Clinical Trial Protocol

	Document Number: c17401132-03
EudraCT No.:	2017-002180-18
BI Trial No.:	1386-0002
BI Investigational Product:	BI 1467335
Title:	Pharmacokinetics, safety and tolerability after multiple dose administration of BI 1467335 in subjects with moderate renal impairment and subjects with normal renal function (a mono-centric, open-label study in matched-group design)
Lay Title:	This study tests how BI 1467335 is taken up in the body of people with normal kidney function and people with reduced kidney function. The study also looks at how well the participants tolerate BI 1467335.
Clinical Phase:	I
Trial Clinical Monitor:	Phone: Fax:
Principal Investigator:	Phone: Fax:
Status:	Final Protocol (Revised Protocol (based on global amendment 2))
Version and Date:	Version: 3.0 Date: 15 March 2018

CLINICAL TRIAL PROTOCOL SYNOPSIS

Name of company: Boehringer Ingelheim		**Tabulated Trial Protocol**	
Name of finished product: Not applicable			
Name of active ingredient: BI 1467335			
Protocol date: 21 July 2017	**Trial number:** 1386-0002		**Revision date:** 15 March 2018

Title of trial:	Pharmacokinetics, safety and tolerability after multiple dose administration of BI 1467335 in subjects with moderate renal impairment and subjects with normal renal function (a mono-centric, open-label study in matched-group design)
Principal Investigator:	
Trial site:	
Clinical phase:	I
Objective:	To investigate the effect of moderate renal impairment on the pharmacokinetics of BI 1467335
Methodology:	Multiple-dose, open-label in matched-group design
No. of subjects:	
total entered:	20
each treatment:	10
Diagnosis:	Male and female subjects (at least 25% of each gender) with moderate renal impairment based on assessment of eGFR (30 – 59 mL/min/1.73m^2); healthy subjects will be matched by gender, race, smoking status and within ±10% of age and BMI to renal impaired subjects
Main criteria for inclusion:	Male and female subjects age 18 to 79 years, body mass index (BMI) 18.5 to 34 kg/m^2 Glomerular filtration rate (GFR), based on CKD-EPI formula: - 30 to 59 mL/min/1.73m^2 for moderate renal impairment (group 1) with at least 5 subjects with an eGFR between 30 and 45 ml/min/1.73m^2 - ≥ 90 mL/min/1.73m^2 for healthy subjects (group 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
Comparator product:	Not applicable
Duration of treatment:	28 days with multiple doses of BI 1467335 q.d.
Criteria for pharmacokinetics:	Primary endpoints: AUC_{0-24} and C_{max} (Day 1); $AUC_{\tau,28}$ and $C_{max,28}$ (Day 28) of BI 1467335 Secondary endpoints: $AUC_{\tau,14}$ and $C_{max,14}$ (Day 14) of BI 1467335 Further parameters of interest as appropriate

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Criteria for safety:	Adverse events (AEs), safety laboratory tests, 12-lead electrocardiogram (ECG), vital signs (blood pressure [BP], pulse rate [PR]), and physical examination		
Statistical methods:	Descriptive statistics for primary and all other parameters will be calculated. To assess the effect of moderate renal impairment on the pharmacokinetics of BI 1467335, point estimates (geometric means) of the intra-subject ratios (moderate renal impaired subjects compared to their matched healthy volunteer controls) of BI 1467335 and the two-sided 90% confidence intervals will be calculated for the primary and secondary PK endpoints mentioned above. The statistical model will be an ANOVA on log-transformed parameters including the fixed effect "degree of renal impairment" and subject pair as a random effect.		

FLOW CHART

Visit	Day	Planned time (relative to first drug administration [h:min]	Approximate clock time of actual day [h:min]	Event and comment	Safety laboratory	PK_{blood}	PK_{urine} [9]	12-lead ECG	Vital signs (BP, PR)	Questioning for AEs and concomitant therapy [6]
1	-21 to -3			Screening (SCR)[1]	x			x	x	
2[15]	-2	-48:00	08:00	Ambulatory visit[7]	x			x	x	x
	-1	-12:00	20:00	Admission to trial site[5]						
	1	-2:00	06:00		x[11,2]	x[12]	x	x[2,3]	x[2]	x[2]
		0:00	08:00	First drug administration[10, 13]			▲			
		0:15	08:15			x	|			
		0:30	08:30			x	|	x[3]	x	
		0:45	08:45			x	|			
		1:00	09:00			x	|	x[3]	x	x
		1:30	09:30			x	|			
		2:00	10:00	240 mL fluid intake and light breakfast[3]		x	|		x	x
		3:00	11:00			x	|			
		4:00	12:00	240 mL fluid intake, thereafter lunch[3]		x	+		x	x
		6:00	14:00			x	|			
		8:00	16:00	Snack (optional)[3]		x	+	x[3]	x	x
		10:00	18:00	Dinner[3]		x	|			
		12:00	20:00			x	+	x[3]	x	x
	2	23:55	07:55			x	|	x[2,3]	x[2]	x[2]
		24:00	08:00	Drug administration, dispense of study medication[10,13]			▼			
		25:00	09:00			x				
		26:00	10:00	Discharge from trial site (confirmation of fitness)[14], optional light breakfast		x		x[3]	x	x
	4	71:55	07:55			x			x[2]	x[2]
		72:00	08:00	Drug administration[10,13]						
		73:00	09:00			x				
		74:00	10:00	Discharge from trial site, optional light breakfast		x			x	x
	7	143:55	07:55			x		x[2,3]	x[2]	x[2]
		144:00	08:00	Drug administration, dispense of study medication[10,13]						
		145:00	09:00			x				
		146:00	10:00	Discharge from trial site, optional light breakfast		x		x[3]	x	x
	10	215:55	07:55			x			x[2]	x[2]
		216:00	08:00	Drug administration[10,13]						
		217:00	09:00			x				
		218:00	10:00	Discharge from trial site, optional light breakfast		x			x	x
	13	300:00	20:00	Admission to trial site[5]						x

Visit	Day	Planned time (relative to first drug administration [h:min]	Approximate clock time of actual day [h:min]	Event and comment	Safety laboratory	PK_{blood}	PK_{urine} [9]	12-lead ECG	Vital signs (BP, PR)	Questioning for AEs and concomitant therapy [6]
2[15]	14	311:55	07:55		x[2]	x		x[2,3]	x[2]	x[2]
		312:00	08:00	Drug administration[10, 13]			▲			
		312:15	08:15			x	|			
		312:30	08:30			x	|	x[3]	x	
		312:45	08:45			x	|			
		313:00	09:00			x	|	x[3]	x	x
		313:30	09:30			x	|			
		314:00	10:00	240 mL fluid intake and light breakfast[3]		x	|		x	x
		315:00	11:00			x	|			
		316:00	12:00	240 mL fluid intake, thereafter lunch[3]		x	+		x	x
		318:00	14:00			x	|			
		320:00	16:00	Snack (optional)[3]		x	+	x	x	x
		322:00	18:00	Dinner[3]		x	|			
		324:00	20:00			x	+	x	x	x
	15	335:55	07:55			x	|	x[2,3]	x[2]	x[2]
		336:00	08:00	Drug administration, dispense of study medication[10,13]			▼			
		337:00	09:00			x				
		338:00	10:00	Discharge from trial site (confirmation of fitness)[14], optional light breakfast		x		x[3]	x	x
	17	383:55	07:55			x			x[2]	x[2]
		384:00	08:00	Drug administration[10,13]						
		385:00	09:00			x				
		386:00	10:00	Discharge from trial site, optional light breakfast		x			x	X
	21	479:55	07:55			x		x[2,3]	x[2]	x[2]
		480:00	08:00	Drug administration, dispense of study medication[10,13]						
		481:00	09:00			x				
		482:00	10:00	Discharge from trial site, optional light breakfast		x		x[3]	x	x
	25	575:55	07:55			x				x[2]
		576:00	08:00	Drug administration, discharge from trial site						
	26	599:55	07:55			x				x[2]
		600:00	08:00	Drug administration, discharge from trial site						
	27	636:00	20:00	Admission to trial site[5]						x

Visit	Day	Planned time (relative to first drug administration [h:min]	Approximate clock time of actual day [h:min]	Event and comment	Safety laboratory	PK_{blood}	PK_{urine} [9]	12-lead ECG	Vital signs (BP, PR)	Questioning for AEs and concomitant therapy [6]
2[15]	28	647:55	07:55		x[2]	x		x[2,3]	x[2]	x[2]
		648:00	08:00	Last drug administration[10, 13]			▲			
		648:15	08:15			x	|	x		
		648:30	08:30			x	|	x	x	
		648:45	08:45			x	|	x	x	
		649:00	09:00			x	|	x	x	x
		649:30	09:30			x	|	x		
		650:00	10:00	240 mL fluid intake and light breakfast[3]		x	|	x	x	x
		651:00	11:00			x	|			
		652:00	12:00	240 mL fluid intake, thereafter lunch[3]		x	+	x	x	x
		654:00	14:00			x	|			
		656:00	16:00	Snack (optional)[3]		x	+	x	x	x
		658:00	18:00	Dinner[3]		x	|			
		660:00	20:00			x	+	x	x	x
	29	672:00	08:00			x	▼	x	x	x
		673:00	09:00	Discharge from trial site (confirmation of fitness)[14]	x	x		x	x	x
	30	696:00	08:00	Ambulatory visit		x				x
	31	720:00	08:00	Ambulatory visit		x				x
	33	768:00	08:00	Ambulatory visit		x				x
	35	816:00	08:00	Ambulatory visit		x				x
3	38 to 41	9999:00	08:00	End of trial (EOT) examination[4, 5, 8]	x	x		x	x	x

1. Screening includes subject information, informed consent, physical examination, check of vital signs, ECG, safety laboratory (including drug screening, pregnancy test and assessment of eGFR), demographics (including determination of body height and weight, smoking status and alcohol history), relevant medical history, concomitant therapy and review of inclusion/exclusion criteria.
2. The time is approximate; the respective procedure is to be performed and completed within 2 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. ECG recording must be conducted before any blood sampling is performed.
4. End of trial examination includes physical examination, body weight, vital signs, ECG, safety laboratory, recording of AEs and concomitant therapies.
5. Urine drug screening and alcohol breath test as well as pregnancy test in all women of childbearing potential will be done at this time point.
6. AEs and concomitant therapies will be recorded throughout the trial, but will be specifically asked for at the time points indicated in the Flow Chart above.
7. Safety laboratory, ECG, blood pressure assessment and AE questioning to be done and medically evaluated within 3 days prior to first administration of study drug; this visit can be omitted, if the screening examination is performed on Days -5, -4 or -3.
8. At End of Trial Examination the time of 9999:00 is only a dummy time for PK sampling.
9. A blank urine sample (x) is to be obtained prior to the administration of trial medication on Day 1. On Day 1, 14 and 28 fractionated urine sampling 0-4, 4-8, 8-12, and 12-24 h will be conducted.
10. Administration under fasting conditions.
11. Includes a blood sample for pharmacogenetic analysis.
12. Samples to be drawn immediately (within 30 minutes) prior to drug administration.
13. On Day 1, 2, 4, 7, 10, 14, 15, 17, 21, 25, 26 and 28 dose to be taken at study site.
14. Confirmation of fitness includes physical examination.
15. On Day 3, Days 5 to 6, Days 8 to 9, Days 11 to 13, Day 16, Days 18 to 20, Days 22 to 24 and Day 27 subjects are allowed to take their study medication at home if deemed appropriate by the investigator. Compliance of medication intake will be monitored by phone call.

TABLE OF CONTENTS

ABBREVIATIONS

AE	Adverse event
AESI	Adverse events of special interest
Ae_{t1-t2}	amount of analyte that is eliminated in urine from the time interval t_1 to t_2
ALT	Alanine amino transferase
AST	Aspartate amino transferase
AOC3	Amine oxidase copper-containing 3
$AUC_{0-\infty}$	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity
AUC_{0-24}	area under the concentration-time curve of the analyte in plasma over the time interval from 0 to 24 hours after administration
$AUC_{\tau,14}$	area under the concentration-time curve of the analyte in plasma over the dosing interval after administration of the 14^{th} dose
$AUC_{\tau,28}$	area under the concentration-time curve of the analyte in plasma over the dosing interval after administration of the 28^{th} dose
BI	Boehringer Ingelheim
BLQ	Below limit of quantification
BMI	Body mass index (weight divided by height squared)
BP	Blood pressure
CA	Competent authority
$CL_{R,\ t1-t2}$	renal clearance of the analyte in plasma from the time point $_{t1}$ to $_{t2}$
C_{max}	Maximum measured concentration of the analyte in plasma
$C_{max,14}$	maximum measured concentration of the analyte in plasma following administration of the 14^{th} dose
$C_{max,28}$	maximum measured concentration of the analyte in plasma following administration of the 28^{th} dose
CML	Clinical Monitor Local
$C_{pre,N}$	Predose concentration of the analyte in plasma immediately before administration of the N^{th} dose after N-1 doses were administered
CRA	Clinical Research Associate
CRF	Case report form
CRO	Clinical Research Organisation
CTCAE	Common Terminology Criteria for Adverse Events
CTP	Clinical trial protocol
CTR	Clinical trial report
CTSU	Clinical Trial Supplies Unit
CV	Arithmetic coefficient of variation
DILI	Drug induced liver injury
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
EDTA	Ethylenediaminetetraacetic acid
eGFR	Estimated glomerular filtration rate
EOT	End of trial
FDA	Food and Drug Administration

fe_{t1-t2}	fraction of administered drug excreted unchanged in urine from time point t_1 to t_2
λ_z	terminal elimination rate constant in plasma
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
GLP	Good Laboratory Practice
gMEAN	Geometric mean
HCL	Hydrochloride
HR	Heart rate
HV	Healthy Volunteers
IB	Investigator's brochure
IEC	Independent Ethics Committee
IPV	Important protocol violations
IRB	Institutional Review Board
ISF	Investigator site file
FSH	Follicle Stimulating Hormone
LC-MS/MS	Liquid chromatography tandem mass spectrometry
MedDRA	Medical Dictionary for Regulatory Activities
MRD	Multiple-rising dose
NAFLD	Non-alcoholic fatty liver disease
NASH	Non-alcoholic steatohepatitis
NCE	New chemical entity
NOA	Not analysed
NOAEL	No observed adverse effect level
NOR	No valid result
NOS	No sample available
PD	Pharmacodynamic(s)
PE	Polyethylene
PK	Pharmacokinetic(s)
PKS	Pharmacokinetic parameter analysis set
PP	Polypropylene
PR	Pulse rate
PTM	Planned time of the measurement
q.d.	*Quaque die*, once daily
QT	Time between start of the Q-wave and the end of the T-wave in an electrocardiogram
QTc	QT interval corrected for heart rate using the method of Fridericia (QTcF) or Bazett (QTcB)
QTcF	Intervalo QT corregido para la frecuencia cardiaca mediante la fórmula de Fridericia
QTcV	Heart-rate corrected QT interval using Van de Water's formula
R	Reference treatment
R_A	Accumulation ratio of the analyte in plasma after multiple dose administration over a uniform dosing interval τ
RDC	Remote Data Capture
REP	Residual effect period

SAE	Serious adverse event
SCR	Screening
SOP	Standard Operating Procedure
SRD	Single-rising dose
SSAO	Semi-carbazide-sensitive amine oxidase
T	Test product or treatment
TDMAP	Trial Data Management and Analysis Plan
TEAE	Treatment-emergent adverse event
t_{max}	time from dosing to maximum measured concentration of the analyte in plasma
TMF	Trial master file
TS	Treated Set
TSAP	Trial statistical analysis plan
TSH	Thyroid stimulating hormone
ULN	Upper limit of normal
VAP-1	Vascular adhesion protein-1
WOCBP	Woman of childbearing potential

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

Boehringer Ingelheim (BI) is developing BI 1467335 (formerly Pharmaxis PXS-4728A), an oral, small-molecule inhibitor of semi-carbazide-sensitive amine oxidase (SSAO), also known as vascular adhesion protein-1 (VAP-1) or amine oxidase copper-containing 3 (AOC3), in the indication of non-alcoholic steatohepatitis (NASH).

NASH is characterised histologically by steatosis, ballooning of hepatocytes, and necroinflammation. NASH can lead to fibrosis which can progress to cirrhosis with a high risk of liver failure. AOC3 in liver sinusoidal endothelial cells is responsible for the firm adhesion and transmigration of leukocytes into the tissue and for the propagation of the inflammatory environment in steatohepatitis. Fibrotic regions of NASH liver sections are strongly positive for AOC3 immune reactivity [R15-5697]. The associated generation of peroxide during the course of amine oxidation is known to activate quiescent stellate cells supporting the differentiation into myofibroblasts, and fibrotic tissue generation. Therefore, targeting the inhibition of AOC3 enzymatic activity might be beneficial for patients with steatohepatitis and fibrosis in order to reduce the recruitment of leukocytes into the liver and reduce cytokine and oxygen stress dependent hepatocyte damage and activation of hepatic stellate cells.

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 20-30% of patients with NAFLD progress to NASH. As the disease progresses, significant fibrosis develops in 37 - 41% of these 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 small molecule irreversible AOC3 inhibitor that exhibits both anti-inflammatory and anti-fibrotic characteristics in various animal models. AOC3 is a membrane bound adhesion protein that facilitates the binding of leukocytes to endothelial

cells and the subsequent transmigration to sites of inflammation. The target indication of the compound will be NASH.

For a more detailed description of the BI 1467335 profile please refer to the current Investigator's Brochure (IB) [c04751792].

Non-clinical findings

Nonclinical pharmacology

In several disease related rodent models, resembling different aspects of NASH, BI 1467335 showed reduced steatosis, inflammatory cell infiltrates and fibrotic area compared to control animals (Stelic Animal Model™ mouse model), a reduction of stellate cell activation (Methionine-Choline deficient Diet model), and an (inconsistent) reduction of biomarkers for inflammation and fibrosis (carbon tetrachloride induced fibrosis model in mice and rats). However, the overall conclusion from these studies was that BI 1467335 demonstrated beneficial signals for main NASH-related pathologies, including myofibroblast activation, necro-inflammation, and fibrogenesis, supported by literature data on the potential role of AOC3 in NASH.

In a cardiovascular safety pharmacology study, male dogs received BI 1467335 single oral doses of 0, 6, 15 and 45 mg/kg with adequate recovery period between dose levels. While no effects were observed with single doses of 6 mg/kg, significant increases in QTc intervals were seen at doses ≥ 15 mg/kg. All other safety pharmacology studies showed no BI 1467335 related changes.

Toxicology

The NOAEL in rats orally exposed to BI 1467335 for 13 weeks was 12.5 mg/kg. This dose corresponded to mean C(max) and AUC(0-24h) levels of 8430 nM and 65700 nM.h, respectively, in rat. The NOAEL in dogs orally exposed to BI 1467335 for 13 weeks was 3 mg/kg. This dose corresponded to mean Cmax and AUC(0-24h) levels of 3000 nM and 25900 nM.h, respectively, taken from the sex with the lower plasma exposure at the NOAEL. This provides an adequate safety window between clinical exposure and exposure at NOAEL levels in animals. For further details, please refer to the current 'Investigator's Brochure (IB)' [c04751792].

These findings are consistent with results of the 4 weeks toxicology studies in rats and dogs [n00244592] [n00247850].

BI 1467335 does not present a genotoxic hazard.

In the study on embryo-fetal development in rabbits with BI 1467335 treatment from day 6-18 of gestation, abortion was noted in one doe treated at 10 mg/kg (with marked maternal toxicity) and in three does at 45 mg/kg. Due to these findings Women of childbearing potential must be willing and able to use a double-barrier contraception (barrier in the meaning of method) with at least one highly effective method of birth control per ICH M3 (R2) that result in a low failure rate of less than 1% per year when used consistently and correctly in this study (1386-0002).

The pharmacokinetic behavior of BI 1467335 in rats and dogs was characterised by rapid absorption, a low to moderate half-life and a predominantly over proportional increase of

plasma exposure with an increase in dose. The in vitro plasma protein binding was low in all investigated species, with ≤25% bound in human plasma. In vitro studies in cryopreserved human hepatocytes indicated a prevalence of oxidative O-dealkylation as primary metabolic pathway.

BI 1467335 inhibited MAO-B catalyzed kynuramine deamination with an IC50 of 1.04 µM and MAO-A catalyzed kynuramine deamination with an IC50 of 74.4 µM (n00257993). Time dependent inhibition of MAO-B catalyzed kynuramine deamination by BI 1467335 was observed indicating an irreversible inhibition mechanism. Inhibition constants for irreversible enzyme inhibition were determined and resulted in an inhibition constant (K_I) of 2.01 µM and an inactivation rate constant (k_{inact}) of 0.087 min^{-1} (n00259383).

Clinical experience

To date one combined SRD and MRD study (c09036683) investigating single doses of 1-20 mg BI 1467335 (HCl, corresponding to 0.885 – 17.7 mg free base) and multiple doses of 3 to 10 mg BI 1467335 HCl q.d. (corresponding to 2.66 to 8.85 mg free base) for 14 days have been completed. An additional phase I study (c08854973) just recently finished investigated multiple doses of 10 mg, 15 mg and 20 mg q.d. for 28 days (doses refer to free base). Preliminary data of this ongoing study have recently become available (c16567028).

Clinical safety in healthy subjects

To date, all doses of BI 1467335 (provided as powder for oral solution) have been well tolerated up to 20 mg q.d.for 28 days. Frequencies of reported AEs were similar between active drug and placebo groups. All reported treatment-emergent adverse events (TEAEs) were of mild or moderate intensity and all subjects recovered. There were no SAEs. Based on an interim analysis (c16567028), all subjects of the 10 mg dose group and 7 of 8 subjects of the 15 mg dose group completed the study per protocol (one subject assigned to 15 mg q.d. discontinued after the 5th dose because of a common cold). In addition there were no noteworthy changes in vital signs or laboratory parameters. A centralized ECG evaluation (based on completed 10 mg dose group and incomplete 15 mg dose group) did not show any relevant individual QT prolongation, i.e. QTcF increase of greater 60 ms from baseline or an absolute QT or QTc value greater than 500 ms. Explorative systemic BI 14567335 exposure versus QTcF, QTcN, and HR analyses did not show any relevant signals (c16567028).

In the completed Phase I SRD/MRD Study PXS-4728A-101, investigating single doses up to 20 mg (HCl salt) and multiple dosing for 14 days up to 10 mg q.d. (HCL salt), there were no changes in ECG parameters or changes that were assessed as clinically significant. There was no relevant individual QT prolongation, i.e. no QTcF increase of greater 60 ms from baseline or an absolute QT value greater than 500 ms. There were no apparent trends in ECG parameters over time. One subject treated with 6 mg q.d. (HCL salt) showed an isolated episode of extra systoles on Day 14, mild in severity, which resolved 3.8 hours after onset. No similar finding was observed in the ongoing MRD study 1386.8.

Pharmacokinetics in healthy subjects

Following both single and multiple doses of 10 and 15 mg, BI 1467335 C_{max} and AUC_{0-24} increased in a more than dose proportional manner on Days 1, 14 and 28 (Figure 1.2: 1). Resulting from the accumulation of BI 1467335 following repeat oral dosing, quantifiable BI

1467335 concentrations could be measured up to 4 h and 8 h postdose for 10 and 15 mg respectively on Day 1; and up to 24 h postdose on Days 14, and Day 28. Resulting from the limited time period over which quantifiable BI 1467335 concentrations could be measured on Day 1; the resulting AUC_{0-24} values on Day 1 need to be regarded with caution, as they may be underestimates, due to the large number of concentrations below the assays lower limit of quantification

The observed apparent elimination half-life (gMean) for BI 1467335 is significantly shorter on Day 1 (<1 h) compared to Days 14 and 28, (<4 h following 10 mg and < 9 h following 15 mg on Day 28). Despite the short apparent elimination half-lives, BI 1467335 significantly accumulates following q.d. dosing. For 10 mg q.d., C_{max} increased by approximately 26-fold on Day 14 and 40-fold on Day 28, and AUC_{0-24} increased by approximately 58-fold on Day 14 and 159-fold on Day 28. For 15 mg q.d. dosing, C_{max} increased by approximately 14-fold on Day 14 and 16-fold on Day 28, and AUC_{0-24} increased by approximately 72-fold on Day 14 and 82-fold on Day 28.

Taking all the BI 1467335 data together, including trough concentrations, 1 h postdose samples along with AUC_{0-24} values, they suggest that steady state may be attained close to Day 14 following 15 mg q.d., whereas it was not attained by Day 14 following 10 mg q.d.. Following 10 mg q.d., C_{max} and AUC_{0-24} are approximately 54% and 180% higher respectively on Day 28 compared to that on Day 14, whereas following 15 mg q.d., C_{max} and AUC_{0-24} are approximately 13 and 15 % higher respectively on Day 28 compared to that on Day 14. For further details, please refer to the current 'Investigator's Brochure (IB)' [c04751792].

Thus, BI 1467335 appears to display both dose and time dependent kinetics, where BI 1467335 C_{max} and AUC_{0-24} values on Days 14 and 28 are greater than predicted from Day 1 data. BI 1467335 accumulation may in part be due to irreversible binding to AOC3 enzymes which are present in many different tissues within the body (Target Mediated Drug Disposition). This may explain the observation that steady state appears to be attained earlier following 15 versus 10 mg q.d. the highest dose tested to date.

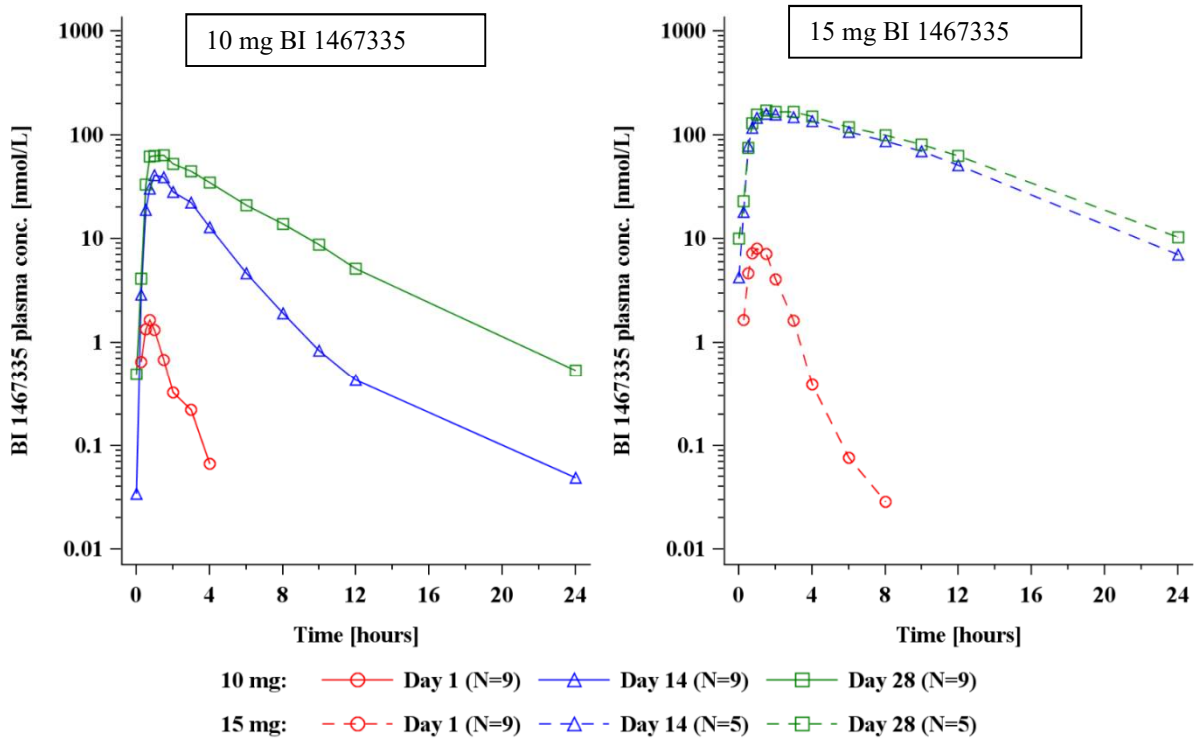


Figure 1.2: 1 Geometric Mean BI 1467335 concentration-time profiles following single and multiple BI 1467335 dosing, 10 mg q.d. (left graph) and 15 mg q.d. (right graph), to healthy subjects on Days 1, 14 and 28 (up to 24 h postdose, semi-log scale)

Pharmacodynamics in healthy subjects

AOC3 activities and their change from baseline were determined throughout study PXS-4728A-101 [c09036683]. During the SRD part of the study, a strong, dose related response to AOC3 activity inhibition could be demonstrated with increasing numbers of subjects achieving a reduction of 90% with increasing doses. At the highest single dose of 20 mg, AOC3 inhibition of greater than 90% was reported up to 12 hours post-dose in 5 of 6 subjects, with the mean SSAO inhibition at 24 hours being greater than 80%. The maximum inhibition was observed within 2 hours of single dose administration for most subjects across all dose groups.

During the MRD part of the study, inhibition of AOC3 activity at 24 hours post-dose on Day 14 remained greater than 90% for all subjects receiving a daily dose of 6 or 10 mg BI 1467335. At the lowest repeat dose level of 3 mg BI 1467335 per day, the AOC3 inhibition was greater than 80% at 24 hours post-dose on Day 14 in all subjects.

For further details, please refer to the current 'Investigator's Brochure (IB)' [c04751792].

2. RATIONALE, OBJECTIVES, AND BENEFIT - RISK ASSESSMENT

2.1 RATIONALE FOR PERFORMING THE TRIAL

An association between NAFLD/NASH and impaired renal function was consistently shown in numerous epidemiological studies [P16-05590] and may be due to common underlying inflammatory pathways in liver and kidney. BI 1467335 is going to enter phase IIb in a NASH population. Taking the published epidemiological data into consideration this may be associated in up to 20% of NASH patients with a reduced GFR < 60 ml/min i.e. at least moderate renal impairment.

Based on both the preclinical and ongoing clinical phase I study 1386.8, renal clearance is considered to be involved in the elimination of BI 1467335, especially following multiple dosing. The study is conducted to support the safe inclusion of NASH patients who may have moderate renal impairment in Phase IIb/III studies.

The PK will be investigated during a 4 week treatment with 10 mg of BI 1467335 q.d. which has already been shown to be well tolerated in healthy subjects. A dose of 10 mg is the planned maximum therapeutic dose in a NASH population. Currently 20 mg q.d. is being investigated in HVs. Preliminary 15 mg q.d. in HVs on Day 28 resulted in gMean C_{max} and AUC_{0-24} values approximately 2.6 and 4.7-fold higher than those observed on Day 28 following 10 mg q.d..

2.2 TRIAL OBJECTIVES

The primary objective of the current study is to investigate the influence of moderate renal impairment on the pharmacokinetics of multiple doses in comparison to a matched control group with normal renal function.

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

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

2.3 BENEFIT - RISK ASSESSMENT

Participation in this study is without any (therapeutic) benefit for healthy subjects or subjects with moderate renal impairment. Their participation in the study, however, is of major importance to the clinical development of BI 1467335. The subjects are exposed to the risks of the study procedures and the risks related to the exposure to the trial medication.

Procedure-related risks

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

The total volume of blood withdrawn during the entire study period of 6 weeks will not exceed about 300 mL per subject. This is less than the volume of a normal blood donation (500 mL). No health-related risk to the subjects is expected from this blood withdrawal.

Drug-related risks and safety measures

Assessment of drug related risks is mainly based on data of an ongoing phase I study investigating safety, tolerability and pharmacokinetics of 10 mg, 15 mg and 20 mg q.d. of BI 1467335 for 28 days in healthy subjects. Data have been obtained for the complete 10 mg dose group (9 on active and 3 on placebo) and 7 subjects (5 on active and 2 on placebo) who completed the 15 mg q.d. treatment. The 20 mg q.d. dose group has recently completed treatment as well, however data evaluation is still ongoing. Regarding the 10 mg and 15 mg dose group and as already observed in a preceding 2 week study [c09036683] there were no SAEs and no AEs considered to be dose limiting. Nearly all of the AEs were of mild intensity. One subject assigned to 15 mg q.d. discontinued after receiving the 5th dose because of a common cold. There were no changes in safety labs, vital signs or ECGs readings considered to be clinically relevant. While the evaluation of the 20 mg dose group is ongoing there were no SAEs and no AEs considered being dose limiting as well. These findings are consistent with results of a preceding SRD/MRD study investigating a dose range of up to 10 mg of BI 1467335 administered for 14 days.

Following both single and multiple doses of 10 and 15 mg of BI 1467335 C_{max} and AUC_{0-24} increased in a more than dose proportional manner on Days 1, 14 and 28 [c04751792]. Despite the short apparent elimination half-lives, BI 1467335 significantly accumulates following q.d. dosing. For 10 mg q.d., C_{max} increased by approximately 26-fold on Day 14 and 40-fold on Day 28, and AUC_{0-24} increased by approximately 58-fold on Day 14 and 159-fold on Day 28. For 15 mg q.d. dosing, C_{max} increased by approximately 14-fold on Day 14 and 16-fold on Day 28, and AUC_{0-24} increased by approximately 72-fold on Day 14 and 82-fold on Day 28.

The exposure ratio (AUC_{0-24}) between the 10 mg and 15 mg dose group is in a range of about 4.7 fold. This should provide a sufficient safety margin in renally impaired subjects receiving a dose of 10 mg q.d., taking into consideration that a 4.7 fold higher exposure was also well tolerated in healthy subjects.

Taken together no specific drug-related risks are anticipated. Still, the following safety measures will be applied in this study in order to minimize the risk for the participating subjects:

- There will be a staggered inclusion of renal impaired subjects starting with a cohort of 3 subjects. The remaining subjects with renal impairment will enter the trial at least 14 days apart after the principal investigator and sponsor have evaluated safety and PK data up to 1 week after start of treatment from this initial cohort.

- Over the entire period the subjects will be under close medical observation either during the hospitalization and ambulatory phase (see Flow Chart).

- 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 and subjects with moderate renal impairment are not expected to have direct medical benefit from participation in this MRD trial with BI 1467335. However, it is considered that all subjects participating in the study will not be exposed to undue risks and adverse events in relation to the information expected from this trial. Considering the medical need of the development of an effective and well tolerated drug for the therapy of NASH, the benefit of this trial is considered to outweigh the potential risks and justifies the exposure of healthy and renally impaired subjects at the intended dose levels and treatment duration.

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

The study will be performed open-label, in a multiple-dose, matched group design with moderate renal impaired and healthy male and female subjects. In this exploratory study it is considered reasonable to aim for at least 25% of either gender.

It is planned to include altogether 20 participants in the trial, of which up to 10 subjects with moderate renal impairment. All subjects will receive over 4 weeks 10 mg of BI 1467335 once daily, the maximum therapeutic target dose in the upcoming phase II studies in a NASH population. Each renally impaired subject will have a healthy subject matched for gender, race, smoking status, age (within ±10%) and BMI (within ±10%). They will build a pair for later evaluation.

Renal impaired subjects will receive a subject number starting with while healthy subjects will receive a subject number starting with

The study will follow a staggered inclusion starting with a subcohort of 3 renally impaired subjects. For this initial subcohort there will be a safety review meeting between sponsor and investigator to decide whether the study can proceed as planned. Matched healthy subjects will be only included if the corresponding renally impaired subjects have completed the study.

Additional safety reviews may be conducted at any time if deemed necessary by the investigator or sponsor.

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

3.1.1 Administrative structure of the trial

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

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

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

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

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

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

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

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

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

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

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

The study will be conducted according to a multiple-dose, open-label design with matched-groups.

BI 1467335 displays non-linear, time dependent kinetics with a 40-fold higher C_{max} and 159-fold higher AUC_{0-24} on Day 28 compared to Day 1 (see Section 1.2, refers to 10 mg of BI 14673335 q.d., the dose selected for the planned study). Since steady state PK is not predicted by single dose data, multiple doses are required to assess the clinically relevant data as BI 14673335 is being developed for chronic dosing. Based on preliminary evaluation, treatment duration of 4 weeks, the currently maximum treatment duration in healthy subjects, and a dose regimen of 10 mg q.d. should provide close to steady state conditions. This should also reliably exclude any transient effects.

The resulting group sizes (see Section 7.1) are considered to be sufficient for the exploratory evaluation of pharmacokinetics. The assignment of matched healthy volunteers is a useful method to control for other factors which may influence the pharmacokinetics of BI 1467335 in a renal impaired population.

The open-label treatment is not expected to bias results, since the primary endpoints are derived from measurement of plasma concentrations of the analytes provided by a bioanalytical laboratory. It is also considered sufficiently accurate as the trial observations are objective (PK, laboratory) and over-reporting of AEs is unlikely.

3.3 SELECTION OF TRIAL POPULATION

It is planned that up to 20 male and female subjects will enter the study (10 in each of two groups). Subjects with moderate renal impairment (estimated GFR based on the CKD-EPI formula 30 to 59 mL/min/1.73m^2) will be assigned to Group 1, while healthy subjects (eGFR $\geq$ 90 mL/min/1.73m^2) matched individually by gender, race, smoking status, age (within ±10%) and BMI (within ±10%) to a renal impaired subjects will be assigned to Group 2.

Group 1 should include at least 25% of either gender and 5 subjects with an estimated GFR between 30 and 45 mL/min/1.73m^2.

The estimated glomerular filtration rate (eGFR) will be determined at the screening examination and on Day -2 of Visit 2 if screening was more than 10 days ago.

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 moderate renally impaired subjects as well as healthy subjects.

3.3.2 Inclusion criteria

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

1. Despite of moderate renal impairment (Group 1) healthy male or female subjects according to the assessment of the investigator, based on a complete medical history including a physical examination, vital signs (BP, PR), 12-lead ECG, and clinical laboratory tests
2. eGFR based on CKD-EPI formula for Group 1 between 30 and 59 mL/min/1.73m^2 and for Group 2 ≥ 90 mL/min/1.73m^2
3. Age of 18 to 79 years (incl.)
4. BMI of 18.5 to 34 kg/m^2 (incl.)
5. Signed and dated written informed consent prior to admission to the study in accordance with GCP and local legislation
6. Male subjects, or female subjects who meet any of the following criteria (according to the CTFG Recommendations related to contraception and pregnancy testing in clinical trials, methods with a failure rate of less than 1% per year) starting from at least 30 days before the first administration of trial medication and until 30 days after trial completion, e.g.:
   - Use of adequate contraception, e.g. any of the following methods *plus* condom: implants, injectables, combined oral or vaginal contraceptives (inhibition of ovulation)
   - Hormonal intrauterine device
   - Sexually abstinent (defined as refraining from heterosexual intercourse during the entire period of risk)
   - A vasectomised sexual partner (provided that vasectomy was performed at least 1 year prior to enrolment and the vasectomised partner has received medical assessment of the surgical success)
   - Surgically sterilised (including bilateral tubal occlusion, hysterectomy)

- Postmenopausal, defined as at least 1 year of spontaneous amenorrhea (in questionable cases a blood sample with simultaneous levels of FSH above 40 U/L and estradiol below 30 ng/L is confirmatory)

3.3.3 Exclusion criteria

Subjects who meet any of the following criteria will not enter into this trial:

Healthy subjects

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. eGRF calculated by CKD-EPI formula < 90 mL/min/1.73m^2

Subjects with moderate renal impairment

7. Subject with significant diseases other than moderate renal impairment.
A significant disease is defined as a disease which in the opinion of the investigator:
- puts the subjects at risk because of participation in the study
- may influence the results of the study
- may influence the subject's ability to participate in the study
- is not in a stable condition
Diabetic or hypertensive subjects can be entered in this trial if the disease is not significant according to these criteria.
8. Any finding of the medical examination (including BP, PR and ECG) of clinical relevance
9. Moderate and severe concurrent liver function impairment (e.g. due to hepatorenal syndrome) or biliary obstruction
10. Clinically relevant laboratory abnormalities (except for renal function tests or deviation of clinical laboratory values that are related to renal impairment)
11. eGRF calculated by CKD-EPI formula ≥ 60 mL/min/1.73m^2 and < 30 mL/min/1.73m^2

For all subjects

12. Cholecystectomy and/or surgery of the gastrointestinal tract that could interfere with the pharmacokinetics of the trial medication (except appendectomy and simple hernia repair)
13. Diseases of the central nervous system (including but not limited to any kind of seizures or stroke), and other relevant neurological or psychiatric disorders
14. History of relevant orthostatic hypotension, fainting spells, or blackouts

15. Chronic or relevant acute infections
16. History of relevant allergy or hypersensitivity (including allergy to the trial medication or its excipients)
17. 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)
18. Participation in another trial where an investigational drug has been administered within 30 days prior to planned administration of trial medication or longer if required by local regulation, or within 5-half-lives of the investigational agent taken (whichever is longer), or current participation in another trial involving administration of investigational drug
19. Smoker (more than 10 cigarettes or 3 cigars or 3 pipes per day)
20. Inability to refrain from smoking on specified trial days
21. Alcohol abuse (consumption of more than 20 g per day for females and 30 g per day for males)
22. Drug abuse or positive drug screening
23. Blood donation of more than 100 mL within 30 days prior to administration of trial medication or intended donation during the trial
24. Intention to perform excessive physical activities within one week prior to administration of trial medication or during the trial
25. Inability to comply with dietary regimen of trial site
26. A marked baseline prolongation of QT/QTc interval (such as QTc intervals that are repeatedly greater than 450 ms in males or repeatedly greater than 470 ms in females) or any other relevant ECG finding at screening
27. A history of additional risk factors for Torsades de Pointes (such as heart failure, hypokalemia, or family history of Long QT Syndrome)
28. 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

Female subjects will not be allowed to participate if any of the following applies:

29. Positive pregnancy test, pregnancy or plans to become pregnant within 30 days after study completion
30. Lactation period

Male subjects will not be allowed to participate if any of the following applies:

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

For study restrictions, refer to Section 4.2.2.

3.3.4 Removal of subjects from therapy or assessments

3.3.4.1 Removal of individual subjects

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

1. The subject withdraws consent for trial treatment or trial participation, without the need to justify the decision
2. The subject needs to take concomitant drugs that interfere with the investigational product or other trial medication
3. The subject is no longer able to participate for other medical reasons (such as pregnancy, 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.

If it is known that a subject becomes pregnant during the trial, administration of the trial medication has to be stopped immediately, and the subject has to be removed from the trial. The subject is to be followed until she has given birth or until the end of pregnancy. The subject's data are to be collected until the end of the trial (last visit of last subject) and reported in the clinical trial report. For reporting of pregnancy and events refer to Section 5.2.2.2.

3.3.4.2 Discontinuation of the trial by the sponsor

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

1. New toxicological findings or serious adverse events invalidate the earlier positive benefit-risk-assessment. More specifically, the trial will be terminated if more than 50%

of the subjects show drug-related and clinically relevant adverse events of moderate or severe intensity, or if at least one drug-related serious adverse event is reported.

2. The expected enrolment goals overall or at a particular trial site are not met
3. Violation of GCP, or the CTP, or the contract with BI by a trial site or investigator, disturbing the appropriate conduct of the trial
4. The sponsor decides to discontinue the further development of the investigational product.

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

3.3.5 Replacement of subjects

In case 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.

4. TREATMENTS

4.1 TREATMENTS TO BE ADMINISTERED

The investigational product has been manufactured by BI Pharma GmbH & Co. KG.

4.1.1 Identity of BI investigational product and comparator product

The characteristics of the test product, dosage and treatment schedule are given below.

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

4.1.2 Method of assigning subjects to treatment groups

This is an open-label trial with one treatment. As all study participants will receive the same treatment, randomisation is not applicable in this trial. The subjects will be assigned to group 1 or group 2 according to the estimated glomerular filtration rate as outlined in Section 3.3.2. At screening the subjects will be allocated to a unique subject identification code. Once a subject is eligible, they will be allocated to a study subject number. Due to the matching criteria, the subjects for the renally impaired Group 1 (eGFR 30 - 59 mL/min/1.73m^2) will be included first in the trial and matched subjects in Group 2 (eGFR ≥90 mL/min/1.73m^2) will be subsequently included.

4.1.3 Selection of doses in the trial

The dose of 10 mg q.d. selected for this trial reflects the maximum planned therapeutic dose of Phase II studies in NASH patients (see Section 1.2).

4.1.4 Drug assignment and administration of doses for each subject

This trial is an open-label study, with a matched-parallel group design. All subjects will receive the same treatment, 10 mg q.d. over 28 days. The inclusion of matched subjects of Group 2 will be done on an individual basis after corresponding renal impaired subjects of Group 1 have completed the treatment period.

If intake of study medication occurs at study site, the trial medication will be administered to the subjects, while in a sitting position, as an oral dose together with about 240 mL of water under supervision of the investigating physician or an authorised designee. The so-called four-eye principle (two-person rule) should be applied for administration of trial medication.

In case of ambulatory intake subjects are required to contact the site by phone to confirm the intake of study medication.

In principal, for both hospitalized and ambulatory conditions intake of study medication should be performed following an overnight fast, which is to start no later than 10 h before the scheduled dosing. During ambulatory conditions subjects may have breakfast about 1 h after drug intake. If a subject misses his morning dose by 6 h, the subject should omit drug intake on this specific day.

To ensure a dosing interval close to 24 h, the administration or intake (during ambulatory periods) of trial medication should take place at a similar time every day.

Subjects will be kept under close medical surveillance from the evening of Day -1 to the morning of Day 2, from the evening of Day 13 to the morning of Day 15, and from the evening of Day 27 to the morning of Day 29. During the first 2 h after drug administration, subjects should not lie down (i.e. no declination of the upper body of more than 45 degrees from upright posture except for medical examination), or to sleep. For restrictions with regard to diet see Section 4.2.2.2.

4.1.5 Blinding and procedures for unblinding

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 and study is an open label design.

4.1.6 Packaging, labelling, and re-supply

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

The clinical trial supply consists of containers holding the trial medication which are labelled with trial identification. Each subject receives on a weekly basis one small box which contains two blisters. The subject number, study week, dispensing date and name of investigator need to be written in the corresponding empty fields on the box label. On the blister labels the subject number need to be included as well.

The required information according to the German Drug Law as well as Annex 13/EU GMP Guideline will be provided on the small boxes and they 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

- Placeholder to include Subject number
- Batch number
- Tick box to include study week
- Placeholder to include dispensing date
- Placeholder to include name of investigator

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.

Re-supply may be required.

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 storage conditions. Where necessary, a temperature log must be maintained to make certain that the drug supplies are stored at the correct temperature. This applies only to the investigational site and not for storage conditions at subjects home. If the storage conditions at the investigational site 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 / pharmacist / investigational drug storage manager will receive the investigational drugs delivered by the sponsor when the following requirements are fulfilled:

- Approval of the trial protocol by the IRB / ethics committee
- Availability of a signed and dated clinical trial contract between the sponsor and the head of the trial site
- 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
- Availability of the Form 1572

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 / pharmacist / investigational drug storage manager must maintain records of the product’s delivery to the trial site, the inventory at the site, the use by each subject, and the 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 / pharmacist will maintain records that document adequately that the subjects were provided the doses specified by the CTP, and that reconcile all investigational products received from the sponsor. At the time of disposal, the investigator / pharmacist must verify that all unused or partially used drug supplies have been returned by the clinical trial subject and that no remaining supplies are in the investigator's possession.

4.2 OTHER TREATMENTS, EMERGENCY PROCEDURES, RESTRICTIONS

4.2.1 Other treatments and emergency procedures

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

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

In healthy subjects, no concomitant therapy is allowed except for hormonal contraceptives or ovary hormone replacement. All concomitant or rescue therapies will be recorded (including time of intake on study days) on the appropriate pages of the CRF.

Concomitant medication is allowed for treatment of concomitant or underlying disease in subjects with renal impairment (group 1). A case-by-case decision may be made after consultation with the sponsor if drug-drug interactions are likely to occur.

Since BI 1467335 demonstrated *in vitro* to be an irreversible inhibitor of monoamine oxidase B (MAO-B), patients should be advised to avoid medications that interact with MAO-B inhibitors. These include for example medications prohibited 2 weeks prior to BI 1467335 dosing and during study participation (Meperidine, Tramadol, Methadone, Propoxyphene, Dextromethorphan, Cyclobenzaprine, Sympathomimetic medications including nasal, oral and ophthalmic decongestants and cold remedies) and medications prohibited 5 weeks prior to BI 1467335 dosing, during study participation, and up to 14 days after last intake of BI 1467335, such as MAO Inhibitors and antidepressants (SSRIs, SNRIs, triazolopyridine, tricyclic or tetracyclic antidepressants).

Any newly introduced medication should be only used after consultation and approval of the medical investigator.

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

4.2.2.2 Restrictions on diet and life style

All subjects should be requested to refrain from meat (and creatin containing products used for bodybuilding) for at least 12 hours before blood sampling for serum creatinine is to be done. All subjects should refrain from heavy exercise for 24 hours before blood sampling for serum creatinine is to be done.

While admitted to the trial site the subjects are restricted from consuming any other foods or drinks than those provided by the staff. Standardised meals will be served at the time points described in the Flow Chart.

On Day 1, Day 14 and Day 28, fluid intake from breakfast until 22 hours post-dose should be within about 1000 to 3000 mL.

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

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

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

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

If female subjects of child bearing potential are included, adequate contraception, double barrier method, is to be maintained throughout the course of the trial (see Section 3.3.2 for adequate measures).

4.3 TREATMENT COMPLIANCE

Compliance will be monitored by either administration of all trial medication in the study centre under supervision of the investigating physician or a designee or during ambulatory period subjects confirm drug intake by phone contact with the study site. 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, please see Section 3.3.4.1).

5. VARIABLES AND THEIR ASSESSMENT

5.1 EFFICACY - CLINICAL PHARMACOLOGY

5.1.1 Endpoints of efficacy

No efficacy endpoints will be evaluated in this trial.

5.1.2 Assessment of efficacy

Not applicable.

5.2 SAFETY

5.2.1 Endpoints of safety

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

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

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

5.2.2 Assessment of adverse events

5.2.2.1 Definitions of adverse events

Adverse event

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

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

Serious adverse event

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

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

- requires inpatient hospitalisation or
- requires prolongation of existing hospitalisation,
- results in persistent or significant disability or incapacity, or
- is a congenital anomaly/birth defect, or
- is deemed serious for any other reason if it is an important medical event when based upon appropriate medical judgment which may jeopardise the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions.

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

AEs considered 'Always Serious'

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

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

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

Adverse events of special interest (AESIs)

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

The following are considered as AESIs in this trial:

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

  These lab findings constitute a hepatic injury alert and the patients showing these lab abnormalities need to be followed up according to the 'DILI checklist' provided in the ISF. In case of clinical symptoms of hepatic injury (icterus, unexplained encephalopathy, unexplained coagulopathy, right upper quadrant abdominal pain, etc.) without lab results (ALT, AST, total bilirubin) available, the Investigator should

make sure these parameters are analysed, if necessary in an unscheduled blood test. Should the results meet the criteria of hepatic injury alert, the procedures described in the DILI checklist should be followed.

Intensity of AEs

The intensity (severity) of adverse events should be classified and recorded in the (e) CRF according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03 dated 14 June 2010 [R10-4848].

Causal relationship of AEs

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

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

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

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

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

5.2.2.2 Adverse event collection and reporting

AE collection

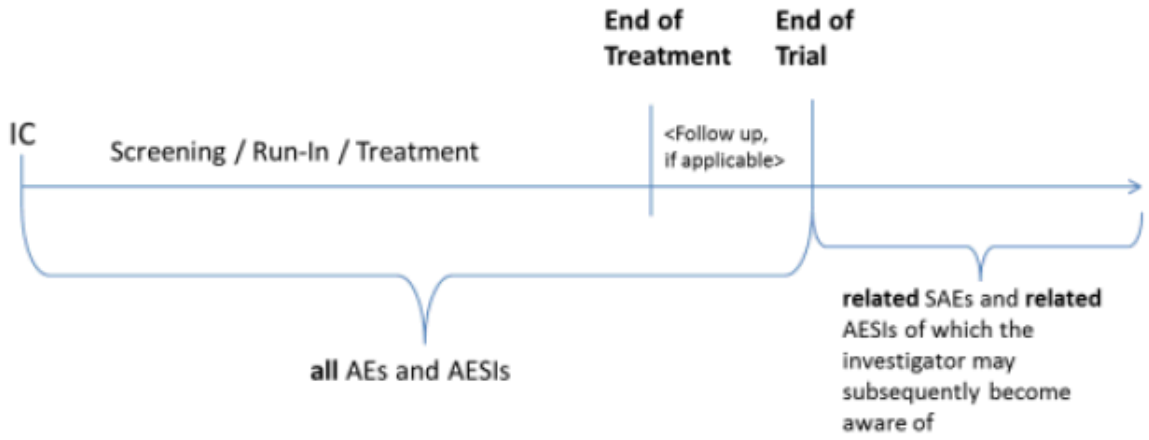
Upon enrolment into a trial, the subject's baseline condition is assessed (for instance, by documentation of medical history/concomitant diagnoses), and relevant changes from baseline are noted subsequently.

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

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

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

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



The REP for BI 1467335, when measurable drug levels or PD effects are still likely to be present after the last administration, is not known for this clinical trial. Therefore, all AEs reported until the end of trial examination (last per protocol contact) will be considered on treatment (please see Section 7.3.3).

AE reporting to sponsor and timelines

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

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

Information required

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

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

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

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

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

Pregnancy

In rare cases, pregnancy might occur in a clinical trial. Once a subject has been enrolled in the clinical trial and has taken trial medication, the Investigator must report any drug exposure during pregnancy in a trial participant immediately (within 24 hours) by means of Part A of the Pregnancy Monitoring Form to the sponsor's unique entry point.

Similarly, potential drug exposure during pregnancy must be reported if a partner of a male trial participant becomes pregnant. This requires a written consent of the pregnant partner.

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

The ISF will contain the Pregnancy Monitoring Form for Clinical Trials (Part A and Part B).

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

5.2.3 Assessment of safety laboratory parameters

For the assessment of laboratory parameters, blood and urine samples will be collected by the trial site at the time points indicated in the Flow Chart after the subjects have fasted for at least 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 the ISF, Section 10.

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

Table 5.2.3: 1 Routine laboratory tests

Functional lab group	Test name
Haematology	Haematocrit
	Haemoglobin
	Red blood cell count (RBC)
	Reticulocyte count
	White blood cell count (WBC)
	Platelet count
Automatic WBC differential (relative and absolute)	Neutrophils, eosinophils, basophils, monocytes, lymphocytes
Manual differential WBC (if automatic differential WBC is abnormal and considered by the investigator clinically relevant)	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[1]	Plasma glucose
	Creatinine (+ calculation of eGFR by CKD-EPI)
	Cystatin
	Total bilirubin
	Direct bilirubin
	Total protein
	Protein electrophoresis (only at screening examination)
	Albumin
	Alpha-1-Globulin
	Alpha-2-Globulin
	Beta-Globulin
	Gamma-Globulin
	C-Reactive Protein (CRP)
	Uric acid
	Total cholesterol
	Triglycerides
Electrolytes	Sodium
	Potassium
	Chloride
	Calcium
	Inorganic phosphate

Table 5.2.3: 1 Routine laboratory tests (cont).

Functional lab group	Test name
Urinalysis (Stix)	Urine nitrite Urine protein Urine glucose Urine ketone Urobilinogen Urine bilirubin Urine 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 Protein electrophoresis only at screening. Hormones only at screening and end of trial.

The tests listed in Table 5.2.3: 2 are exclusionary laboratory tests which may be repeated as required. The results will not be entered in the CRF/database and will not be reported in the CTR. Except for pregnancy test and drug screening, it is planned to perform these tests during screening only. Pregnancy testing in women will be performed at screening and as part of the end of trial examination in plasma and on Days -1, 13 and 27 in urine. Drug screening will be performed at screening and on Days -1, 13, 27 and end of trial examination.

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 C antibodies (qualitative) HIV-1 and HIV-2 antibody (qualitative)
Pregnancy test (urine)	Beta human chorionic gonadotropin (beta-HCG)

To encourage compliance with alcoholic restrictions, a breath alcohol test (ACE Alcoscan III) will be performed at screening and prior to each PK profiling day, and may be repeated at any time during the study at the discretion of an investigator or designee. The results will not be included in the CTR.

The laboratory tests listed in Table 5.2.3: 1 and 5.2.3: 2 will be performed at

with the exception of the drug screening and pregnancy tests. These tests will be performed at the trial site using hcG meditrol, medichem and 10TC, nal von minden, respectively.

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 (MAC 5500 GE Medical Systems) at the time points given in the Flow Chart.

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

Electrode placement will be performed according to the method of Wilson, Goldberger and Einthoven modified by Mason and Likar (hips and shoulders instead of ankles and wrists). Precise electrode placement will be marked with an indelible mark on the skin to allow reproducible placement throughout the study.

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

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

5.2.5 Assessment of other safety parameters

5.2.5.1 Vital signs

Systolic and diastolic blood pressures (BP) as well as pulse rate (PR) or heart rate (heart rate is considered to be equal to pulse rate) will be measured by a blood pressure monitor (Dinamap ProCare Monitor DPC220X-GE, GE Healthcare Mock) at the times indicated in the Flow Chart, after subjects have rested for at least 5 min in a supine position. All recordings should be made using the same type of blood pressure recording instrument on the same arm if possible.

5.2.5.2 Medical examinations

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

laboratory tests, and a physical examination. At the end of trial examination, it will include review of vital signs, 12-lead ECG, laboratory tests, and a physical examination with determination of weight.

5.3 OTHER

5.3.1 Pharmacogenomic evaluation

Pharmacogenomics investigates genetic variations to explain and to predict an individual's response to drugs. Therefore, a blood sample for pharmacogenomic testing will be taken from each subject. In case of unexplainable variability in pharmacokinetic parameters, DNA might be extracted from these samples and used for exploratory analysis of variants of genes involved in Absorption, Distribution, Metabolism and Excretion (ADME) of drugs. It is not intended to include these data in the final report. However, the data may be part of the report if necessary. All remaining samples will be destroyed no later than three years after the end of the trial.

5.3.1.1 Methods and timing of sample collection

One blood sample of at approximately 3 mL will be taken from an arm vein into an EDTA drawing tube at Visit 2. If not feasible at Visit 2, the sample may also be drawn at any later visit.
After drawing, the tube needs to be gently inverted about 10 times. The blood sample has to be stored at a temperature of approximately -20°C or below. Once frozen, thawing of the samples should be avoided.
Frozen blood samples should be shipped on dry ice to:
Boehringer Ingelheim Pharma GmbH & Co. KG
Zentrale Logistik Biberach E147
Pharmacogenomics; Attn: or representative
Hubertus-Liebrecht-Straße 32
88400 Biberach/Riß, Germany

5.3.1.2 Analytical determinations

Genomic DNA may be extracted from blood samples according to standard molecular genetics methods and analysed by DMET analysis or other standard genotyping technologies.

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 administration of trial medication. The safety assessments are standard, are accepted for evaluation of safety and tolerability of an orally administered drug, and are widely used in clinical trials. The pharmacokinetic parameters and measurements outlined in Section 5.5 are generally used assessments of drug exposure. The biomarker 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 in the CRFs.

5.5.1 Pharmacokinetic endpoints

The following pharmacokinetic parameters will be determined if feasible:

5.5.1.1 Primary endpoints

After the first dose (Day 1), for BI 1467335 :

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

After the last dose (Day 28), for BI 1467335:

- $AUC_{\tau,28}$ (area under the concentration-time curve of the analyte in plasma over the dosing interval after administration of the 28^{th} dose)
- $C_{max,28}$ (maximum measured concentration of the analyte in plasma following administration of the 28^{th} dose)

5.5.1.2 Secondary endpoints

After the 14th dose (Day 14), for BI 1467335:

- $AUC_{\tau,14}$ (area under the concentration-time curve of the analyte in plasma over the dosing interval after administration of the 14^{th} dose)
- $C_{max,14}$ (maximum measured concentration of the analyte in plasma following administration of the 14^{th} dose)

5.5.1.3 Further parameters of interest

Further pharmacokinetic parameters will be calculated as feasible and may include (but are not limited to):

For DI 629956 and CD 6652 (major metabolites of BI 1467335):

- Same parameters as mentioned in 5.5.1.1 and 5.5.1.2 for BI 1467335
- $RAUC_{x,M/P}$ (ratio of the AUC value of the metabolite versus AUC value of the parent compound). To be calculated for AUCs on Day 1, 14 and 28, if feasible.
- $RC_{max,\ M/P}$ (ratio of the C_{max} value of the metabolite versus C_{max} value of the parent compound).

For BI 1467335, DI 629956 and CD 6652

After the first dose (Day 1) if the data allows:

- 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)
- $AUC_{0-\infty}$ (area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity)
- $\%AUC_{tz-\infty}$ (the percentage of $AUC_{0-\infty}$ obtained by extrapolation)
- AUC_{t1-t2} (area under the concentration-time curve of the analyte in plasma over the time interval t_1 to t_2)
- t_{max} (time from dosing to maximum measured concentration of the analyte in plasma)
- λ_z (terminal elimination rate constant in plasma)
- $t_{1/2}$ (terminal elimination half-life of the analyte in plasma)
- MRT_{ex} (mean residence time of the analyte in the body after oral administration)
- (apparent clearance of the analyte in the plasma after extravascular administration), *for BI 1467335 only*
- V_z/F (apparent volume of distribution during the terminal phase after extravascular administration), *for BI 1467335 only*
- Ae_{t1-t2} (amount of analyte that is eliminated in urine from the time interval t_1 to t_2)
- fe_{t1-t2} (fraction of administered drug excreted unchanged in urine from time point t_1 to t_2)
- $CL_{R,\,t1-t2}$ (renal clearance of the analyte in plasma from the time point $_{t1}$ to $_{t2}$)

After the 14^{th} dose (Day 14) and the 28^{th} dose (Day 28):

- $AUC_{t1-t2,N}$ (area under the concentration-time curve of the analyte in plasma over the time interval t_1 to t_2 following N doses)
- (time from the N^{th} dosing to maximum concentration of the analyte in plasma following N doses)
- $\lambda_{z,N}$ (terminal rate constant in plasma following N doses)
- $t_{1/2,N}$ (terminal half-life of the analyte in plasma following N doses)
- $MRT_{ex,N}$ (mean residence time of the analyte in the body following N orally administered doses)
- $CL_{,N}/F$ (apparent clearance of the analyte in the plasma following N doses of extravascular administration; calculated as $Dose/AUC_{0-24,N}$), *for BI 1467335 only*
- $V_{z,N}/F$ (apparent volume of distribution during the terminal phase λ_z following N doses of extravascular administration; calculated as $CL_{,N}/F/\lambda_{z,N}$), *for BI 1467335 only*
- $R_{A,Cmax,N}$ (accumulation ratio based on C_{max} after N doses)
- $R_{A,AUC,N}$ (accumulation ratio based on AUC_τ after N doses)
- $Ae_{t1-t2,N}$ (amount of analyte that is eliminated in urine following N doses from the time point t_1 to time point t_2)
- $fe_{t1-t2,N}$ (fraction of analyte eliminated in urine following N doses from time point t_1 to time point t_2)
- $CL_{R,t1-t2,N}$ (renal clearance of the analyte in plasma from the time point t_1 to time point t_2 following N doses)

On days 2, 4, 7, 10, 14, 15, 17, 21, 25, 26 and 28:

- $C_{pre,N}$ (predose concentration of the analyte in plasma immediately within 30 minutes before administration of the N^{th} dose)

Further pharmacokinetic parameters might be calculated as appropriate.

5.5.2 Methods of sample collection

5.5.2.1 Plasma sampling for pharmacokinetic analysis

For quantification of BI 1467335 plasma concentrations, approx. 2.7 mL of blood will be taken from an antecubital or forearm vein into a K3-EDTA (tripotassium ethylenediaminetetraacetic acid)-anticoagulant blood drawing tube at the times indicated in the Flow Chart. Blood will be withdrawn by means of either an indwelling venous catheter or by venipuncture with a metal needle.

All blood samples will be centrifuged using a cooled centrifuge at about 2000 x g to 4000 x g and at a temperature of 4 - 8°C for at least 10 minutes (intermittent storage on ice). The obtained K3-EDTA plasma will be split into two cryotubes (e.g. Nunc tubes) which will be frozen immediately and not later than 60 min after blood sampling with interim storage on ice. One of the aliquots should contain at least 0.5 mL plasma which was pretreated with 10 µL phenelzine solution (approx. 25 mM/L). The second aliquot containing the remaining plasma will be used as analytical back-up sample. Until transfer on dry ice to the analytical laboratory, the plasma samples will be stored frozen and in upright position at about –20°C or below at the clinical site and at the analytical laboratory until analysis.

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

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

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

5.5.2.2 Plasma sampling for drug metabolism analysis

No additional plasma samples for the quantification of drug metabolites will be collected. For quantification of metabolites backup samples collected for the pharmacokinetic analysis will be used (see Section 5.5.2.1).

Metabolite analysis will be performed under non-GxP conditions in the laboratory of

Boehringer Ingelheim Pharma GmbH & Co. KG
Drug Metabolism and Pharmacokinetics
Birkendorfer Straße 65
88397 Biberach/Riß, Germany

Only data related to the parent compound and its metabolites will be acquired. Evaluation of the drug metabolism will be reported separately but not included in the CTR of this trial. The study samples will be discarded after completion of the experiments but not later than 3 years after the final study report has been signed.

5.5.2.3 Urine sampling for pharmacokinetic analysis

A blank urine sample will be collected before administration of trial medication (within 2 h before drug dosing on days 1) and two 0.5 mL aliquots will be retained to check for analytical interference by concomitant or rescue medication.

All urine voided during the sampling intervals indicated in the Flow Chart will be collected in 3 L polyethylene (PE) containers and stored at room temperature. Subjects will be told to empty their bladders prior to start of urine sampling interval (this urine will be discarded) and at the end of each sampling interval (this urine will be collected).

The urine weight/volume (weight will be set equal to volume, i.e. 1 kg = 1 L, without correction for specific gravity of urine) for each collection interval will be documented and two 2 mL aliquots (e.g. Nunc tubes) will be stored for bioanalytical measurement. The weight of the empty container including lid will be determined and the weight of the container at the end of each sampling interval will be determined.

Until transfer to the analytical laboratory, the urine samples will be stored at about -20°C or below at the clinical site and stored at the analytical laboratory at –20°C or below until analysis. The back-up aliquots will be transferred to the analytical laboratory after the bioanalyst has acknowledged safe arrival of the first aliquot.

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

5.5.3 Analytical determinations

5.5.3.1 Analytical determination of analyte plasma concentration

BI 1467335, DI 629956 and CD 6652 concentrations in plasma will be determined by a validated LC-MS/MS (liquid chromatography tandem mass spectrometry) assay.

The analysis will be performed at:

Boehringer Ingelheim Pharma GmbH & Co. KG
Drug Metabolism and Pharmacokinetics
Birkendorfer Straße 65
88397 Biberach/Riß, Germany

As described in Section 4.1.5, the bioanalyst will be unblinded during sample analysis.

5.5.3.2 Analytical determination of analyte urine concentration

BI 1467335, DI 629956 and CD 6652 concentrations in urine will be determined by a validated LC-MS/MS assay

The analysis will be performed at:

Boehringer Ingelheim Pharma GmbH & Co. KG
Drug Metabolism and Pharmacokinetics
Birkendorfer Straße 65
88397 Biberach/Riß, Germany

5.6 BIOMARKER(S)

Not applicable.

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

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

Study measurements and assessments scheduled to occur 'before' trial medication administration on Day 1 are to be performed and completed within a 2 h-period prior to the trial drug administration (only on Day 1 this includes blank values for PK in urine and plasma).

On Day 14 and 28, same time windows apply except of the plasma PK sample which will be collected 5 minutes before drug administration.

The acceptable deviation from the scheduled time for vital signs and ECG will be ± 30 min for the first 4 h after trial drug administration and ± 60 min thereafter when not already stated otherwise in the Flow Chart.

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

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

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

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

6.2.1 Screening period

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

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

Pharmacogenomic genotyping will be performed in all volunteers (for details see Section 5.3).

6.2.2 Treatment period

Each subject will receive a single dose of BI 1467335 from Day 1 to Day 28.

Study participants will be admitted to the trial site in the evening of day -1 and kept under close medical surveillance for at least 24 h following the first drug administration. The subjects will be kept hospitalized from the evening of Day -1 to the morning of Day 2, the evening of Day 13 to the morning Day 15 and from the evening of Day 27 to the morning of Day 29. On all other time periods the study will be performed in an ambulatory fashion provided there are no medical reasons preventing the discharge from the unit.

The safety measurements performed during the treatment period are specified in Section 5.2. of this protocol and in the Flow Chart. For details on time points for all other trial procedures, refer to the Flow Chart. AEs and concomitant therapy will be assessed continuously from screening until the end of trial examination. For details on time points and procedures for collection of plasma and urine samples for PK analysis, refer to Flow Chart and Section 5.5.2.

6.2.3 End of trial period

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

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

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

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

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 STATISTICAL DESIGN – MODEL

7.1.1 Objectives

The primary objective of this trial is to investigate the effect of moderate renal impairment (test, T) on the pharmacokinetics and safety of BI 1467335 in comparison to a control group with normal renal function (reference, R) after single 10 mg BI 1467335 treatment for 28 days. The trial is designed to allow intra-subject comparisons (via pairs of renal impaired subjects and their matching healthy controls) and will be evaluated statistically by use of an appropriate linear model which is further described in Section 7.1.3.

The secondary objective is the evaluation and comparison of several pharmacokinetic parameters between subject groups (moderate renal impaired and normal renal function). The secondary objectives will be assessed by descriptive statistics.

The assessment of safety and tolerability will be an additional objective of this trial, and will be evaluated by descriptive statistics.

7.1.2 Endpoints

The effect of moderate renal impairment is to be determined on the basis of the primary endpoints C_{max}, $AUC_{0\text{-}24}$ of BI 1467335 on Day 1, and $C_{max,28}$ and $AUC_{\tau,28}$ of BI 1467335 on Day 28 (see Section 5.5.1) as well as the secondary pharmacokinetic endpoints $C_{max,14}$ and $AUC_{\tau,14}$ of BI 1467335 on Day 14 (see Section 5.5.2)

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

7.1.3 Model

The statistical model used for the analysis will be an ANOVA (analysis of variance) model on the logarithmic scale including the effect "degree of renal impairment" as a fixed effect as well as subject pair as a random effect. The model is described by the following equation:

$$y_{ik} = \mu + \tau_k + s_i + \varepsilon_{ik},$$ where

y_{ik} logarithm of response (endpoint for relative bioavailability evaluation, (see in Section 7.1.3) measured on the degree of renal impairment k for subject pair i,

μ the overall mean,

s_i the ith subject pair (each renal impaired subject has his own matching healthy control), i=1,…,10

τ_k the kth degree of renal impairment, k = 1 for normal and k=2 for moderate renal impaired

ε_{ik}, the random error associated with the kth degree of renal impairment for subject pair i.

7.2 NULL AND ALTERNATIVE HYPOTHESES

The effect of renal impairment on the pharmacokinetics of BI 1467335 will be evaluated via comparing moderate renal impaired subjects to their matched subjects with normal renal function. This will be estimated by the ratios of the geometric means (test/reference) for the PK endpoints mentioned in Section 7.1.2. 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, that is, no hypothesis will be tested.

7.3 PLANNED ANALYSES

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

The following analysis sets will be defined for this trial:

Further analysis sets will be defined in the TSAP, if needed.

- Randomised set (RS):

  This subject set includes all subjects who were randomized, i.e., who have been assigned a study subject number, whether treated or not.

- Treated set (TS):

  This subject set includes all subjects in the RS who were documented to have receivedone dose of study drug. This is the full analysis set population in the sense of ICH-E9.

- PK analysis set (PKS):

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

Relevant protocol violations may be

- Incorrect dose of trial medication taken
- Use of restricted medications.

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

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

The PK analysis set (PKS) includes all subjects in the TS who provide at least one PK parameter that was defined as primary or secondary endpoint and was not excluded according to the description above. Thus, a subject will be included in the PKS, even if he/she contributes only one PK parameter value to the statistical assessment.

- PK statistical analysis set (PKS-stat):

  This subject set includes all subjects from the PKS who built a subject pair of renal impaired subject and his matching healthy volunteer control and provide at least one PK parameter that was defined as primary or secondary endpoint and was not excluded according to the description above.

7.3.1 Primary analyses

The primary analyses of the primary endpoint will be based on the PKS-stat (cf. Section 7.3).

Point estimates of the ratios of the geometric means (T/R) for the endpoints described in Section 7.1.2 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 (cf. 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.

7.3.2 Secondary analyses

Pharmacokinetic endpoints defined in Section 5.5.1 will be compared between subject groups (moderate renal impaired and normal renal function) by means of descriptive evaluations, as described in Section 7.3.5 based on the PKS. In addition, the same pharmacokinetic parameters that will be evaluated with inferential statistics for BI 1467335, will be evaluated

in the same manner for the 2 major metabolites, DI 629956 and CD 6652 and the ratios of parent to CD6652 and parent to DI 629956.

Additionally the relationship of estimated renal function and the primary and secondary PK endpoints will be investigated using a regression model, if the data allows. In case of too narrow renal function range only a scatterplot will be provided.

Safety and tolerability will be evaluated by descriptive evaluations, as described in Section 7.3.3.

7.3.3 Safety analyses

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

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

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, measurements planned or AEs recorded prior to first intake of trial medication will be assigned to 'screening' and those between first trial medication intake until the trial completion date will be assigned to the treatment period. These assignments including the corresponding time intervals will be defined in detail in the TSAP.

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

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

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

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

Relevant ECG findings will be reported as AEs.

7.3.4 Interim analyses

No interim analysis is planned. However, as mentioned in Section 2.3 a staggered inclusion of renally impaired subjects will be applied, where based on the safety and PK data of the first 3 subjects up to one week after start of dosing, it will be decided whether the remaining subjects can be dosed. For this purpose exploratory evaluation of safety and PK data will be performed.

7.3.5 Pharmacokinetic analyses

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

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

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

Descriptive evaluations of PK parameters listed in 5.5.1 are based on PKS.

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

7.4 HANDLING OF MISSING DATA

7.4.1 Safety

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

7.4.2 Plasma/urine drug concentration - time profiles

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

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

limit of quantification) will be displayed as such and not replaced by zero at any time point (this rule also applies also to the lag phase, including the pre-dose values).

7.4.3 Pharmacokinetic parameters

No imputation of missing PK parameters will be performed

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

7.5 RANDOMISATION

Not applicable.

7.6 DETERMINATION OF SAMPLE SIZE

It is planned that 20 volunteers will take part in this study, 10 of them within each subject group (moderate renal impaired and normal renal function). The planned sample size is not based on a power calculation, but is judged to be adequate to get reliable results that meet the objectives of this study.

8. INFORMED CONSENT, DATA PROTECTION, TRIAL RECORDS

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

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

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

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

8.1 STUDY APPROVAL, SUBJECT INFORMATION, AND INFORMED CONSENT

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

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

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

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

8.2 DATA QUALITY ASSURANCE

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

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

8.3 RECORDS

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

8.3.1 Source documents

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

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

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

8.3.2 Direct access to source data and documents

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

8.3.3 Storage period of records

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

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

8.4 EXPEDITED REPORTING OF ADVERSE EVENTS

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

8.5 STATEMENT OF CONFIDENTIALITY

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

Data protection and data security measures are implemented for the collection, storage and processing of patient data in accordance with the principles 6 and 12 of the WHO GCP handbook. Treatment data may be provided to the subject's personal physician or to other

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

8.5.1 Collection, storage and future use of biological samples and corresponding data

Measures are in place to comply with the applicable rules for the collection, storage and future use of biological samples from clinical trial participants and the corresponding data, in particular

- A Quality Management System has been implemented to ensure the adherence with the Principles of Good Clinical Practice as outlined in 'Note For Guidance On Good Clinical Practice' (CPMP/ICH/13 5/95)
- The BI-internal facilities storing and analysing biological samples and data from clinical trial participants as well as the laboratories' activities for clinical trials sponsored by Boehringer Ingelheim are regularly audited. The analytical groups and the banking facility are therefore assessed to be qualified for the storage and use of biological samples and data collected in clinical trials.

8.6 SAMPLES AND DATA ARE USED ONLY IF AN APPROPRIATE INFORMED CONSENT IS AVAILABLE.COMPLETION OF TRIAL

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

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n00259383 Irreversible in vitro inhibition of MAO-B catalyzed kynuramine deamination by BI 1467335 A442/17LU B6114 01 Dec 2017.

10. APPENDICES

10.1 CKD-EPI FORMULA

eGFR = 141 x min(SCr/κ, 1)α x max(SCr /κ, 1)-1.209 x 0.993Age x 1.018 [if female] x 1.159 [if Black]

SCr (standardized serum creatinine) = mg/dL

κ = 0.7 (females) or 0.9 (males)

α = -0.329 (females) or -0.411 (males)

min = indicates the minimum of SCr/κ or 1

max = indicates the maximum of SCr/κ or 1

age = years

See reference [R12-1392] and [R13-4387].

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

Number of global amendment		1
Date of CTP revision		11 September 2017
EudraCT number		2017-002180-18
BI Trial number		1386-0002
BI Investigational Product(s)		BI 1467335
Title of protocol		Pharmacokinetics, safety and tolerability after multiple dose administration of BI 1467335 in subjects with moderate renal impairment and subjects with normal renal function (a mono-centric, open-label study in matched-group design)
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		Section 3.3.2, Inclusion criteria
Description of change		Contraceptive measures were further detailed. In addition it was particularly mentioned that only contraceptive methods with a failure rate of less than 1% per year are acceptable.
Rationale for change		To be compliant with recommendations by regulatory bodies.

Number of global amendment		2
Date of CTP revision		15 March 2018
EudraCT number		2017-002180-18
BI Trial number		1386-0002
BI Investigational Product(s)		BI 1467335
Title of protocol		Pharmacokinetics, safety and tolerability after multiple dose administration of BI 1467335 in subjects with moderate renal impairment and subjects with normal renal function (a mono-centric, open-label study in matched-group design)
To be implemented only after approval of the IRB / IEC / Competent Authorities		☐
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		☒
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		☐
Section to be changed		1.2 Drug profile 4.2.2 Restrictions
Description of change		Section 1.2: Implementation of new *in vitro* data classifying BI 1467335 as potential irreversible MAO-B inhibitor. Section 4.2.2: Addition of prohibited foods and drugs to mitigate the risk of relevant adverse reactions.
Rationale for change		Time dependent inhibition of MAO-B catalyzed kynuramine deamination by BI 1467335 was observed indicating an irreversible inhibition mechanism.

APPROVAL / SIGNATURE PAGE

Document Number: c17401132 **Technical Version Number:3.0**

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

Title: Pharmacokinetics, safety and tolerability after multiple dose administration of BI 1467335 in subjects with moderate renal impairment and subjects with normal renal function (a mono-centric, open-label study in matched-group design)

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Approval-Team Member Medicine		19 Mar 2018 08:24 CET
Author-Trial Clinical Pharmacokineticist		19 Mar 2018 08:28 CET
Approval-Therapeutic Area		19 Mar 2018 08:32 CET
Author-Trial Clinical Monitor		19 Mar 2018 08:52 CET
Author-Trial Statistician		19 Mar 2018 10:53 CET
Verification-Paper Signature Completion		21 Mar 2018 08:44 CET

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed