\infty/}Dose)_{oral}/((AUC_{0-\infty/}Dose)_{iv}*100$

Day 28 $(AUC_{\tau/}Dose)_{oral}/((AUC_{0-\infty,28/}Dose)_{iv}*100$

5.5.2 Methods of sample collection

5.5.2.1 Plasma sampling for pharmacokinetic analysis

For quantification of BI 1467335 plasma concentrations, approx. 3 mL of blood will be taken from an antecubital or forearm vein into a K2-EDTA (tripotassium ethylendiaminetetraacetic acid)-anticoagulant blood drawing tube at the times indicated in the Flow Chart.

For quantification of [C-14] BI 1467335 plasma concentrations, an additional 3 mL K2-EDTA tube needs to be collected as indicated in the Flow Chart. Blood will be withdrawn by means of either an indwelling venous catheter or by venipuncture with a metal needle.

All blood samples will be centrifuged

The remaining plasma will be used as analytical back-up sample. 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.

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

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

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

The study samples will be discarded after completion of the additional investigations but not later than 5 years upon the final study report has been signed the analytical laboratory after the bioanalyst has acknowledged safe arrival of the first aliquot.

5.5.3 Analytical determinations

5.5.3.1 Analytical determination of analyte plasma concentration

Cold BI 1467335 concentrations in plasma will be determined by a validated LC-MS/MS (liquid chromatography coupled to tandem mass spectrometry) assay.

[C-14] BI 1467335 will be determined by a validated AMS (accelerator mass spectrometry) assay.

5.6 PHARMACOKINETIC - PHARMACODYNAMIC RELATIONSHIP

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

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

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

The acceptable deviation from the scheduled time for vital signs, ECG and safety laboratory tests will be ± 30 min on Day 1 (SD) or on Day 28 (MD) and ± 90 min on all other days of Visit 2.

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

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

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

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

6.2.1 Screening period

Screening visit is defined as Visit 1.

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

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

6.2.2 Treatment period

Each subject will receive on Day 1 a single 10 mL infusion of 50 µg BI 1467335 (C-14) (containing 8,85 µg [C-14] BI 1467335 free base and 41,15 µg of BI 1467335 free base) over a period of 15 minutes, 1 h after oral intake of 10 mg of BI 1467335 (film-coated tablets). All subjects will continue to receive a single oral dose of 10 mg BI 1467335 from Day 2 up to Day 28. On Day 28 all subjects will again receive a single 10 mL infusion of 50 µg BI 1467335 (C-14) (containing 5 µg [C-14] BI 1467335 free base and 45 µg of BI 1467335

free base) over a period of 15 minutes, 1 h after oral intake of 10 mg of BI 1467335 free base (film-coated tablets).

On Day 6, Day 13 and Day 20 (due to assessments and dispensing of study medication in the morning of the next day) participants will be admitted to the trial site and kept under close medical surveillance as indicated in the Flow Chart and Section 5.2.5.

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

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

6.2.3 End of trial period

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

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

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

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

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 STATISTICAL DESIGN – MODEL

7.1.1 Objectives

The primary objective of this trial is to investigate the absolute bioavailability of BI 1467335 with an intravenous microdose formulation containing labelled [C-14] BI 1467335 (reference, R) and an unlabelled oral tablet formulation of BI 1467335 (test, T) in healthy male subjects.

The study will be conducted as an open-label, single arm, multiple oral dose trial. The trial design consists of an intravenous microtracer dose being administered at the gMean t_{max} of the oral dose, which allows accurate estimates of absolute bioavailability. This means that the intersubject variability is removed from the comparison between formulations, as well as the day to day variability within one subject. Due to the time dependent kinetics, the absolute bioavailability will be analysed on Day 1 and Day 28. The trial will be evaluated statistically by use of an appropriate linear model.

The evaluation of further pharmacokinetic parameters of BI 1467335 as well as the assessment of safety and tolerability will be additional objectives of this trial, and will be evaluated by descriptive statistics. Inferential statistics is not planned.

7.1.2 Endpoints

Absolute oral bioavailability is to be determined for Day 1 and Day 28, on the basis of the individually dose normalized primary pharmacokinetic endpoints (see Section 5.5.1). Other PK endpoints are mentioned in Section 5.5.1.3 and will be analysed descriptively only.

Safety and tolerability will be determined on the basis of the parameters specified in Section 5.2.1.

7.1.3 Model

The statistical model used for the analysis of primary endpoints will be an ANOVA (analysis of variance) model on the logarithmic scale. This model will include effects accounting for the following sources of variation: ‘subject’ and ‘formulation’. The effect ‘subjects’ will be considered as random, whereas the effect ‘formulation’ will be considered as fixed.

The model is described by the following equation:

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

y_{km} = logarithm of response (dose normalized primary endpoint, see Section 5.5.1) measured on subject m receiving formulation k,

μ = the overall mean,

s_m = the effect associated with the mth subject, m = 1, 2, ..., n

τ_k = the kth formulation effect (either tablet or i.v.), k = 1, 2,

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

7.2 NULL AND ALTERNATIVE HYPOTHESES

It is not planned to test any statistical hypotheses in a confirmatory sense.

The absolute oral bioavailability of BI 1467335 by comparing 8,85 µg (Day 1) or 5 µg (Day 28) intravenously administered [C-14] BI 1467335 free base with an oral dose of 10 mg of BI 1467335free base after single and multiple oral doses will be estimated by the ratios of the geometric means (test/reference) for the dose normalized primary PK endpoints.

Additionally, their two-sided 90% confidence intervals (CIs) will be provided. This method corresponds to the two one-sided t-tests procedure, each at the 5% significance level. Confidence intervals will have to be interpreted in the perspective of the exploratory character of the trial, 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 will be identified no later than in the report planning meeting (RPM) and provided in the trial statistical analysis plan (TSAP).

The following analysis sets will be defined for this trial:

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

- PK analysis set (PKS):
  This subject set includes all subjects from the TS who provide at least one primary PK endpoint value that is judged as PK evaluable and is not affected by protocol violations relevant to the statistical evaluation of PK endpoints. Thus, a subject will be included in the PKS, even if he contributes only one PK endpoint value for one formulation (at Day 1 or Day 28) to the statistical assessment.

Whether a PK endpoint is evaluable or a protocol violation is relevant will be decided no later than at the RPM.

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

Pharmacokinetic endpoint values of a subject will be included in the analysis if they are not flagged for exclusion, e.g. due to PK non-evaluability or a protocol violation relevant to the evaluation of PK endpoints.

7.3.1 Primary analyses

The pharmacokinetic endpoints listed in Section 5.5.1 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 derived 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 RPM) 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.

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

- The subject experiences emesis at or before two times median t_{max}. Median t_{max} is to be taken either from the median t_{max} for the reference product or from median t_{max} for the test product, depending on whether the subject had experienced emesis after taken the test or the reference product. Median t_{max} is to be determined excluding the subjects experiencing emesis.
- Missing samples/concentration data at important phases of PK disposition curve.

The primary PK parameters C_{max} and $AUC_{0-\infty}$ on Day 1 and $C_{max,28}$, $AUC_{0-24,28}$ (after oral administration) and $AUC_{0-\infty,28}$ (after intravenous administration) on Day 28 (refer to Section 5.5.1) of BI 1467335 in plasma will be dose normalized and then log-transformed (natural logarithm) prior to fitting the ANOVA model. The difference between the expected means for log(Test)-log(Reference) will be estimated by the difference in the corresponding least square means (point estimate) and two-sided 90% confidence intervals based on the t-distribution will be computed.

These quantities will then be back-transformed to the original scale to give the point estimator (geometric mean) and 90% confidence interval estimates for the intra-subject ratio of the geometric means for treatments test and reference.

This will be done for Day 1 and Day 28 separately, thus the analysis variables are the following:

Day 1 for C_{max}:	normalised C_{max} after oral and intravenous administration
Day 1 for AUC:	normalised $AUC_{0-\infty}$ after oral and intravenous administration
Day 28 for C_{max}:	normalised $C_{max,\ 28}$ after oral and intravenous administration
Day 28 for AUC:	normalised $AUC_{0-24,28}$ after oral administration and normalised $AUC_{0-\infty,\ 28}$ after intravenous administration

The primary analysis will be based on the pharmacokinetic analysis set (see Section 7.3).

7.3.2 Secondary analyses

As a sensitivity analysis, the ANOVA performed as primary analysis will be repeated with subject as fixed effect instead of random effect. The results will be presented in the same manner as for the primary analyses.

The secondary parameters (refer to Section 5.5.1) will be calculated according to the BI SOP 'Standards and processes for analyses performed within Clinical Pharmacokinetics/ Pharmacodynamics' (001-MCS-36-472) and will statistically be assessed using the same methods as described for the primary endpoints.

The following descriptive statistics will be calculated for primary and secondary PK parameters and for further endpoints: N, arithmetic mean, standard deviation, minimum, median, maximum, arithmetic coefficient of variation, geometric mean, and geometric coefficient of variation. The data format for descriptive statistics of concentrations will be identical with the data format of the respective concentrations. The descriptive statistics of PK 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 3 significant digits in the clinical trial report.

7.3.3 Safety analyses

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

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

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

Measurements (such as ECG, vital signs, or laboratory parameters) or AEs will be assigned to 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.

Additionally, further treatment intervals (analysing treatments) may be defined in order to provide summary statistics for time intervals, such as combined treatments, on-treatment totals or periods without treatment effects (such as screening). Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Frequency, severity and causal relationship of AEs will be tabulated by treatment, system organ class and preferred term. SAEs, AESIs (see Section 5.2.2.1) and other significant AEs (according to ICH E3) will be listed separately.

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

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

Relevant ECG findings will be reported as AEs.

7.3.4 Interim analyses

No interim analysis is planned.

7.3.5 Pharmacokinetic analyses

The pharmacokinetic parameters listed in Section 5.5.1 for drug BI 1467335 will be calculated according to the relevant SOP of the Sponsor (001-MCS-36-472).

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

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

Plasma concentrations will be plotted graphically versus time for all subjects as listed in the drug plasma concentration-time tables. For the presentation of the mean profiles, the arithmetic mean, geometric mean and the planned blood sampling times will be used.

In addition to the analysis described Section 7.3.1, the absolute bioavailability factor F will be calculated for each subject on Day 1 as

$$F = \text{normalised } AUC_{0-\infty} \text{ (oral)} / \text{normalised } AUC_{0-\infty} \text{ (i.v.)}$$

and for each subject on Day 28 as

$$F = \text{normalised } AUC_{0-24,\,28} \text{ (oral)} / \text{normalised } AUC_{0-\infty,\,28} \text{ (i.v.)}.$$

The calculated parameter at Day 1 and Day 28 will be analysed with descriptive statistics.

7.4 HANDLING OF MISSING DATA

7.4.1 Safety

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

7.4.2 Plasma drug concentration - time profiles

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

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).

7.4.3 Pharmacokinetic parameters

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

For the non-compartmental analysis, concentration data identified with NOS, NOR or NOA will generally not be considered. Concentration values in the lag phase identified as BLQ 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.

7.5 RANDOMISATION

All subjects will receive the same treatments in one fixed sequence. Therefore, no randomisation is necessary in this trial (see also Section 4.1.2). A list of consecutive subject numbers will be provided for procedural reasons (see Section 4.1.2).

7.6 DETERMINATION OF SAMPLE SIZE

It is planned to enter a total of at least 10 and most 12 subjects into the trial, because this sample size is considered sufficient to achieve the aims of this exploratory trial.

All calculations were performed as described by Kupper and Hafner [R12-0972] using R Version 3.3.1.

8. INFORMED CONSENT, DATA PROTECTION, TRIAL RECORDS

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

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

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

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

8.1 STUDY APPROVAL, SUBJECT INFORMATION, AND INFORMED CONSENT

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

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

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

8.2 DATA QUALITY ASSURANCE

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

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

8.3 RECORDS

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

8.3.1 Source documents

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

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

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

8.3.2 Direct access to source data and documents

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

8.3.3 Storage period of records

Trial site:

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

Sponsor:

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

8.4 EXPEDITED REPORTING OF ADVERSE EVENTS

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

8.5 STATEMENT OF CONFIDENTIALITY

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

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

8.6 COMPLETION OF TRIAL

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

9. REFERENCES

9.1 PUBLISHED REFERENCES

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

9.2 UNPUBLISHED REFERENCES

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c04751792 Investigator's Brochure: BI 1467335 15 Mar 2018.

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c08980589 . A multi-centre, double-blind, parallel-group, randomised, placebo controlled phase II a study to investigate safety, tolerability, pharmacodynamics, and pharmacokinetics of different doses of orally administered BI 1467335 during a 12-week treatment period compared to placebo in patients with 1386.4. 19 May 2017.

c09036683 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.

c14141887 A Randomized, double-masked, placebo-controlled exploratory study to evaluate safety, tolerability, pharmacodynamics and pharmacokinetics of orally administered BI 1467335 for 12 weeks with a 12 week follow up period in patients with

1386.12. 18 Jan 2018.

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n00252396 Excretion of radioactivity in urine, faeces and bile after oral and intravenous administration of [^{14}C]BI 1467335 to rats. 18 Oct 2016.

n00252404 Pharmacokinetics of radioactivity and BI 1467335 after oral and intravenous administration of [^{14}C]BI 1467335 to rats. 18 Oct 2016.

10. APPENDICES

Not applicable.

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

Number of global amendment		1
Date of CTP revision		22 March 2018
EudraCT number		2017-003853-41
BI Trial number		1386-0019
BI Investigational Product(s)		BI 1467335
Title of protocol		A phase I, open-label, single-arm multiple dose trial to investigate pharmacokinetics and absolute bioavailability of BI 1467335 administered as an oral dose simultaneously with an intravenous microtracer dose of [C-14] BI 1467335 after single and multiple oral doses in healthy male volunteers
To be implemented only after approval of the IRB / IEC / Competent Authorities		☐
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		☒
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		☐
Section to be changed		1.2 Drug profile 4.2.2 Restrictions
Description of change		Section 4.2.2: Addition of prohibited foods to mitigate the risk of relevant adverse reactions.

Number of global amendment		1
Rationale for change		

Number of global amendment		2
Date of CTP revision		24 April 2018
EudraCT number		2017-003853-41
BI Trial number		1386-0019
BI Investigational Product(s)		BI 1467335
Title of protocol		A phase I, open-label, single-arm multiple dose trial to investigate pharmacokinetics and absolute bioavailability of BI 1467335 administered as an oral dose simultaneously with an intravenous microtracer dose of [C-14] BI 1467335 after single and multiple oral doses in healthy male volunteers
To be implemented only after approval of the IRB / IEC / Competent Authorities		☐
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		☐
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		☒
Section to be changed		4.1 Treatments to be administered
Description of change		The mixture of [C-14] BI 1467335 and unlabelled BI 1467335 and the solution from this mixture are made by
Rationale for change		Previous wording suggests that the mixture of [C-14] BI 1467335 and unlabelled BI 1467335 is made by BI Pharma GmbH & Co. KG.

APPROVAL / SIGNATURE PAGE

Document Number: c19596566 **Technical Version Number:3.0**

Document Name: clinical-trial-protocol-revision-02

Title: A phase I, open-label, single-arm multiple dose trial to investigate pharmacokinetics and absolute bioavailability of BI 1467335 administered as an oral dose simultaneously with an intravenous microtracer dose of [C-14] BI 1467335 after single and multiple oral doses in healthy male volunteers

Signatures (obtained electronically)

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Approval-Therapeutic Area		25 Apr 2018 17:40 CEST
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