Clinical Trial Protocol

	Document Number: c09164690-01
EudraCT No.:	2016-001534-97
BI Trial No.:	1386.17
BI Investigational Product:	BI 1467335
Title:	Relative bioavailability of a BI 1467335 tablet compared to a BI 1467335 oral solution and the effect of food on the bioavailability of the tablet following oral administration (a randomised, open-label, single dose, three-way crossover trial in healthy male subjects)
Clinical Phase:	I
Trial Clinical Monitor:	[redacted] Phone: [redacted] Fax: [redacted]
Principal Investigator:	[redacted] Phone: [redacted] Fax: [redacted]
Status:	Final Protocol
Version and Date:	Version: 1.0 Date: 12 October 2016

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: 12 October 2016	**Trial number:** 1386.17		**Revision date:** Not applicable

Title of trial:	Relative bioavailability of a BI 1467335 tablet compared to a BI 1467335 oral solution and the effect of food on the bioavailability of the tablet following oral administration (a randomised, open-label, single dose, three-way crossover trial in healthy male subjects)
Principal Investigator:	[redacted]
Trial site:	Human Pharmacology Centre, Department of Translational Medicine & Clinical Pharmacology, Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach an der Riß, Germany
Clinical phase:	I
Objective(s):	To investigate (1) the relative bioavailability of 10 mg BI 1467335, administered as 2 x 5 mg film-coated tablets (Treatment A), compared to 10 mg BI 1467335 administered as oral solution (Treatment B), and (2) the effect of food on relative bioavailability of the tablet formulation (Treatment C)
Methodology:	Randomised, open-label, single dose, three-way crossover trial in healthy subjects
No. of subjects:	
total entered:	18
each treatment:	18
Diagnosis:	Not applicable
Main criteria for inclusion:	Healthy male subjects, age of 18 to 55 years, body mass index (BMI) of 18.5 to 29.9 kg/m^2
Test product:	BI 1467335 film-coated tablet formulation
dose:	10 mg (2 x 5 mg)
mode of admin.:	Oral with 240 mL of water after an overnight fast of at least 10 h (Treatment A) and in fed state (Treatment C)
Comparator product:	BI 1467335 oral solution formulation
dose:	10 mg
mode of admin.:	Oral with 240 mL of water after an overnight fast of at least 10 h (Treatment B)
Duration of treatment:	One day for each treatment (3 single doses), separated by washout periods of at least 21 days
Criteria for pharmacokinetics:	Primary endpoints: AUC_{0-tz} and C_{max} of BI 1467335 [redacted]

Name of company: Boehringer Ingelheim		**Tabulated Trial Protocol**	
Name of finished product: Not applicable			
Name of active ingredient: BI 1467335			
Protocol date: 12 October 2016	**Trial number:** 1386.17		**Revision date:** Not applicable
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:	Relative bioavailability will be estimated by the ratios (tablet formulation fasted/oral solution fasted; tablet fed/tablet fasted) of the geometric means for the primary 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. Since the main focus is on estimation and not testing, an acceptance range is not specified. The statistical model will be an ANOVA on the logarithmic scale including effects for 'sequence', 'subjects nested within sequences', 'period' and 'treatment'. CIs will be calculated based on the residual error from ANOVA. Descriptive statistics will be calculated for all endpoints.		

FLOW CHART

Period	Visit	Day	Planned time (relative to first drug administration) [h:min]	Approximate clock time of actual day [h:min]	Event and comment	Safety laboratory	PK blood	[redacted]	12-lead ECG	Vital signs (BP, PR)	Questioning for AEs and concomitant therapy [6]
SCR	1	-21 to -1			Screening (SCR)[1]	x			x	x	
1/2/3 (three identical periods with a wash-out of at least 21 days)	2/3/4	-5 to -1	-123:00		Visits 3 and 4 only	x[8]					x[8]
		-1	-12:00	20:00	Admission to trial site [7]	x[5,7]					x[7]
		1	-1:00	07:00	Allocation to treatment[2] (Visit 2 only)		x[2]	[redacted]	x[2]	x[2]	x[2]
			-0:30	07:30	High fat, high calorie breakfast (only in fed state - Treatment C)						
			0:00	08:00	Drug administration						
			0:15	08:15			x				
			0:30	08:30			x		x	x	
			0:45	08:45			x				
			1:00	09:00			x		x	x	x
			1:15	09:15			x				
			1:30	09:30			x				
			1:45	09:45			x				
			2:00	10:00	240 mL fluid intake		x		x	x	
			2:30	10:30			x				
			3:00	11:00			x				
			4:00	12:00	240 mL fluid intake, thereafter lunch[3]		x				x
			6:00	14:00			x				
			8:00	16:00	Snack (voluntary)[3]		x				
			10:00	18:00	Dinner [3]		x				
			12:00	20:00			x		x	x	x
		2	24:00	08:00	Discharge from trial site, breakfast[3] (voluntary)	x	x	[redacted]	x	x	x
EOT	5	22-29			End of trial (EOT) examination[4]	x			x	x	x

1. Subjects must be informed and written informed consent obtained prior to starting any screening procedures. Screening procedures include physical examination, check of vital signs, ECG, safety laboratory (including drug screening), demographics (including determination of body height and weight, smoking status and alcohol history), relevant medical history, concomitant therapy and review of inclusion/exclusion criteria. [redacted]
2. The time is approximate; the procedure is to be performed and completed within 3 h prior to drug administration
3. If several actions are indicated at the same time point, the intake of meals will be the last action
4. End of trial examination includes physical examination, body weight, vital signs, ECG, safety laboratory, recording of AEs and concomitant therapies
5. Only urine drug screening and alcohol breath test
6. AEs and concomitant therapies will be recorded throughout the trial, but will be specifically asked for at the time points indicated in the Flow Chart above
7. The time is approximate; the procedure is to be performed no later than 10 h prior to scheduled drug administration
8. Safety laboratory to be taken within 5 days prior to administration of study drug; in visits 3 and 4, only. AE and CT questioning to be done at this occasion.

TABLE OF CONTENTS

ABBREVIATIONS

ADME	Absorption, Distribution, Metabolism and Excretion
AE	Adverse event
AESI	Adverse events of special interest
ANOVA	Analysis of variance
[redacted]	
AUC_{0-tz}	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 to the last quantifiable data point
BA	Bioavailability
BCS	Biopharmaceutics classification system
BI	Boehringer Ingelheim
BLQ	Below limit of quantification
BMI	Body mass index (weight divided by height squared)
BP	Blood pressure
CA	Competent authority
CI	Confidence interval
[redacted]	
C_{max}	Maximum measured concentration of the analyte in plasma
$C(')_{tz}$	Measured (predicted) concentration of the analyte in plasma at the last time t_z at which quantification of the analyte in plasma was still possible
CT	Concomitant treatment
CTP	Clinical trial protocol
CTR	Clinical trial report
CTS	Clinical trial supply
CV	Arithmetic coefficient of variation
DILI	Drug induced liver injury
ECG	Electrocardiogram
EDC	Electronic data capture
[redacted]	
EOT	End of trial
F	Absolute bioavailability
GCP	Good clinical practice
gCV	Geometric coefficient of variation

GLP	Good laboratory practice
gMean	Geometric mean
HPC	Human Pharmacology Centre
HPLC-MS/MS	High performance liquid chromatography with tandem mass spectrometry
HR	Heart rate
IB	Investigator's brochure
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ISF	Investigator site file
[redacted]	[redacted]
LLOQ	Lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
[redacted]	[redacted]
NAFLD	Non-alcoholic fatty liver disease
NASH	Non-alcoholic steatohepatitis
NC	Not calculated
NCE	New chemical entity
NOA	Not analysed
NOAEL	No observed adverse effect level
NOR	No valid result
NOS	No sample available
PD	Pharmacodynamic(s)
PfoS	Powder for reconstitution of an oral solution
PK	Pharmacokinetic(s)
PKS	Pharmacokinetic set
PR	Pulse rate
QT	Time between start of the Q-wave and the end of the T-wave in an electrocardiogram
R	Reference treatment
RDC	Remote data capture
REP	Residual effect period
SAE	Serious adverse event
SCR	Screening
SfOS	Solvent for oral solution
ss	(at) steady state
[redacted]	[redacted]
SUSAR	Suspected Unexpected Serious Adverse Reaction
T	Test product or treatment

[redacted]

TDMAP	Trial Data Management and Analysis Plan
TMF	Trial master file
TS	Treated set
TSAP	Trial statistical analysis plan
ULN	Upper limit of normal
VAP	Vascular adhesion protein
[redacted]	[redacted]

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

Boehringer Ingelheim (BI) is developing BI 1467335 [redacted] in the indication of non-alcoholic steatohepatitis (NASH).

NASH is characterised histologically by a high level of steatosis, ballooning of hepatocytes, and necro-inflammation. NASH often leads to fibrosis which can progress to cirrhosis with a high risk of liver failure. [redacted]

With a prevalence of about 20 - 30% in the general population of Western countries, non-alcoholic fatty liver disease (NAFLD) is rapidly becoming the most common liver disease worldwide [R15-5365]. While simple hepatic steatosis can have a benign, non-progressive course, about 40% of patients with NAFLD progress to NASH. As the disease progresses, significant fibrosis develops in 37 - 41% of subjects within 15 years. In the United States, NASH is believed to be the most common cause of liver cirrhosis [R15-6070] which is estimated to be the 12th leading cause of death [R15-6057]. Patients with NASH are also at increased risk of hepatocellular carcinoma, even in the absence of cirrhosis [R15-5365]. By 2023, about 13 million patients are projected to have NASH with advanced stages (i.e. ≥ stage 3) of fibrosis (of those, 2.9 million in the US, 3.5 million in EU, 5 million in China). Individuals with advanced fibrosis are estimated to progress with a 4% annual event rate to cirrhosis. The risk of liver-related death in Western patients with NASH ranges from 10% over 13.7 years to 18% over 18.5 years [P13-02280].

To date, no approved therapy for liver fibrosis or effective disease modifying regimen for NASH is available, despite the strong interface with metabolic syndrome, obesity and Type 2 diabetes mellitus. The current standard of care for NASH is weight loss through diet and exercise to improve insulin resistance and lower fat mass which is a clinically challenging goal to achieve and shows minimal impact on disease progression [R15-6044].

1.2 DRUG PROFILE

BI 1467335 is a [redacted] that is expected to reduce oxidative stress and hepatic inflammation in steatohepatitis and prevent progression to fibrosis.

Non-clinical findings

Nonclinical pharmacology

[redacted]

Toxicology

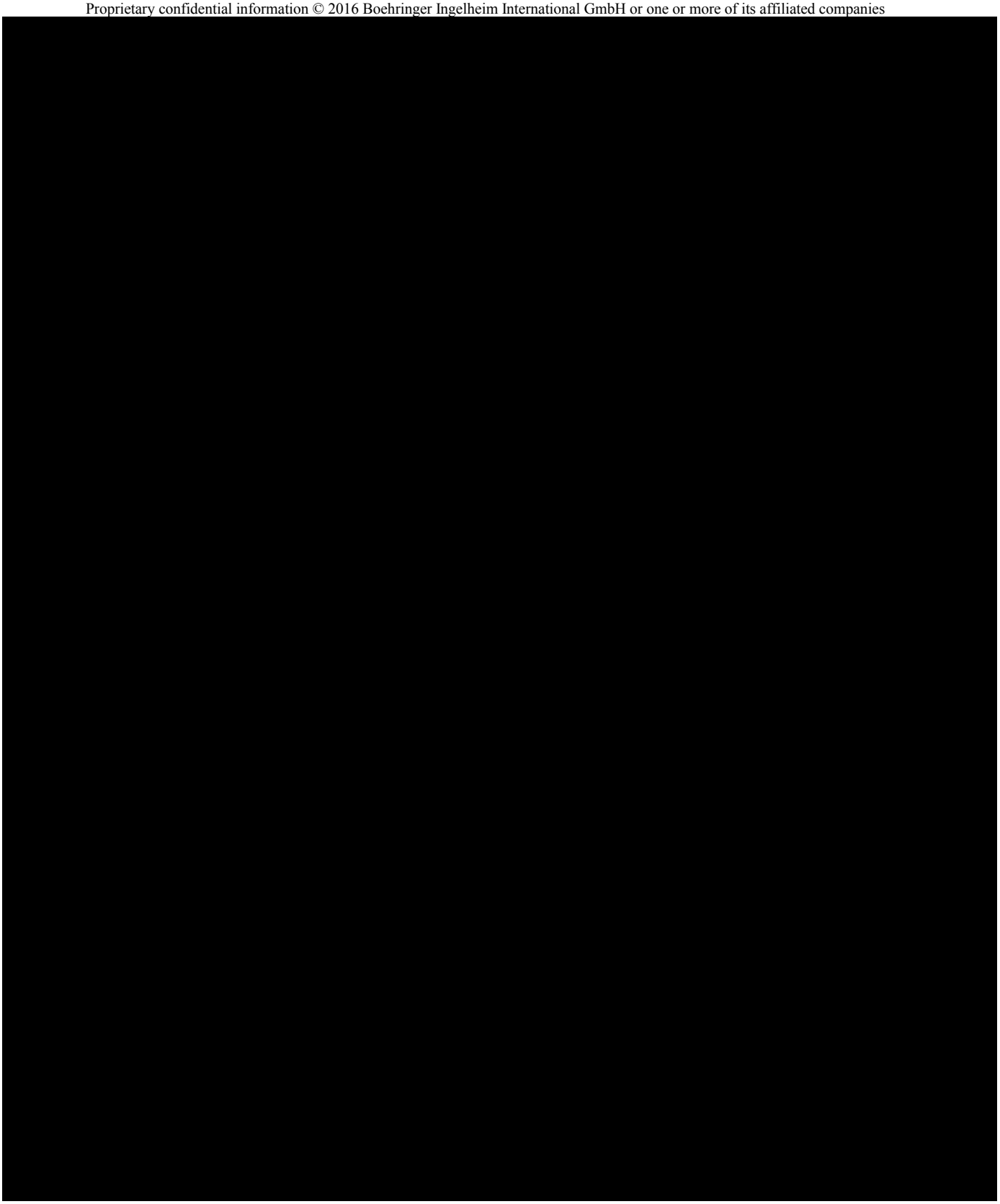
[redacted]

[redacted]

Clinical experience

BI 1467335 is currently in Phase I and has been tested in one completed and one ongoing healthy volunteer study, the combined single rising dose (SRD)/multiple rising doses (MRD) study [redacted] [c09036683] and the MRD study 1386.8 [data on file]. Drug doses in study [redacted] [c09036683], [redacted], were based on the HCL salt [redacted] of BI 1467335, whereas the already applied (study 1386.8 [data on file]) and further planned doses in BI studies refer to the free base [redacted]

[redacted]



2. RATIONALE, OBJECTIVES, AND BENEFIT - RISK ASSESSMENT

2.1 RATIONALE FOR PERFORMING THE TRIAL

This study is performed to compare (1) the bioavailability between oral solution and tablets, and to investigate (2) the influence of food on the absorption of BI 1467335 when administered as tablets.

Although BI 1467335 is characterised as [redacted] and 'important food effects on bioavailability are least likely for some drugs in this class, food can influence bioavailability, when there is a high first pass effect, extensive adsorption, complexation or instability of the drug substance in the gastrointestinal tract. In some cases, excipients or interactions between excipients and the food induced changes in the gut physiology can contribute to these food effects' [R03-2269].

In future clinical studies, the preferred mode of administration of BI 1467335 will be 'independent of food intake'. Currently, only pharmacokinetic data under fasted conditions are available. The planned food interaction study will generate pharmacokinetic information under fed conditions to support the future development in patients.

[redacted]

The dose of 10 mg was selected in this study, since it is intended to be used as maximum dose in NASH-patients.

2.2 TRIAL OBJECTIVES

The primary objective of this trial is to investigate the relative bioavailability of 10 mg of BI 1467335, given as film-coated tablet compared to BI 1467335, given as oral solution. This assessment will be performed under fasted conditions. Furthermore, the effect of food on relative bioavailability of the tablet formulation of BI 1467335 will be investigated.

[redacted].

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.

However, their participation in the study is of major importance to the development of a new therapy for NASH. Subjects are exposed to risks related to (1) study procedures and (2) exposure to trial medication.

Procedure-related risks

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

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

Drug-related risks and safety measures

Polymorph nuclear leukocytes (PMNs) migrate from the blood into areas of inflammation by binding to the endothelial cells of blood vessels via adhesion molecules. [redacted]

On target effects

BI 1467335 could cause on-target toxicity as its anti-inflammatory effects may reduce the immune response and thus worsen infections. However, a deleterious effect relating to a reduction in leukocyte or lymphocyte migration was not seen in any of the preclinical models. Nonetheless, close monitoring of clinical and laboratory signs of reduced immune response will be performed throughout the study.

Cardiac safety

[redacted]

Genotoxicity and fertility

[redacted]

Eye toxicity

[redacted]

[redacted]

Human safety profile

The human safety and tolerability profile in male healthy subjects was satisfactory for single doses of up to 17.7 mg ([redacted] [c09036683]) and for multiple doses given over 28 consecutive days of up to 10 mg in study 1386.8 [data on file] (see Section 1.2). There were no deaths or other serious adverse events. Adverse events, mostly reported as mild, had no apparent dose or exposure relationship.

Conclusion

Overall, no specific drug-related risks are anticipated. Still, the following safety considerations were made in order to minimize the risk for subjects in this study:

- Dose selection of BI 1467335 is based on previous clinical experience [redacted] [c09036683] and 1386.8 [data on file]) and the available preclinical package. For details, please refer to 'IB' [c04751792].
- The dose of 10 mg was selected in this study, since it is intended to be used as maximum dose in patients of the NASH clinical development program. Good safety and tolerability was demonstrated for a single dose [redacted] [c09036683]. Also, 14 consecutive daily [redacted] doses of BI 1467335 were safe and well tolerated in this study, and resulted in about 25-fold and 45-fold higher peak (C_{max}) and systemic (AUC) exposures, respectively, as compared to respective single doses. Even an unlikely food effect (see above) with a 10 mg dose should result in a range of exposure already previously experienced. Hence, subjects should therefore not be exposed to an undue risk
- Nonetheless, subjects will be clinically observed (e.g. for infections) and their laboratory, vital signs and ECG parameters will be closely monitored.
- Due to the large safety margins to the NOAEL in rats and dogs, no specific ophthalmological examinations (lens findings in rats) seem to be warranted in this study.

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

Healthy subjects are not expected to have direct medical benefit from participation in this study. However, it is considered that healthy subjects will not be exposed to undue risks and adverse events in relation to the information expected from this trial. Considering the medical need for the development of an effective and well tolerated drug to treat NASH, the benefit of this trial is considered to outweigh the potential risks and justifies the exposure of healthy human volunteers to 3 single doses of 10 mg of BI 1467335.

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

The study will be performed as a randomised, open-label, single dose, three-way crossover trial in healthy male subjects in order to compare the tablet under fasted conditions (Treatment A) to the oral solution under fasted conditions (Treatment B) and to assess the food effect on the PK of BI 1467335 by comparing the tablet under fed conditions (Treatment C) with the tablet under fasted conditions (Treatment A).

A total of 18 healthy male subjects are planned to participate in the trial. Subjects will be randomly allocated to 3 treatment sequences (ABC, BCA and CAB). The treatments will be 2 x 5 mg BI 1467335 tablet in the fasted state (Treatment A), 10 mg BI 1467335 oral solution in the fasted state (Treatment B) and 2 x 5 mg BI 1467335 tablet in fed state after a high caloric breakfast (Treatment C). For details, see Section 4.1.

There will be a washout period of at least 21 days between drug administrations in consecutive treatment periods.

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 (TCM), responsible for coordinating all required activities, in order to

- Manage the trial in accordance with applicable regulations and internal standard operation procedures (SOPs)
- Direct the clinical trial team in the preparation, conduct, and reporting of the trial
- Ensure appropriate training and information of local clinical monitors (CML), clinical research associates (CRAs), and participating trial sites

[redacted]

On-site monitoring, data management and statistical evaluation will be performed by BI according to BI SOPs or a contract research organisation appointed by BI.

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 GROUPS

For relative bioavailability trials, the crossover design is preferred due to its efficiency. Since each subject serves as his own control, the comparison between formulations/treatments is based on a comparison within subjects rather than between subjects. Therefore, this trial design removes intersubject variability from the comparison between formulations/treatments [see R94-1529].

Blinding is not possible because the treatments are distinguishable.

The open-label treatment is not expected to bias results, since the study endpoints are derived from measurement of plasma concentrations of the analyte provided by a bioanalytical laboratory which is blinded to treatment allocation.

3.3 SELECTION OF TRIAL POPULATION

It is planned that 18 healthy male subjects will enter the study. They will be recruited from the volunteers' pool of the trial site.

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

3.3.1 Main diagnosis for study entry

The study will be performed in healthy subjects.

3.3.2 Inclusion criteria

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

1. Healthy male subjects according to the investigators 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 55 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. Willingness to comply with contraception requirements. Subjects who are sexually active, must use, with their female partner, adequate contraception throughout the study and until one month after the last administration of trial medication. Adequate methods are:
    - Sexual abstinence *or*
    - A vasectomy performed at least 1 year prior to screening in combination with a barrier method (condom or diaphragm) *or*
    - Surgical sterilisation (including bilateral tubal occlusion, hysterectomy or bilateral oophorectomy) of the subjects female partner *or*
    - The use of condoms, if the female partner uses in addition an adequate contraception method, e.g., intrauterine device (IUD), hormonal contraception (e.g. implants, injectables, combined oral or vaginal contraceptives) that started at least 2 months prior to first drug administration, or barrier method (e.g. diaphragm with spermicide)

    Unprotected sexual intercourse with a pregnant female partner is not allowed throughout the study and until one month after the last administration of trial medication.

3.3.3 Exclusion criteria

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

1. Any finding in the medical examination (including BP, PR or ECG) is deviating from normal and judged as clinically relevant by the investigator
2. Repeated measurement of systolic blood pressure outside the range of 90 to 140 mmHg, diastolic blood pressure outside the range of 50 to 90 mmHg, or pulse rate outside the range of 50 to 90 bpm
3. Any laboratory value outside the reference range that the investigator considers to be of clinical relevance
4. Any evidence of a concomitant disease judged as clinically relevant by the investigator
5. Gastrointestinal, hepatic, renal, respiratory, cardiovascular, metabolic, immunological or hormonal disorders
6. Cholecystectomy and/or surgery of the gastrointestinal tract that could interfere with the pharmacokinetics of the trial medication (except appendectomy and simple hernia repair)

7. Diseases of the central nervous system (including but not limited to any kind of seizures or stroke), and other relevant neurological or psychiatric disorders
8. History of relevant orthostatic hypotension, fainting spells, or blackouts
9. Chronic or relevant acute infections
10. History of relevant allergy or hypersensitivity (including allergy to the trial medication or its excipients)
11. Use of drugs within 30 days prior to administration of trial medication, if that might reasonably influence the results of the trial (incl. QT/QTc interval prolongation)
12. Participation in another trial where an investigational drug has been administered within 60 days prior to planned administration of trial medication or current participation in another trial involving administration of investigational drug
13. Smoker (more than 10 cigarettes or 3 cigars or 3 pipes per day)
14. Inability to refrain from smoking on specified trial days
15. Alcohol abuse (consumption of more than 30 g per day)
16. Drug abuse or positive drug screening
17. Blood donation of more than 100 mL within 30 days prior to administration of trial medication or intended donation during the trial
18. Intention to perform excessive physical activities within 7 days prior to administration of trial medication or during the trial
19. Inability to comply with dietary regimen of trial site
20. A marked baseline prolongation of QT/QTc interval (such as QTc intervals that are repeatedly greater than 450 ms) or any other relevant ECG finding at screening
21. A history of additional risk factors for Torsades de Pointes (such as heart failure, hypokalaemia, or family history of Long QT Syndrome)
22. Subject is assessed as unsuitable for inclusion by the investigator, for instance, because considered not able to understand and comply with study requirements, or has a condition that would not allow safe participation in the study

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

23. Cataract in the medical history

For study restrictions, see Section 4.2.2.

3.3.4 Removal of subjects from therapy or assessment

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.

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

If a subject is removed from or withdraws from the trial prior to first administration of trial medication, the data of this subject will not be entered in the case report form (CRF) or trial database and will not be reported in the clinical trial report (CTR). If a subject is removed from or withdraws from the trial after first administration of trial medication, this will be documented and the reason for discontinuation must be recorded in the CRF. In this case, the data will be included in the CRF/trial database and will be reported in the CTR.

At the time of discontinuation, a complete end of trial examination will be performed, if possible, and the information will be recorded in the CRFs. If the discontinuation occurs before the end of the REP (see Section 5.2.2.2), the discontinued subject should, if possible, be questioned for AEs and concomitant therapies at or after the end of the REP in order to ascertain collection of AEs and concomitant therapies throughout the REP, if not contrary to any consent withdrawal of the subject. These discontinuations will be discussed in the CTR.

3.3.4.2 Discontinuation of the trial by the sponsor

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

1. New toxicological findings or serious adverse events invalidate the earlier positive benefit-risk-assessment. More specifically, the trial will be terminated, if more than 50% of the subjects show drug-related and clinically relevant adverse events of moderate or severe intensity or, if at least one drug-related serious adverse event is reported that is considered to be unacceptable
2. The expected enrolment goals overall or at a particular trial site are not met
3. Violation of GCP, or the CTP by a trial site or investigator, disturbing the appropriate conduct of the trial
4. The sponsor decides to discontinue the further development of the investigational product

3.3.5 Replacement of subjects

In case some subjects do not complete the trial, the trial clinical monitor together with the trial pharmacokineticist and the trial statistician are to decide, if and how many subjects will be replaced. A replacement subject will be assigned a unique study subject number, and will be assigned to the same treatment as the subject [redacted] replaces.

4. TREATMENTS

4.1 TREATMENTS TO BE ADMINISTERED

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

Doses refer to the dose of the free base.

4.1.1 Identity of BI investigational product and comparator product

The characteristics of the test product are given below. For details about dosage and treatment schedule, see Table 4.1.4: 1.

Substance:	BI 1467335 Treatment A (fasted) and Treatment C (fed)
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.

The characteristics of the reference product are given below:

Substance:	BI 1467335 Treatment B (fasted)
Pharmaceutical formulation:	Oral solution
Source:	BI Pharma GmbH & Co. KG, Germany
Unit strength:	0.5 mg/mL
Posology:	20 mL -0-0
Route of administration:	p.o.

A detailed description of the reconstitution instruction for the oral solution is given in Section 10.1 of this CTP.

4.1.2 Method of assigning subjects to treatment groups

The randomisation list of study subject numbers and assigned treatment sequences will be provided to the trial site in advance.

According to the planned sample size, the study is planned to be performed in two cohorts. Prior to start of the study, subjects willing to participate will be recruited to cohorts according to their temporal availability.

The allocation of subjects to study subject numbers will be performed prior to the first administration of trial medication in the morning of Day 1 (Visit 2). For this purpose, subjects will be allocated to a study subject number by drawing lots. By use of the randomisation list subjects are then assigned to a treatment sequence.

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 dose of 10 mg selected for this trial reflects the maximal dose intended to be applied to patients throughout the NASH development program. For this dose, safety data in humans are available (see Section 1.2).

4.1.4 Drug assignment and administration of doses for each subject

This trial is a three-way crossover study. All subjects will receive the three treatments in a randomised order. The treatments to be evaluated are outlined in Table 4.1.4: 1 below.

Table 4.1.4: 1 Dosage and treatment schedule

Treatment	Substance	Predose status	Formulation	Unit strength	Dosage	Total dose
A	BI 1467335	fasted	Film-coated tablet	5 mg/tablet	2 tablets, single dose	10 mg
B	BI 1467335	fasted	Oral solution	0.5 mg/mL	20 mL, single dose	10 mg
C	BI 1467335	fed	Film-coated tablet	5 mg/tablet	2 tablets, single dose	10 mg

The oral solution will be prepared according to the reconstitution instruction (Section 10.1) by qualified medical study personnel at the trial site under the responsibility of the investigator.

The medication will be administered as a single oral dose together with about 240 mL of water to a subject in the standing position under supervision of the investigating physician or an authorised designee. For details of drug application, please see Section 10.1.6.

The so-called four-eye principle (two-person rule) should be applied for the administration of trial medication and, if applicable, its preparation (e.g. reconstitution), if correct dosage cannot be ensured otherwise. Except for the breakfast in Treatment C, administration will be performed following an overnight fast starting not later than 10 h before scheduled dosing.

To evaluate the food effect on the PK of BI 1467335 tablet, in Treatment C, a high-fat, high-caloric meal will be served within 30 min before drug administration. The meal must be completely consumed prior to drug administration.

The composition of the standard high-fat, high-caloric meal will be in compliance with the FDA guidance 'Food-Effect Bioavailability and Fed Bioequivalence Studies' [R03-2269] as detailed in Table 4.1.4: 2.

Table 4.1.4: 2 Composition of the high-fat, high-caloric meal

Ingredients	kcal
2 chicken eggs (whole content)[1] for scrambled eggs	192
10 g butter for frying scrambled eggs	75
35 g fried bacon	186
2 toasted slices of wheat bread	130
15 g butter for buttering toast slices	113
115 g hash brown potatoes	132
240 mL whole milk (3.5% fat)	156
Sum[2]	984

[1] Alternatively liquid egg (consisting of pasteurized whole chicken egg) with an amount corresponding to 2 chicken eggs may be used

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

Subjects will be kept under close medical surveillance until 24 h following drug administration. During the first 4 h after drug administration, except for ECG and vital signs measurements and blood withdrawals or other medical reasons, they are not allowed to lie down (i.e. no declination of the upper body of more than 45 degrees from upright posture). For restrictions with regard to diet, see Section 4.2.2.2.

The treatments will be separated by a wash-out phase of at least 21 days.

4.1.5 Blinding and procedures for unblinding

No blinding will be performed because treatments are distinguishable from each other.

This Phase I trial will be handled in an open fashion throughout (i.e. 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 all subjects receive the same dose of different formulations in an open label design.

PK samples will be labelled in such a way that treatment allocation cannot be derived by the analytical site.

4.1.6 Packaging, labelling, and re-supply

[redacted]

The clinical trial supply consists of containers holding the trial medication which are labelled with trial identification.

The required information according to the German Drug Law as well as Annex 13/EU GMP Guideline will be provided on the containers. Smaller boxes within the clinical trial supply containers will be labelled with:

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

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

No re-supply is planned.

4.1.7 Storage conditions

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

4.1.8 Drug accountability

The investigator will receive the investigational drugs delivered by the sponsor when the following requirements are fulfilled:

- Approval of the study protocol by the IRB / ethics committee
- Approval/notification of the regulatory authority, e.g. competent authority
- Availability of the curriculum vitae of the principal investigator
- Availability of a signed and dated clinical trial protocol

Only authorised personnel, as documented in the form 'Trial Staff List', may dispense medication to trial subjects. The trial medication must be administered in the manner specified in the CTP. All unused medication will be disposed locally by the trial site upon

written authorisation by the clinical monitor. Receipt, usage and disposal must be documented on the respective forms. Account must be given for any discrepancies.

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

4.2 OTHER TREATMENTS, EMERGENCY-PROCEDURES, RESTRICTIONS

4.2.1 Other treatments and emergency procedures

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

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

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

4.2.2.2 Restrictions on diet and life style

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

From 1 h before drug intake until lunch, fluid intake is restricted to the milk (in Treatment C) served with breakfast (see Table 4.1.4: 2), the water administered with the drug, and an additional 240 mL of water at 2 h and 4 h post-dose (mandatory for all subjects). From lunch until 24 h post-dose, total fluid intake is restricted to 3000 mL.

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

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

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

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

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

4.3 TREATMENT COMPLIANCE

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

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

Adverse reaction

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

Serious adverse event

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

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

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

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

AEs considered ‘Always Serious’

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

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

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

Adverse events of special interest (AESIs)

The term AESI relates to any specific AE that has been identified at the project level as being of particular concern for prospective safety monitoring and safety assessment within this trial, e.g. the potential for AEs based on knowledge from other compounds in the same class. AESI need to be reported to the sponsor’s Pharmacovigilance Department within the same timeframe that applies to SAE, see Section 5.5.2.2.

The following are considered as AESIs in this trial:

Hepatic injury, as defined by the following alterations of hepatic laboratory parameters:

- An elevation of AST and/or ALT ≥3-fold ULN combined with an elevation of total bilirubin ≥2-fold ULN measured in the same blood sample, and/or
- Marked peak aminotransferase (ALT, and/or AST) elevations ≥10 fold ULN

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

Intensity of AEs

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

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

Causal relationship of AEs

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

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

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

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

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

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

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

5.2.2.2 Adverse event collection and reporting

AEs collection

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

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

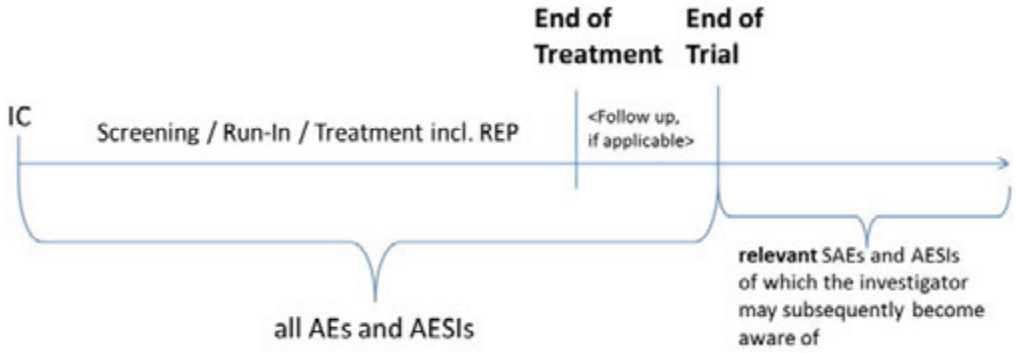
A carefully written record of all AEs shall be kept by the investigator in charge of the trial. Records of AEs shall include data on the time of onset, end time, intensity of the event and any treatment or action required for the event and its outcome.

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

- From signing the informed consent onwards through the residual effect period (REP), until 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 the trial due to screening failures prior to administration of any trial medication.

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

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



The REP of BI 1467335, when measurable drug levels or PD effects are still likely to be present, has not been defined yet. [redacted] (see Section 2.1), a preliminary REP is defined as [redacted] after administration of BI 1467335. Therefore, all AEs which will occur throughout the treatment phases and the preliminary REP will be considered as 'on treatment' (see Section 7.3.3). Events which occur after the preliminary REP and prior to the next drug administration will be considered as 'follow-up' events.

AE reporting to sponsor and reporting timelines

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

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

Information required

For each AE, the investigator should provide the information requested on appropriate CRF pages and the BI SAE form (if applicable).

The investigator should determine the causal relationship to the trial medication.

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

- Worsening of the underlying disease or of other pre-existing conditions

- Changes in vital signs, ECG, physical examination and laboratory test results, if they are judged clinically relevant by the investigator

If such abnormalities have already pre-existed prior to trial inclusion, they will be considered as baseline conditions.

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

5.2.3 Assessment of safety laboratory parameters

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

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

Manual differential white blood cell counts 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)
	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)
	Fibrinogen
Enzymes	Aspartate transaminase (AST/GOT)
	Alanine transaminase (ALT/GPT)
	Alkaline phosphatase (AP)
	Gamma-glutamyl transferase (GGT)
	Glutamate dehydrogenase (GLDH)
	Creatine kinase (CK)
	CK-MB, only if CK is elevated
	Lactate dehydrogenase (LDH)
	Lipase
	Amylase
Hormones[1]	Thyroid stimulating hormone (TSH)
	fT3, fT4
Substrates	Plasma glucose
	Creatinine
	Total bilirubin
	Direct bilirubin
	Total protein
	Protein electrophoresis[1]
	Albumin[1]
	Alpha-1-Globulin[1]
	Alpha-2-Globulin[1]
	Beta-Globulin[1]
	Gamma-Globulin[1]
	C-Reactive Protein (CRP)
	Uric acid
	Total cholesterol
	Triglycerides
Electrolytes	Sodium
	Potassium
	Chloride
	Calcium

Table 5.2.3: 1 Routine laboratory tests (cont.)

Functional lab group	Test name
Urinalysis[1] (Stix)	Urine nitrite Urine protein Urine glucose Urine ketone Urobilinogen Urine bilirubin Urine erythrocytes Urine leukocytes Urine pH
Urine sediment (microscopic examination, if erythrocytes, leukocytes nitrite or protein are abnormal in urine)	Only positive findings will be reported (for instance, the presence of sediment bacteria, casts in sediment, squamous epithelial cells, erythrocytes, leukocytes)

[1] Only at screening and end of trial: Hormones, protein electrophoresis, and urinalysis / urine sediment

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

Table 5.2.3: 2 Exclusionary laboratory tests

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

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

Laboratory tests listed in Table 5.2.3: 1 and 5.2.3: 2 will be performed at [redacted] with the exception of drug screening. This test will be performed at the trial site using AccuSign® DOA 10 test.

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

5.2.4 Electrocardiogram

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

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

All ECGs will be stored electronically on the Muse CV Cardiology System (GE Medical Systems, Freiburg, Germany). Electrode placement will be performed according to the method of Wilson, Goldberger and Einthoven modified by Mason and Likar (hips and shoulders instead of ankles and wrists).

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 carefully be monitored and, if necessary, a 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, Freiburg, Germany) at the time 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 at the same arm, if possible.

5.2.5.2 Medical examinations

At the screening visit, the medical examination will include demographics, including height and body weight, smoking and alcohol history, relevant medical history and concomitant therapy, review of inclusion and exclusion criteria, review of vital signs (BP, PR), 12-lead ECG, laboratory tests, and a physical examination. At the end of trial examination, it will include review of vital signs, 12-lead ECG, laboratory tests, body weight, 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 and pharmacodynamic 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 trial medication. Safety assessments are standard. They are accepted as safety and tolerability evaluation 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. Biomarkers and measurements outlined in Section 5.6 are of exploratory nature only.

5.5 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

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

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

5.5.1 Pharmacokinetic endpoints

5.5.1.1 Primary endpoints

The following primary endpoints will be determined for BI 1467335:

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

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

5.5.1.2 Key /Secondary endpoint

- No secondary endpoints are defined in this study

[redacted]

5.5.2 Methods of sample collection

5.5.2.1 Plasma sampling for pharmacokinetic analysis

For quantification of BI 1467335 plasma concentrations, approximately 2.7 mL of blood will be taken from an antecubital or forearm vein into an [redacted] at the times indicated in the Flow Chart. Blood will be withdrawn by means of either an indwelling venous catheter or by venipuncture with a metal needle.

After blood withdrawal, [redacted] will be centrifuged at about 2000 g to 4000 g and at a temperature of 4 - 8°C for about 10 minutes. Two plasma aliquots will be obtained [redacted]

Until transfer on dry ice to the analytical laboratory, the aliquots will be stored upright at about -20°C or below at the trial site. At the analytical laboratory plasma samples will be stored at about -20°C or below until analysis.

[redacted]

After centrifugation, aliquots should be pipetted and frozen as soon as possible. The first aliquot should contain at least 0.7 mL plasma. The second aliquot that might contain 0.7°ml or less plasma will be used as analytical back-up sample. For each aliquot, the time when the sample is placed in the freezer will be documented. The second aliquot will be transferred to the analytical laboratory after the bioanalyst has acknowledged safe arrival of the first aliquot.

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

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

5.5.3 Analytical determinations

5.5.3.1 Analytical determination of BI 1467335 plasma concentration

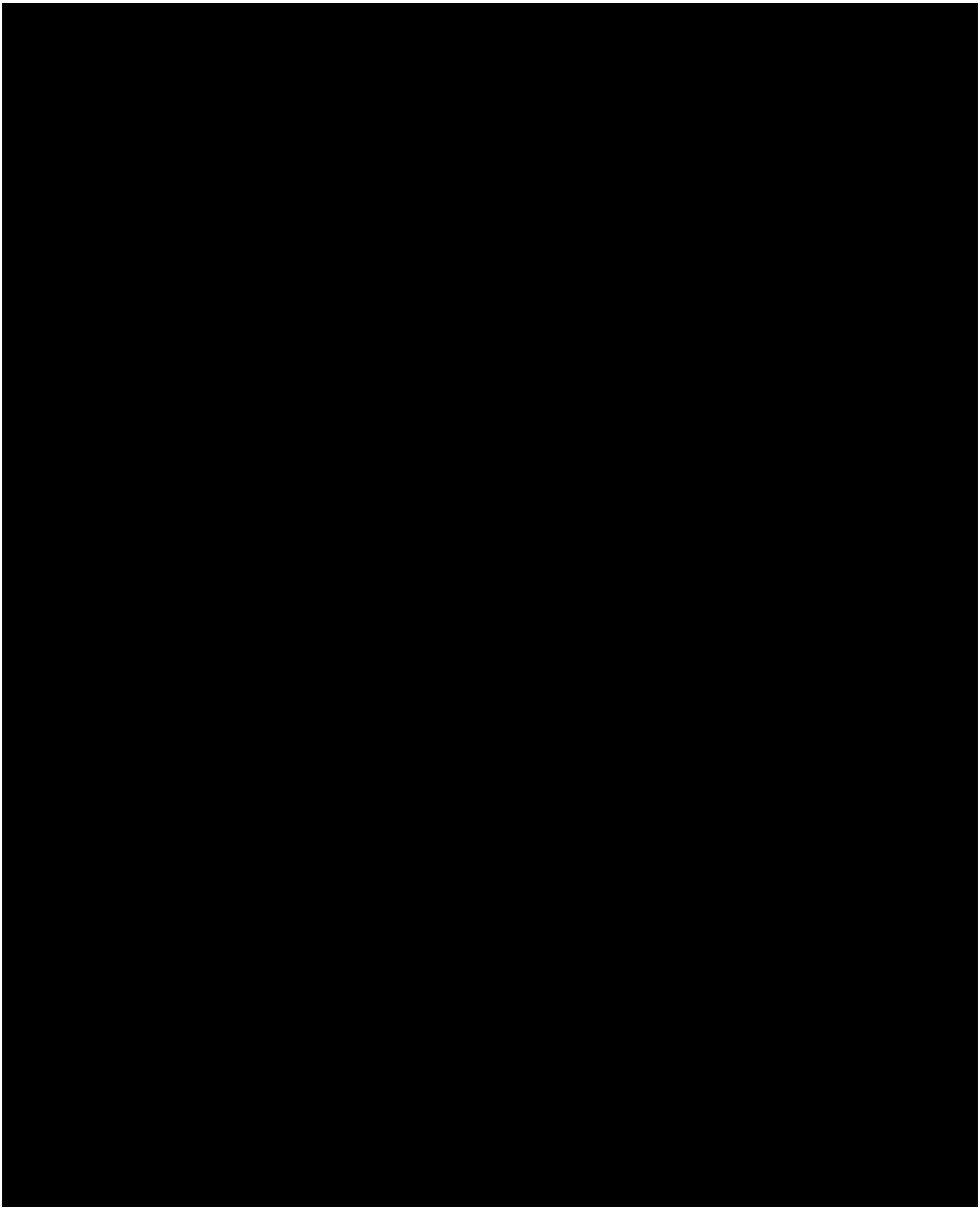
BI 1467335 concentrations in plasma will be determined by a validated LC-MS/MS (liquid chromatography tandem mass spectrometry) assay. All details of the analytical method will be available prior to the start of sample analysis.

The analysis will be performed at:

[redacted]

During sample analysis, the bioanalyst will be blinded to treatment allocation and will have no access to the random code.

5.6 BIOMARKERS



[redacted]

5.7 PHARMACOKINETIC - PHARMACODYNAMIC RELATIONSHIP

[redacted]

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

Exact times of measurements outside the permitted time windows will be documented. The acceptable time windows for screening, Visits 3 and 4, and end of trial examination are given in the Flow Chart.

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

The acceptable deviation from the scheduled time for vital signs, ECG and laboratory tests will be ± 30 min on Day 1, and ± 60 min on Day 2.

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

For planned sampling times of the PK [redacted] blood samples, see Flow Chart. While these nominal times should be adhered to as closely as possible, 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

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, see Sections 5.2.3 to 5.2.5.

[redacted]

6.2.2 Treatment periods

Each subject is expected to participate in each of the three treatment periods (drug administration on Day 1 of each period, see Table 4.1.4: 1). Treatment periods will be separated by at least 21 days between drug administrations.

On Day -1 of each treatment period study participants will be admitted to the trial site and kept under close medical surveillance for at least 24 h following drug administration on Day 1. Subjects will then be allowed to leave the trial site after formal assessment and confirmation of their fitness. Within the time window Day -5 to -1 of Visits 3 and 4, safety laboratory will be taken and AE/ concomitant questioning will be done.

For details on time points and procedures for collection of plasma samples for PK [redacted] analysis, refer to Flow Chart and Sections 5.5.2 and 5.6.3.

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, see Flow Chart. AEs and concomitant therapy will be assessed continuously from screening until the end of trial examination.

6.2.3 End of trial examination

For AE assessment, laboratory tests, body weight, recordings 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 objectives of this trial are to investigate by means of pharmacokinetic parameters (1) the relative bioavailability of 10 mg BI 1467335 administered as 2 x 5 mg tablets compared to 10 mg BI 1467335 administered as an oral solution, and (2) the effect of food on the bioavailability of the tablet formulation, following oral administration. The trial is designed to allow intra-subject comparisons and will be evaluated statistically by use of an appropriate linear model.

The secondary objective is the evaluation and comparison of several further pharmacokinetic parameters between treatments. The secondary objective will be assessed by descriptive statistics.

An additional objective of the trial will be the assessment of safety and tolerability that will be evaluated by descriptive statistics.

7.1.2 Endpoints

Relative bioavailability and food effect is to be determined on the basis of primary pharmacokinetic endpoints (see Section 5.5.1.1).

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

7.1.3 Model

The statistical model used for the analysis of primary endpoints will be an analysis of variance (ANOVA) model on the logarithmic scale. This model will include effects accounting for the following sources of variation: ‘sequence’, ‘subjects nested within sequences’, ‘period’ and ‘treatment’. The effect ‘subjects within sequences’ will be considered as random, whereas the other effects will be considered as fixed. The model is described by the following equation:

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

y_{ijkm} = logarithm of response (endpoint, see Section 5.5.1) measured on subject m in sequence i receiving treatment k in period j

μ = the overall mean

ζ_i = the ith sequence effect, i = 1, 2, 3

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

π_j = the j^{th} period effect, j = 1, 2, 3

τ_k = the k^{th} treatment effect, k = 1, 2, 3

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

7.2 NULL AND ALTERNATIVE HYPOTHESES

The relative bioavailability of BI 1467335 tablet formulation (Test, T1) compared to BI 1467335 oral solution (Reference, R1) will be estimated by the ratios of the geometric means (T1/R1) for the primary PK endpoints. The effect of food on the bioavailablity of BI 1467335 will be estimated by the ratios of the geometric means (T2/R2) of the tablet under fed conditions (T2) and under fasted conditions (R2) for the 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. Since the main focus is on estimation (and not testing), an acceptance range was not specified, i.e. no hypothesis will be tested.

7.3 PLANNED ANALYSES

7.3.1 Primary endpoint analyses

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

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

Plasma concentration data and parameters of a subject will be included in the statistical PK analyses, if they are not flagged for exclusion due to a protocol violation relevant to the evaluation of PK (to be decided not later than in the Report Planning Meeting) or due to PK non-evaluability (as revealed during data analysis, based on the criteria specified below). Exclusion of a subject’s data will be documented in the CTR.

Relevant protocol violations may be:

- Incorrect trial medication taken, i.e. the subject received at least one dose of trial medication to which the subject was not assigned to
- Incorrect dose of trial medication taken
- Use of restricted medications (refer to Section 4.2.2.1)

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

- The subject experienced emesis at or before two times median t_{max} of the respective treatment (Median t_{max} is to be determined excluding subjects having experienced emesis)
- Pre-dose concentration is >5% of the C_{max} value of that subject
- Samples/concentration data at critical phases of PK disposition curve are missing

The PK parameter analysis set (PKS) will include all subjects in the Treated Set (TS) who provide at least one primary PK parameter that is not excluded according to the description above. Thus, a subject will be included in the PKS, even if he contributes only one PK parameter value for one period to the statistical assessment.

Point estimates, the ratios of the geometric means (T/R) for the primary endpoints (see Section 5.5.1.1), and their two-sided 90% confidence intervals (CIs) will be provided.

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

[redacted]

7.3.3 Safety analyses

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

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

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

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, all AEs which will occur throughout the treatment phase and the preliminary REP will be considered as 'on treatment'. Events which occurred after the preliminary REP will be considered as 'follow-up' events (refer to Section 5.2.2.2).

These assignments, including the corresponding time intervals, will be defined in detail in the TSAP.

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

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

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

Relevant ECG findings 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 (see Section 7.3.1) will be reported with their individual plasma concentrations and individual pharmacokinetic parameters. However, they will not be included in descriptive statistics or other statistical assessments for pharmacokinetic parameters.

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

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 applies also to the lag phase, including pre-dose values).

7.4.3 Pharmacokinetic parameters

Handling of missing PK data will be performed according to the relevant SOP of the Sponsor (001-MCS-36-472). Missing PK parameters will not be imputed.

For the non-compartmental analysis, concentration data, identified as NOS, NOR or NOA will, in general, 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

Subjects will be randomised to one of three treatment sequences in a 1:1:1 ratio. The block size will be documented in the CTR.

The sponsor will arrange for the randomisation as well as packaging and labelling of trial medication.

The randomisation list will be generated using a validated system which involves a pseudo-random number generator and a supplied seed number so that the resulting allocation is both reproducible and non-predictable.

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

7.6 DETERMINATION OF SAMPLE SIZE

It is planned to include a total of 18 subjects in the trial because this sample size is considered sufficient to achieve the aims of this exploratory trial.

With this sample size, the below precision of the ratio of geometric means (test/reference) can be expected. Precision is defined as the ratio of upper to lower confidence interval limit.

Note that the precision is independent of the actual ratio of geometric means.

The observed geometric coefficient of variation (gCV) for BI 1467335 after single oral doses of 10 mg [redacted] BI 1467335 was 104% for $AUC_{0\text{-}tz}$ and 94% for C_{max} [redacted], [c09036683]). The reported variability listed in this trial (calculated from 6 individuals) originates from a parallel group design and is an estimate of the total variability and not of the between-subject variability. For a crossover study, an estimate of the intra-individual gCV is needed. Together with the correlation between two responses of the same subject ρ, we can estimate the intra-individual variability out of the total variability. A reasonable range for ρ in PK trials based on former experience is 0.6 to 0.7, where $\rho = 0.6$ is the conservative choice. Table 7.6: 1 provides an overview of the resulting intra-individual gCVs.

Table 7.6: 1 Estimates of the intra-individual gCV

ρ	Endpoint	gCVT*	σ_T^2	σ_W^2	gCVw**
0.6	C_{max}	94%	0.635	0. 254	53.8%
	$AUC_{0\text{-}tz}$	104%	0. 733	0. 293	58.4%
0.7	C_{max}	94%	0. 635	0. 190	45.8%
	$AUC_{0\text{-}tz}$	104%	0. 733	0. 220	49.6%

* gCV_T indicates the gCV for total variability
** gCV_W indicates the gCV for intra-individual variability

Assuming a gCV of 58.4% for $AUC_{0\text{-}tz}$ of BI 1467335 and given the chosen sample size of 18 subjects, the precision of the two-sided 90% confidence interval of the gMean ratio will be approximately 2.09 (upper confidence limit/lower confidence limit); for a larger correlation of ρ =0.7 and assumed intra-individual gCV of 49.6% for $AUC_{0\text{-}tz}$ of BI 1467335, the precision would be approximately 1. 89.

Table 7.6: 2 provides an overview of the 90% confidence intervals that are expected with 95% probability, for possible scenarios of the ρ, gCV and intra-subject ratios (T/R).

Table 7.6: 2 Precision and expected two-sided 90% confidence intervals around the ratios of geometric means for different correlations (*ρ)* and ratios in a 3x3x3 cross-over trial (N=18)

ρ	PK parameter	Total gCV(%)[1]	Intra-indiv. gCV (%)	T/R (%)	90% CI (%)	Precision (Upper CL /Lower CL)
0.6	C_{max}	94%	53.8%	50	(36, 70)	1.98
				100	(71, 141)	1.98
				150	(107, 211)	1.98
	AUC_{0-tz}	104%	58.4%	50	(35, 72)	2.09
				100	(69, 144)	2.09
				150	(104, 217)	2.09
0.7	C_{max}	94%	45.8%	50	(37, 67)	1.81
				100	(74, 134)	1.81
				150	(112, 202)	1.81
	AUC_{0-tz}	104%	49.6%	50	(36, 69)	1.89
				100	(73, 137)	1.89
				150	(109, 206)	1.89

[1]The total gCV in this table was calculated from individuals taken 10 mg [redacted] [c09036683])

All calculations were performed as described by Kupper and Hafner [R12-0972] using R Version 3.0.3.

8. INFORMED CONSENT, DATA PROTECTION, TRIAL RECORDS

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

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

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

Insurance Coverage: 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 to 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 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 is to be retained by the investigator as part of the trial record. 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 laws. The level of disclosure must also be explained to the subject.

The subject must be informed that his medical records may be examined by authorised monitors (CML/CRA) 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.

Data management procedures to ensure the quality of 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.

[redacted]

8.3.1 Source documents

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

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

[redacted]

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 (CRA)/on site monitor and auditor may review all CRFs, and written informed consents. The accuracy of the data will be verified by reviewing the documents described in Section 8.3.1.

8.3.3 Storage period of records

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

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

8.4 EXPEDITED REPORTING OF ADVERSE EVENTS

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

8.5 STATEMENT OF CONFIDENTIALITY

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

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

8.6 COMPLETION OF TRIAL

The IEC / competent authority of the 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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R94-1529 Chow SC, Liu JP, editors. Design and analysis of bioavailability and bioequivalence studies. New York: Marcel Dekker Inc., 1992.

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

R15-5365 Weston CJ, Shepherd EL, Claridge LC et al. Vascular adhesion protein-1 promotes liver inflammation and drives hepatic fibrosis. Journal of Clinical

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

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

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

9.2 UNPUBLISHED REFERENCES

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

c04751792 [redacted] Investigator's Brochure: BI 1467335 in NASH 28 Apr 2016.

c09036683 Single ascending dose and multiple ascending dose Phase 1 study [redacted] administered orally in healthy adult males. [redacted] 13 Nov 2015.

n00244592 BI 1467335: 4-week oral (gavage) supplementary toxicity study in Sprague Dawley rats. [redacted].

n00247850 [redacted] A Four-Week Oral Repeat Dose Toxicity and Toxicokinetic Study of [redacted] in Beagle Dogs[redacted]. 4 Nov 2014.

10. APPENDICES

10.1 RECONSTITUTION INSTRUCTION

10.1.1 Drug supplies overview

a) BI 1467335 Powder for Oral Solution 40 mg (target solution concentration BI 1467335: 0.5 mg/mL), provided in 100 mL brown glass bottles with screw cap

b) Solvent for Oral Solution 80 mL ([redacted] provided in 100 mL glass vials with tear-off caps

10.1.2 Required equipment and dosing aids - overview

a) Mechanical (orbital) shaker for bottles (e.g. Bühler Type KL2)

b) Dosing dispensers/syringes and bottle adapters

For the withdrawal of respective volume aliquots from the final oral solution to be administered, amber oral dispensers/ syringes (e.g. BAXA/ BAXTER ExactaMed) should be used in a size as close as possible to the required dose volume. For this purpose a range of syringe sizes from 1 mL up to 60 mL should be stocked at the trial site. In order to ease the withdrawal of the oral solution from glass bottles with the above syringes, bottle adapters (e.g. BAXA/ BAXTER AdaptaCap, Bottle Adapters (E-28 mm), Order No. H9385105) and dispenser tip caps (e.g. Order No 50300) should be used and stocked in the trial sites.

Possible amber BAXA ExactaMed dispensers/ syringes

- BAXA ExactaMed amber oral dispenser 1 mL – e.g. Order No – 1601*
- BAXA ExactaMed amber oral dispenser 3 mL – e.g. Order No – 1602*
- BAXA ExactaMed amber oral dispenser 5 mL – e.g. Order No – 1605*
- BAXA ExactaMed amber oral dispenser 10 mL – e.g. Order No – 1610*
- BAXA ExactaMed amber oral dispenser 20 mL – e.g. Order No – 1620*
- BAXA ExactaMed amber oral dispenser 35 mL – e.g. Order No – 1635*
- BAXA ExactaMed amber oral dispenser 60 mL – e.g. Order No – 1650*

* … or corresponding BAXTER Order-No

Only CE certified syringes are to be used!

10.1.3 Reconstitution procedure

2 bottle concept, see also Section 10.1.4.

[redacted]

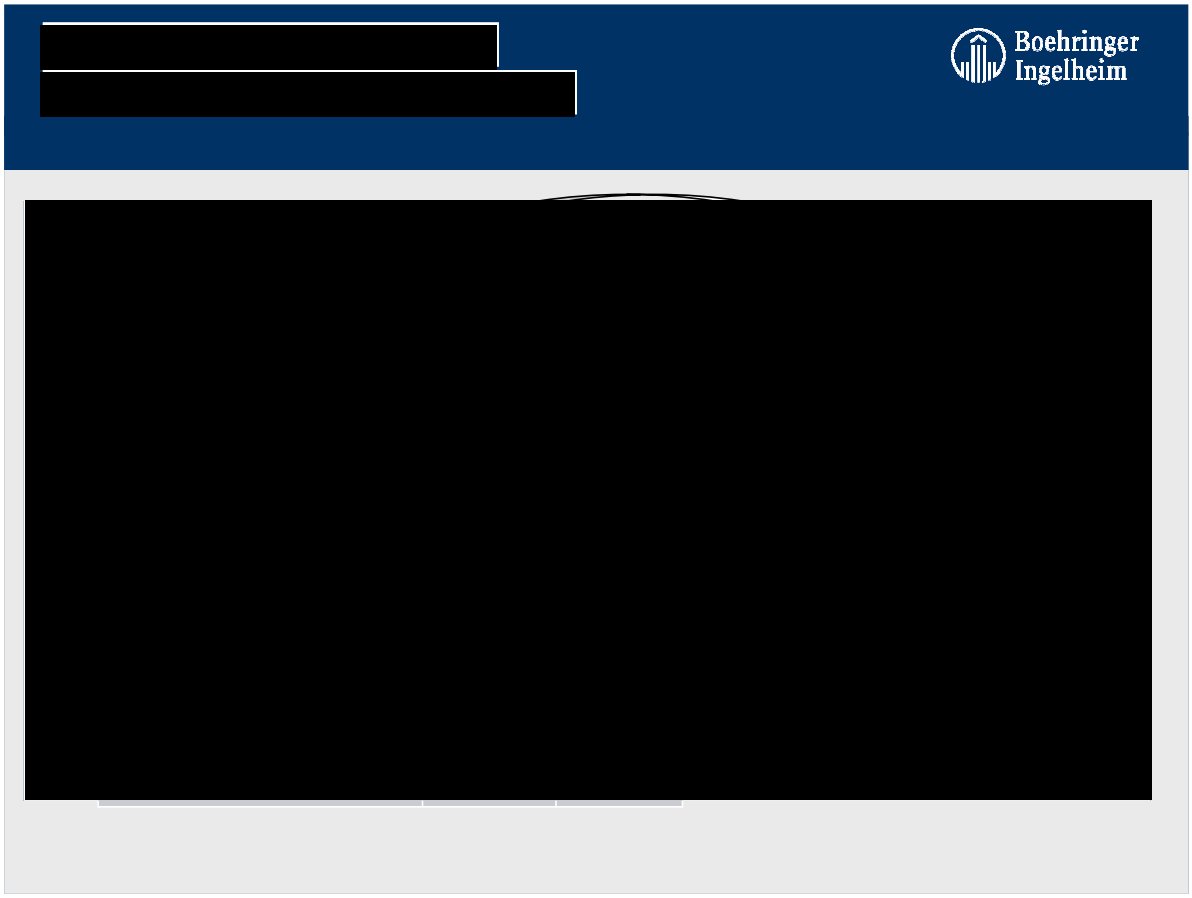
Step 2: Open the vial containing the solvent for oral solution

[redacted]

The final BI 1467335 oral solution concentration is 0.5 mg/mL.

10.1.4 Illustration of reconstitution procedure

The following scheme on the principle followed for the present PfoS formulation, 2-bottle concept, should serve as an additional illustration to clarify, how the reconstitution has to be performed.



The following picture shows an example of the powder and solvent bottles needed for the preparation of the final oral solution for administration.

10.1.5 In-use stability

The in-use stability of the reconstituted solution is [redacted] after its preparation, incl. storage in BAXA dispensers/syringes until administration. Therefore, it must be prepared in the morning of the administration. Further details are given on the CTS labels.

10.1.6 Mode of application

Withdraw the required volume aliquot with amber dispensers/syringes (e.g. BAXA/ BAXTER ExactaMed) to obtain the required doses. If the complete content of a bottle is to be used, it can be administered directly out of the bottle. Use syringes at a volume size as close as possible to the volume to be withdrawn.

Please note that it is the responsibility of the investigator to assure that appropriate supplies are used for administration of a dose, based on guidance in the clinical trial protocol, and dosing is limited to the allowed dosing range for a specific dose formulation as stated in this Reconstitution Instruction.

10.1.7 General remarks - important!

Because of lacking analytical coverage beyond the instructed preparation procedure of the different dose formulations, no further (external) dilutions of the reconstituted solutions are allowed!

The present Reconstitution Instruction does not contain any advice how to withdraw a specific dose from the reconstituted solutions. The specific dose volumes to be withdrawn from the described dose formulations in order to obtain a required dose will be calculated and documented by TransMed in the Clinical Trial Protocol (CTP) and subsequent documents (e.g. work sheets)!

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

This is the original protocol.

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

APPROVAL / SIGNATURE PAGE

Document Number: c09164690 **Technical Version Number:1.0**

Document Name: clinical-trial-protocol

Title: Relative bioavailability of a BI 1467335 tablet compared to a BI 1467335 oral solution and the effect of food on the bioavailability of the tablet following oral administration (a randomised, open-label, single dose, three-way crossover trial in healthy male subjects)

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Author-Trial Clinical Monitor	[redacted]	13 Oct 2016 15:52 CEST
Approval-Team Member Medicine	[redacted]	13 Oct 2016 16:51 CEST
Author-Trial Clinical Pharmacokineticist		14 Oct 2016 16:48 CEST
Approval-Therapeutic Area [redacted]		14 Oct 2016 18:32 CEST
Author-Trial Statistician		15 Oct 2016 14:27 CEST
Verification-Paper Signature Completion		18 Oct 2016 11:38 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed