Clinical Trial Protocol

	Document Number: c17932132-03
EudraCT No.:	2017-002879-26
BI Trial No.:	1386-0011
BI Investigational Product:	BI 1467335
Title:	A phase I, open-label, single and multiple dose trial to investigate metabolism and pharmacokinetics of [^{14}C]BI 1467335 administered as oral solution in healthy male volunteers
Lay Title:	This study tests BI 1467335 in healthy male volunteers. The study tests how different doses of BI 1467335 are taken up and handled by the body.
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: 14 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: 14 November 2017	**Trial number:** 1386-0011		**Revision date:** 14 March 2018

Title of trial:	A phase I, open-label, single and multiple dose trial to investigate metabolism and pharmacokinetics of [^{14}C]BI 1467335 administered as oral solution in healthy male volunteers
Principal Investigator:	
Trial site:	
Clinical phase:	I
Objectives:	To investigate the basic pharmacokinetics after single and multiple doses of BI 1467335, its metabolites [^{14}C]-radioactivity, including mass balance, excretion pathways and metabolism following a single oral dose of 10 mg [^{14}C]BI 1467335 given to healthy male subjects (subjects assigned to multiple doses will have a preceding 27 days treatment with non-radiolabelled compound at a dose of 10 mg of BI 1467335 QD).
Methodology:	Open-label, single period and single arm design with 2 treatment groups (1. single dosing and 2. multiple dosing)
No. of subjects:	
total entered:	16
each treatment:	8
Diagnosis:	Not applicable
Main criteria for inclusion:	Healthy male subjects, age of 30 to 65 years, body mass index (BMI) of 18.5 to 29.9 kg/m^2
Test product 1:	Carbon 14 labelled BI 1467335 ([^{14}C]BI 1467335) as oral solution
dose:	10 mg (calculated as free base BI 1467335) – in 20 mL oral solution (0.5 mg/mL) – corresponding to 11.3 mg BI 1467335 HCl salt containing a radioactive dose of 2.0 MBq (54 µCi)
mode of admin.:	Oral with 240 mL of water

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Test product 2:	BI 1467335 film-coated tablet formulation
dose:	10 mg (2 x 5 mg) QD
mode of admin.:	Oral with 240 mL of water
Comparator product:	Not applicable
Duration of treatment:	Treatment Group 1: On Day 1 [^{14}C]BI 1467335 as oral solution (Test product 1) Treatment Group 2: Non-radiolabelled film-coated tablets (Test product 2) from Day 1 to Day 27 and Day 29 to a maximum of Day 40. On Day 28 single dose of radiolabelled oral solution (Test product 1)
Criteria for pharmacokinetics:	*Primary endpoints:* Mass balance recoveries of total radioactivity in urine and faeces: Amount of radioactivity excreted as a percentage of the administered dose (fe_{0-tz}) for urine and faeces *Secondary endpoints:* Assessment of the oral pharmacokinetics of [^{14}C]BI 1467335 by calculating the following parameters for total radioactivity C_{max} and AUC_{0-tz} and cold BI 1467335 in plasma: C_{max} and AUC_{0-tz} or $C_{max,ss}$ and AUC_{τ}
Criteria for safety:	Adverse events (AEs) including clinically relevant findings from the physical examination, safety laboratory tests, 12-lead electrocardiogram (ECG), vital signs (blood pressure [BP], pulse rate [PR])
Statistical methods:	Descriptive statistics will be calculated for all endpoints.

FLOW CHART

Flow chart: Treatment Group 1 (Single dose)

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 $_{blood/plasma}$ [2]	PK $_{urine}$ [6]	PK $_{faeces}$ [5]		12-lead ECG	Vital signs (BP, PR)	Questioning for AEs and concomitant therapy
1	-21 to -2			Screening (SCR)[1]	x					x	x	
2	-1	-18:00	14:00	Admission to trial site[14]	x							x
	1	-2:00	06:00		x[3,9]	x[3,15]	x	x[16]		x[3]	x[3]	▲
		0:00	08:00	Drug administration[9] (labelled compound)			▲	▲				│
		0:20	08:20			x	│	│				│
		0:45	08:45			x	│	│				│
		1:00	09:00		x[4]	x	│	│		x	x	│
		2:00	10:00	240 mL water intake		x	│	│				│
		3:00	11:00			x	│	│				│
		4:00	12:00	Lunch, 240 mL water intake		x	┼	│		x	x	│
		6:00	14:00			x	│	│				│
		8:00	16:00			x	┼	│				│
		10:00	18:00	Dinner		x	│	│				│
		12:00	20:00	Snack[7]	x[4]	x	┼	│		x	x	│
	2	24:00	08:00		x[4]	x	┼	┼		x	x	│
		36:00	20:00			x	│	│				│
	3	48:00	08:00			x	┼	┼				│
	4	72:00	08:00			x	┼	┼				│
	5	96:00	08:00			x	┼	┼				│
	6	120:00	08:00			x	┼	┼				│
	7	144:00	08:00			x	┼	┼				│
	8	168:00	08:00				┼	┼				│
	9	192:00	08:00			x	┼	┼				│
	10	216:00	08:00				┼	┼				│
	11	240:00	08:00			x	┼	┼				│
	12	264:00	08:00				┼	┼				│
	13	288:00	08:00			x	┼	┼				│
	14	312:00	08:00				┼	┼				│
	15	336:00	08:00	Discharge from trial site	x[9]	x	▼	▼		x	x	▼

Visit	Day	Planned time (relative to drug administration) [h:min]	Approximate clock time of actual day [h:min]	Event and comment	Safety laboratory	PK blood/plasma [2, 10]	PK urine [6]	PK faeces [5]	Vital signs (BP, PR), ECG	Questioning for AEs & concomitant medication
2	20	461:00	13:00	Start home collection[11, 12]				▲		▲
	21	485:00	13:00	Admission to trial site[11]		x	▲	┼		┼
	22	509:00	13:00	Discharge from trial site[11]			▼	▼		┼
	27	629:00	13:00	Start home collection[11, 12]				▲		┼
	28	653:00	13:00	Admission to trial site[11]		x	▲	┼		┼
	29	677:00	13:00	Discharge from trial site[11]			▼	▼		┼
	34	797:00	13:00	Start home collection[11, 12]				▲		┼
	35	821:00	13:00	Admission to trial site[11]		x	▲	┼		┼
	36	845:00	13:00	Discharge from trial site[12]			▼	▼		┼
	41	965:00	13:00	Start home collection[11,12]				▲		┼
	42	989:00	13:00	Admission to trial site[11]		x	▲	┼		┼
	43	1013:00	13:00	Discharge from trial site[11]			▼	▼		┼
	48	1133:00	13:00	Start home collection[11, 12]				▲		┼
	49	1157:00	13:00	Admission to trial site[11]		x	▲	┼		┼
	50	1181:00	13:00	Discharge from trial site[11]			▼	▼		▼
3	16-50			End of trial (EOT) examination[8,13]	x[9]				x	x

1. Screening includes subject information, informed consent, physical examination, check of vital signs, ECG, safety laboratory (including drug and virus screening), demographics (including determination of body height and weight, smoking status and alcohol history), relevant medical history, concomitant therapy and review of inclusion/exclusion criteria.
2. Pharmacokinetics (PK): BI 1467335 and metabolites in plasma; [^{14}C]-radioactivity in whole blood and plasma. At all time points, samples for [^{14}C]-radioactivity in whole blood and plasma will be taken. Samples for PK assessment of cold BI 1467335 will be collected up to 10 h
   after intake of radiolabelled drug on Day 1.
3. The time is approximate; the procedure is to be performed within a time window of 3 h prior to drug administration.
4. At these time point, a sample is taken for measurement of haematocrit.
5. All stools (for [^{14}C]-radioactivity assessment) will be collected quantitatively from Day 1 in sampling intervals: 0-24, 24-48, 48-72, 72-96, 96-120, 120-144, 144-168, 168-192, 192-216, 216-240, 240-264, 264-288, 288-312 and 312-336 hours after intake of [^{14}C]BI 1467335. Thereafter, if warranted, 24 h collections are to be performed on days 21-22, 28-29, 35-36, 42-43, and 49-50. A blank sample will be collected before drug administration on Day 1. Collection of the predose faeces sample will start from approximately -48 h before drug administration. Faeces sampling for [^{14}C]-radioactivity assessment will be stopped when the release criteria for radioactivity recovery (Section 3.1) have been met (earliest stopping on day 15). "┼" means end of last collection interval, start of following collection interval. All samples: planned for determination of [^{14}C]-radioactivity. For technical reasons, the planned times used in the CRF and result transfer files will have 5 minutes added to the planned times in the Flow Chart (i.e. 0:05-24:04, 24:05-48:05, …)
6. Urine collection intervals (for PK/[^{14}C]-radioactivity assessment (planned time): on Day -1 or Day 1 predose (blank) sample, on Day 1 prior to start of urine collection voiding of the bladder, 0-4, 4-8, 8-12, 12-24, 24-48, 48-72, 72-96, 96-120, 120-144, 144-168, 168-192, 192-216, 216-240, 240-264, 264-288, 288-312, and 312-336 hours after drug administration. Thereafter, if warranted, 24 h collections are to be performed on days 21-22, 28-29, 35-36, 42-43, and 49-50. Urine sampling for PK will be stopped when release criteria for radioactivity recovery (Section 3.1) have been met (earliest stopping on day 15). "┼" means end of last collection interval, start of following collection interval. All samples: planned for determination of [^{14}C]-radioactivity, BI 1467335
7. If several actions are indicated at the same time point, the intake of meals will be the last action.

8. End-of-trial (EOT) examination to be performed within 1 to 7 days after last discharge from the study centre, or, if all once-weekly 24 h sampling periods are needed, prior to discharge on Day 50. EOT examination includes physical examination, vital signs, ECG, safety laboratory, recording of AEs and concomitant therapies.
9. Subjects are to be fasted for at least 10 h before sample is taken.
10. Blood sampling for an individual subject can be stopped if [^{14}C]-radioactivity in plasma is below limit of detection (<LLOQ 10 dpm/mL) at two consecutive sampling time points for this subject.
11. The planned times for admission, discharge, start and end of the urine and faeces collection intervals are approximate. The procedures are to be performed within a time window of +/- 4 h to the planned time.
12. Subjects are to collect faeces at home within 24 h intervals before admission to once-weekly in-house collection intervals. Home collection intervals: Day 20-21, 27-28, 34-35, 41-42, and 48-49. If faeces are collected in the subsequent in-house collection interval, faeces collected at home will be discarded. If no faeces is collected in the subsequent in-house collection interval (no defecation), faeces collected at home will be used instead for analysis.
13. For definition of the individual subject's end of trial see Section 6.2.3
14. Urine drug and alcohol screening will be done at this time point.

16. Subjects will collect a predose faeces sample at home in specific containers provided by

Flow chart: Treatment Group 2 (Multiple dose)

Visit	Day	Planned time (relative to first drug administration [h:min]	Approximate clock time of actual day [h:min]	Event and comment[18]	Safety laboratory	PK blood/plasma[2]	PK urine[6]	PK faeces[5]		12-lead ECG	Vital signs (BP, PR)	Questioning for AEs and concomitant therapy
1	-21 to -2			Screening (SCR)[1]	x[6]					x	x	
2	-1	-12:00	20:00	Admission to trial site	x[14]							x
	1	-2:00	06:00		x[3,9]	x[3,16]	x	x[17]		x[3]	x[3]	▲
		0:00	08:00	Ambulatory visit, dispense of study medication								|
		0:15	08:15			x						|
		1:00	9:00			x						|
		2:00	10:00									|
	2	24:00	8:00	Discharge		x						|
	6	132:00	20:00	Admission to trial site								|
	7	144:00	08:00	Ambulatory visit, dispense of study medication, discharge	x[9]	x[3]				x[3]	x[3]	|
	13	300:00	20:00	Admission to trial site	x[14]							|
	14	312:00	08:00	Ambulatory visit, dispense of study medication, discharge	x[9]	x[3]				x[3]	x[3]	|
	20	468:00	20:00	Admission to trial site								|
	21	480:00	08:00	Ambulatory visit, dispense of study medication, discharge	x[9]	x[3]				x[3]	x[3]	|
	27	631:00	15:00	Admission to trial site	x[14]						x[3]	|
	28	646:00	06:00		x[3, 9]	x[3]				x[3]	x[3]	|
		648:00	08:00	Drug administration (+labelled compound)			▲	▲				|
		648:20	08:20			x	|	|				|
		648:45	08:45			x	|	|				|
		649:00	09:00		x[4]	x	|	|				|
		650:00	10:00	240 mL water intake		x	|	|				|
		651:00	11:00			x	|	|				|
		652:00	12:00	Lunch, 240 mL water intake[7]		x	+	|				|
		654:00	14:00			x	|	|				|
		656:00	16:00			x	+	|				|
		658:00	18:00	Dinner		x	|	|				|
		660:00	20:00	Snack[7]	x[4]	x	+	|		x	x	▼

Visit	Day	Planned time (relative to first drug administration [h:min]	Approximate clock time of actual day [h:min]	Event and comment	Safety laboratory	PK blood/plasma [2, 10]	PK urine [6]	PK faeces [5]		12-lead ECG	Vital signs (BP, PR)	Questioning for AEs and concomitant therapy
2	29	672:00	08:00	Drug administration	x[4]	x	┼	┼			x	▲
		684:00	20:00			x	|	|				
	30	696:00	08:00	Drug administration		x	┼	┼				
	31	720:00	08:00	Drug administration		x	┼	┼				
	32	744:00	08:00	Drug administration		x	┼	┼				
	33	768:00	08:00	Drug administration		x	┼	┼				
	34	792:00	08:00	Drug administration		x	┼	┼				
	35	816:00	08:00	Drug administration	x[9]	x	┼	┼		x	x	
		817:00	09:00			x	|	|				
	36	840:00	08:00	Drug administration[15]			┼	┼				
	37	864:00	08:00	Drug administration[15]		x	┼	┼				
	38	888:00	08:00	Drug administration[15]			┼	┼				
	39	912:00	08:00	Drug administration[15]		x	┼	┼				
	40	936:00	08:00	Drug administration[15]		x	┼	┼				
		937:00	09:00			x	|	|				
	41	960:00	08:00			x	┼	┼				
	42	984:00	08:00				┼	┼				
	43	1008:00	08:00	Discharge from trial site	x[9]	x	▼	▼		x	x	
	48	1133:00	13:00	Start home collection[11,12]				▲				
	49	1157:00	13:00	Admission to trial site[11]			▲	┼				
	50	1181:00	13:00	Discharge from trial site[11]		x	▼	▼				
	55	1301:00	13:00	Start home collection[11,12]				▲				
	56	1325:00	13:00	Admission to trial site[11]			▲	┼				
	57	1349:00	13:00	Discharge from trial site[11]		x	▼	▼				
	62	1469:00	13:00	Start home collection[11,12]				▲				
	63	1493:00	13:00	Admission to trial site[11]			▲	┼				
	64	1517:00	13:00	Discharge from trial site[11]		x	▼	▼				
	69	1637:00	13:00	Start home collection[11,12]				▲				
	70	1661:00	13:00	Admission to trial site[11]			▲	┼				
	71	1685:00	13:00	Discharge from trial site[11]		x	▼	▼				
	76	1805:00	13:00	Start home collection[11,12]				▲				
	77	1829:00	13:00	Admission to trial site[11]			▲	┼				
	78	1853:00	13:00	Discharge from trial site[11]		x	▼	▼				
3	43-78			End of trial (EOT) examination[8,13]	x[9]					x	x	x

1. Screening includes subject information, informed consent, physical examination, check of vital signs, ECG, safety laboratory (including drug and virus screening), demographics (including determination of body height and weight, smoking status and alcohol history), relevant medical history, concomitant therapy and review of inclusion/exclusion criteria.
2. Pharmacokinetics (PK): BI 1467335 in plasma; [^{14}C]-radioactivity in whole blood and plasma. From Day 28, samples for [^{14}C]-radioactivity in whole blood and plasma will be taken at all time points. Samples for PK assessment of BI 1467335 in plasma will be collected up to 24 h after intake of radiolabelled drug on Day 28.
3. The time is approximate; the procedure is to be performed within a time window of 3 h prior to drug administration.

4. At each of these time points, an additional sample is taken for measurement of haematocrit.
5. All stools (for [^{14}C]-radioactivity assessment) will be collected quantitatively from Day 28 after drug administration of labelled compound in portions in sampling intervals (planned times): 648:00-672:00,672:00-696:00, 696:00-720:00, 720:00-744:00, 744:00–768:00, 768:00- 792:00, 792:00-816:00, 816:00–840:00, 840:00-864:00, 864:00–888:00, 888:00-912:00, 912:00–936:00, 936:00-960:00, 960:00-984:00, 984:00–1008:00. Thereafter, if warranted 24 h collections are to be performed on days 49-50, 56-57, 63-64, 70-71 and 77-78. A blank sample will be collected before drug administration on Day 1. Collection of the predose faeces sample will start from approximately -48 h before drug administration. Faeces sampling for [^{14}C]-radioactivity assessment will be stopped when the release criteria (Section 3.1) for radioactivity recovery (Section 3.1) have been met (earliest stopping on day 43). "┼" means end of last collection interval, start of following collection interval. All samples: planned for determination of [^{14}C]-radioactivity. For technical reasons, the planned times used in the CRF and result transfer files will have 5 minutes added to the planned times in the Flow Chart (i.e. 0:05-24:04, 24:05-48:05, …).
6. Urine collection intervals (for PK/[^{14}C]-radioactivity assessment ; planned time):. A predose urine sample collected on Day -1 or Day 1 predose will serve blank sample. Before dosing of labelled compound on Day 28, subjects should be asked to void bladder. Urine collection starts -648:00-652:00,652:00-656:00, 656:00-660:00, 660:00-672:00, 672-696:00, 696:00-720:00, 720:00-744:00, 744:00–768:00, 768:00- 792:00, 792:00-816:00, 816:00–840:00, 840:00-864:00, 864:00–888:00, 888:00-912:00, 912:00–936:00, 936:00-960:00, 960:00-984:00, 984:00–1008:00. Thereafter, if warranted 24 h collections are to be performed on days 49-50, 56-57, 63-64, 70-71 and 77-78. Urine sampling will be stopped when release criteria for radioactivity recovery (Section 3.1) have been met (earliest stopping on day 43). "┼" means end of last collection interval, start of following collection interval. All samples: planned for determination of [^{14}C]-radioactivity. Samples of the collection interval on Day 28/29 planned for analysis of BI 1467335
7. If several actions are indicated at the same time point, the intake of meals will be the last action.
8. End-of-trial (EOT) examination to be performed within 1 to 7 days after last discharge from the study centre, or, if all once-weekly 24 h sampling periods are needed, prior to discharge on Day 78. EOT examination includes physical examination, vital signs, ECG, safety laboratory, recording of AEs and concomitant therapies.
9. Subjects are to be fasted for at least 10 h before sample is taken.
10. Beginning at time point 684:00 only samples for analysis of [^{14}C]-radioactivity in whole blood and plasma to be taken. Blood sampling for an individual subject can be stopped at 816:00h or later if [^{14}C]-radioactivity in plasma is below limit of detection (<LLOQ 10 dpm/mL) at two consecutive sampling time points for this subject.
11. The planned times for admission, discharge, start and end of the urine and faeces collection intervals are approximate. The procedures are to be performed within a time window of +/- 4 h to the planned time.
12. Subjects are to collect faeces at home within 24 h intervals before admission to once-weekly in-house collection intervals. Home collection intervals: Day 48-49,. Day 55-56, Day 62-63, Day 69-70, and Day 76-77. If faeces are collected in the subsequent in-house collection interval, faeces collected at home will be discarded. If no faeces is collected in the subsequent in-house collection interval (no defecation), faeces collected at home will be used instead for analysis.
13. For definition of the individual subject's end of trial see Section 6.2.3
14. Urine drug and alcohol screening will be done at this time point.
15. Treatment will be stopped from Day 35 onwards if [^{14}C]-radioactivity in plasma is below limit of detection (LLOQ 10 dpm/mL) for this subject.

17. Subjects will collect a predose faeces sample at home in specific containers provided by
18. On specific study days (Day 3 to Day 6, Day 8 to Day 13, Day 15 to Day 20 and Day 22 to 27) intake of study medication under ambulatory conditions.

TABLE OF CONTENTS

ABBREVIATIONS

ADME	Absorption, Distribution, Metabolism and Excretion
AE	Adverse event
AESI	Adverse events of special interest
Ae	Amount of analyte excreted
%Ae (fe)	Fraction excreted (percentual amount of analyte excreted)
$Ae_{faeces,\ 0\text{-}t2}$	Amount of analyte excreted in faeces over the time interval from 0 to the last quantifiable time point
$Ae_{faeces,\ t1\text{-}t2}$	Amount of analyte excreted in faeces over the time interval from t1 to t2
$Ae_{urine,\ 0\text{-}t2}$	Amount of analyte excreted in urine over the time interval from 0 to the last quantifiable time point
$Ae_{urine,\ t1\text{-}t2}$	Amount of analyte excreted in urine over the time interval from t1 to t2
ALT	Alanine amino transferase
AOC3	Amine oxidase copper-containing 3
AST	Aspartate amino transferase
$AUC_{0\text{-}tz}$	Area under the concentration-time curve of the analyte over the time interval from 0 to the last quantifiable data point
AUC_{τ}	Area under the concentration-time curve of the analyte over the time interval from 0 to interval tau
BI	Boehringer Ingelheim
bid/BID	*Bis in die*, twice daily
BLQ	Below limit of quantification
BMI	Body mass index (weight divided by height squared)
BP	Blood pressure
CA	Competent authority
[^{14}C]BI 1467335	[^{14}C]-labelled BI 1467335
C_{max}	Maximum measured concentration of the analyte
CML	Clinical Monitor Local

CRA	Clinical Research Associate
CRF	Case report form
CRO	Clinical Research Organization
CTCAE	Common Terminology Criteria for Adverse Events
CTP	Clinical trial protocol
CTR	Clinical trial report
CTSU	Clinical Trial Supplies Unit
Cum Ae	Cumulative recovery of [^{14}C]-radioactivity
Cum %Ae (fe)	Cumulative recovery of [^{14}C]-radioactivity expressed as a percentage of the dose
DILI	Drug-induced liver injury
ECG	Electrocardiogram
EDTA	Ethylenediaminetetraacetic acid
EOT	End of trial
EU	European Union
F	Absolute bioavailability factor
FDA	Food and Drug Administration
$fe_{faeces,\ 0\text{-}t2}$	Fraction excreted in faeces as percentage of the administered dose over the time interval from 0 to the last quantifiable time point
$fe_{faeces,\ t1\text{-}t2}$	Fraction excreted in faeces as percentage of the administered dose over the time interval from t1 to t2
$fe_{urine,\ 0\text{-}t2}$	Fraction excreted in urine as percentage of the administered dose over the time interval from 0 to the last quantifiable time point
$fe_{urine,\ t1\text{-}t2}$	Fraction excreted in urine as percentage of the administered dose over the time interval from t1 to t2
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
gMean	Geometric Mean
GMP	Good Manufacturing Practice
IB	Investigator's brochure
ICH	International Conference of Harmonization
ICRP	International Commission on Radiological Protection
IEC	Independent Ethics Committee
ILD	Interstitial lung disease
IPV	Important protocol violation
IRB	Institutional Review Board
ISF	Investigator site file
LC-MS/MS	Liquid chromatography tandem mass spectrometry

LLOQ	Lower Limit of Quantitation
MedDRA	Medical Dictionary for Regulatory Activities
MAT	Mean absorption time
M(R)D	Multiple (rising) dose
MRTex	Mean residence time of the analyte in the body after oral administration
NAFLD	Non-alcoholic fatty liver disease
NASH	Non-alcoholic steatohepatitis
NOA	Not analysed
NOAEL	No observed adverse effect level
NOR	No valid result
NOS	No sample available
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PKS	Pharmacokinetic set
PR	Pulse rate
QC	Quality control
qd/QD	*Quaque die*, once daily
QT	Time between start of the Q-wave and the end of the T-wave in an electrocardiogram
QTc	Heart rate-corrected QT interval
QTcF	Heart rate-corrected QT interval following the formula of Fridericia
RDC	Remote Data Capture
REP	Residual effect period
SAE	Serious adverse event
SCR	Screening
SOP	Standard Operating Procedure
S(R)D	Single (rising) dose
SSAO	Semi-carbazide-sensitive amine oxidase
SUSAR	Suspected Unexpected Serious Adverse Reaction
TDMAP	Trial Data Management and Analysis Plan
t_{max}	Time from dosing to the maximum measured concentration of the analyte
TMF	Trial master file
TS	Treated set
TSAP	Trial statistical analysis plan
t_z	Time of last measurable concentration of the analyte

ULN	Upper Limit of Normal
US	United States
VAP-1	Vascular adhesion protein-1

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 a high level of steatosis, ballooning of hepatocytes, and necroinflammation. NASH often leads to fibrosis which can progress to cirrhosis with a high risk of liver failure.

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

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

1.2 DRUG PROFILE

BI 1467335 is a small molecule 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].

Clinical experience

The clinical part of a phase I study [c08854973] just recently finished. This study investigated safety, tolerability, PK and PD of multiple doses

2. RATIONALE, OBJECTIVES, AND BENEFIT - RISK ASSESSMENT

2.1 RATIONALE FOR PERFORMING THE TRIAL

This trial is intended to examine the metabolism in humans, the mass-balance of excretion, plasma and urinary concentrations of BI 1467335

Major tasks involve the structure elucidation of metabolites as well as the [C]-radioactivity in blood cells, plasma, urine and faeces. This study will also help to determine the metabolic pathways following oral administration of [^{14}C]BI 1467335 in healthy volunteers.

The data are necessary for in-depth understanding of the pharmacokinetics of BI 1467335 including quantitative determination of elimination pathways and drug metabolites and are required for submission to regulatory authorities.

2.2 TRIAL OBJECTIVES

The main objective of this trial is to investigate the basic pharmacokinetics of BI 1467335, its metabolites, [^{14}C]-radioactivity, including mass balance, excretion pathways and metabolism following a single oral dose of 10 mg [^{14}C]BI 1467335 on Day 1 or on Day 28 during multiple dose treatment (Day 1 to Day 27 then Days 29 to last day of treatment) as determined by radioactivity collection with q.d. administration of non-labelled 10 mg BI 1467335 given to healthy male volunteers.

Primary objective is:

- To assess the mass balance recovery from excreta (urine and faeces) of [^{14}C]BI 1467335

Secondary objective is:

- To assess the C_{max} and AUC_{0-tz} for total radioactivity after single dose and after repeated doses and C_{max} and AUC_{0-tz} of BI 1467335 in plasma after single dose.
- To assess the $C_{max,ss}$ and $AUC_{0-\tau}$ for BI 1467335 in plasma after repeated doses.

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

2.3 BENEFIT - RISK ASSESSMENT

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

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

Drug-related risks and safety measures

On target effects

BI 1467335 could cause on-target toxicity as its anti-inflammatory effects may reduce the immune response and thus worsen infections. However, a deleterious effect relating to a reduction in leukocyte or lymphocyte migration was not seen in any of the preclinical models. This also true for two completed phase I studies in healthy male and female subjects Nonetheless, clinical and laboratory signs of reduced immune response will be monitored throughout the study.

Drug-induced liver injury (DILI)

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

Administration of ^{14}C-marked BI 1467335

[^{14}C]BI 1467335 is labelled with the isotope [^{14}C] which is necessary for the purposes of this mass balance trial. Therefore, subjects will be exposed to ionizing radiation. The effective dose that each subject receives from one administration of 2 MBq is approximately 0.56 mSv (see Appendix 10.1). For biomedical investigations in small groups of healthy volunteers, an effective dose ≤ 1.0 mSv is considered acceptable.

Summary of benefit-risk assessment

In a previous trial in healthy subjects, multiple oral doses of BI 1467335 administered once daily over 28 days were safe and well-tolerated. In the current trial, either single or multiple oral doses of 10 mg of BI 1467335 will be administered to healthy male volunteers. Each participating subject will receive only one radioactive dose.

The trial design is optimized to collect as much relevant information as possible on the pharmacokinetics of BI 1467335 without exposing participating volunteers to undue risk. However, there is always the potential of serious adverse events (SAEs) occurring with intake of trial medication. Risks to subjects will be minimized and addressed by eligibility criteria, safety laboratory examinations, ECG and vital sign measurements, in-house observation periods and verbal communication concerning AEs.

If the investigator should have any clinical concern, the safety of the subjects will be of paramount importance. The investigator has the discretion to remove subjects from the study should there be any safety concerns or if the subject's wellbeing is at jeopardy.

The risk associated with the expected maximal radiation burden falls in ICRP category IIa with minor level risk. This is considered to be acceptable.

The results of this trial are necessary for development of BI 1467335. Successful development of BI 1467335 is expected to provide a new valuable treatment for patients with NASH.

The risks of the participating volunteers are minimized and justified when compared to the potential benefits of this trial.

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

The study will be performed as an open-label, single-arm and single- or multiple dose trial in healthy male subjects in order to investigate the basic pharmacokinetics of BI 1467335, and [^{14}C]-radioactivity, including mass balance following a single oral dose of [^{14}C]BI 1467335. For subjects assigned to the multiple dose treatment, the single oral dose of [^{14}C]BI 1467335 is dosed following multiple dosing of cold drug (Days 1-27 and 29-last dose given based on radioactive recovery, maximum Day 40).

The planned radioactive dose per subject is 2.0 MBq (54 µCi).

For the single dose part Day 1 is the day of [^{14}C] labelled drug administration. Subjects will stay in the study centre up to the morning of day 15 for the collection of samples of blood, urine, and faeces. Subjects will be readmitted to the study centre for 24 h collection intervals of urine and faeces on days 21, 28, 35, 42, and 49, if release criteria have not been met. Within 24 h before each of these once-weekly in-house collection intervals, subjects are to collect faeces at home. This 24 h interval home collection faeces will be used for analysis in case no defecation occurs in the subsequent 24 h in-house collection interval.

For the multiple dose part Day 28 is the day of [^{14}C] labelled drug administration. Non-labelled compound will be administered at site or at home during Day 1 to Day 27 and from Day 29 to Day 40 (dosing may be stopped before Day 40 if release criteria based on [^{14}C]-radioactivity have been reached for individual subjects, see below). From the evening of Day 27 to the morning of Day 43 subjects will remain in the study centre for the entire duration. Subjects will be released from the centre on Day 43. Subjects will then be readmitted to the study centre for 24 h collection intervals of urine and faeces on days 49, 56, 63, 70, and 77, if release criteria have not been met. Within 24 h before each of these once-weekly in-house collection intervals, subjects are to collect faeces at home. This 24 h interval home collection faeces will be used for analysis in case no defecation occurs in the subsequent 24 h in-house collection interval.

Single dose and multiple dose part will be conducted in different subjects. The study is planned to start with the multiple dose part, while the single dose part will be scheduled close to Day 28 of the multiple dose part.

For determination of whether release criteria have been reached for individual subjects, [^{14}C]-radioactivity will be measured in excreta (urine and faeces). The actual recovery results will be reported as a percentage of the administered dose.

If one of the following release criteria is true (i.e., release criteria have been met), 24 h collection intervals after day 15 (single dose) or Day 43 (multiple dose) will not be performed / will be stopped:

- Greater than or equal to 90% of the administered dose has been recovered in urine and faeces combined over the investigational period, *or*

- If <1% of the dose administered has been collected in urine and faeces within 2 separate, consecutive 24 h intervals, *and*

- Concentration of total radioactivity in plasma <5% of C_{max} of total radioactivity in plasma

In the event that excretion release criteria are met after Day 15 (single dose) or Day 43 (multiple dose), but the mass balance recovery is less than 90%, subjects will still be asked to return to the clinic for 24 hour collection of urine and faeces on Days 21, 28, 35, 42, and 49 (single dose) or on Days 49, 56, 63, 70 and 77 (multiple dose) or until the recovery is deemed to be sufficient for mass balance purposes. If a subject is unable to attend one of these visits, they may be allowed to reschedule the visit if needed."

Irrespective of whether release criteria have been met or not after collection interval Day 49-50 (single dose) or Day 77-78 (multiple dose), no further collections are planned.

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

3.1.1 Administrative structure of the trial

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

BI has appointed a Trial Clinical Monitor, responsible for coordinating all required activities, in order to
- manage the trial in accordance with applicable regulations and internal SOPs,
- direct the clinical trial team in the preparation, conduct, and reporting of the trial.
- ensure appropriate training and information of local clinical monitors (CML), Clinical Research Associates (CRAs), and participating trial sites.

The non-labelled trial medication will be provided by
BI Pharma GmbH & Co. KG

The radiolabelled trial medication will be provided by

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

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

The analyses of BI 1467335 concentrations in plasma, the identification in urine, plasma, and faeces will be

performed at BI Pharma GmbH & Co. KG

Blood, plasma, urine, and faeces concentrations of [^{14}C]-radioactivity will be determined at

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

This is a standard design for a [^{14}C]-human study for investigation of absorption, distribution, metabolism, and excretion including determination of mass balance. Inclusion of a control groups is not required for this investigation. Despite of rapid elimination of radioactivity in rat ADME trials (Section 1.2), it cannot be excluded that prolonged sampling is still necessary in humans. Therefore, following 14 days in-house excreta collection after radioactive dosing (Treatment Group 1 on Day 1, Treatment Group 2 on Day 28 following a preceding treatment of unlabeled compound from Day 1 to Day 27), subjects will return on a weekly basis for in-house 24 h collection intervals for up to 7 weeks after last dosing as long as release criteria are not met (Section 3.1).

Blinding is not necessary, because all subjects receive the same dose per treatment group.

3.3 SELECTION OF TRIAL POPULATION

It is planned that 16 healthy male subjects will enter the study. They will be recruited from the volunteers' pool of the trial site or, if necessary, via advertisement.

The current trial is designed to investigate the basic pharmacokinetics of BI 1467335 including absorption, metabolism, and elimination and quantitative determination of excretion by mass balance. Healthy male subjects are an ideal population for the objectives of this trial, since they provide relatively stable physiological, biochemical and hormonal conditions, i.e. the absence of disease-related variations and relevant concomitant medications.

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

3.3.1 Main diagnosis for study entry

The study will be performed in healthy male subjects.

3.3.2 Inclusion criteria

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

1. Healthy male subjects according to the investigator's assessment, based on a complete medical history including a physical examination, vital signs (BP, PR), 12-lead ECG, and clinical laboratory tests

2. Age of 30 to 65 years (incl.)

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

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

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

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

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

3.3.3 Exclusion criteria

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

1. Any finding in the medical examination (including BP, PR or ECG) is deviating from normal and judged as clinically relevant by the investigator
2. Any laboratory value outside the reference range that the investigator considers to be of clinical relevance
3. Any evidence of a concomitant disease judged as clinically relevant by the investigator

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

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

21. Participation in another ADME study with a radiation burden of >0.1 mSv in the period of 1 year prior to screening
22. Exposure to radiation for diagnostic reasons (except dental X-rays and plain X-rays of thorax and bony skeleton (excluding spinal column) in the period of 1 year prior to screening
23. Irregular defecation pattern (less than a mean of one bowel movement every 1 or 2 days)

For study restrictions, refer to Section 4.2.2.

3.3.4 Removal of subjects from therapy or assessments

3.3.4.1 Removal of individual subjects

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

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

If a subject is removed from or withdraws from the trial prior to first administration of trial medication, the data of this subject will not be entered in the case report form (CRF) or trial database and will not be reported in the clinical trial report (CTR). If a subject is removed from or withdraws from the trial after first administration of trial medication, this will be documented and the reason for discontinuation must be recorded in the CRF. In this case, the data will be included in the CRF/trial database and will be reported in the CTR. At the time of discontinuation a complete end of trial examination will be performed if possible and the information will be recorded in the CRFs. These discontinuations will be discussed in the CTR.

3.3.4.2 Discontinuation of the trial by the sponsor

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

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

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

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. Replacement of subjects should always be done in mutual agreement with the principal investigator. A replacement subject will be assigned a unique study subject number, and will be assigned to the same treatment as the subject he or she replaces.

4. TREATMENTS

4.1 TREATMENTS TO BE ADMINISTERED

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

Radiolabelled BI 1467335 (test product 1) is administered as oral solution of the HCl salt. The oral solution contains a mixture of [^{14}C]-radiolabelled BI 1467335 and unlabelled BI 1467335 and is manufactured by BI Pharma GmbH & Co. KG. The solution from this mixture is made by

Unlabelled film coated tablets (test product 2) have been manufactured by BI Pharma GmbH & Co. KG.

4.1.1 Identity of BI investigational product

The characteristics of the test products are given below.

Test product 1

Name:	[^{14}C]BI 1467335 oral solution 0,5 mg/mL (20 mL; 2.0 MBq)
Substance:	BI 1467335 mixed with [^{14}C]BI 1467335
Pharmaceutical formulation:	Oral solution
Source:	
Unit strength:	10 mg BI 1467335 calculated as free base - Corresponding to 11.3 mg BI 1467335 HCl salt - Containing [^{14}C]-radiolabeled BI 1467335 HCl corresponding to a radioactive dose of 2.0 MBq (54 µCi) - In a solution of 20 mL volume (concentration of BI 1467335 calculated as free base: 0.5 mg/mL)
Posology:	1-0-0
Route of administration:	p.o.
Duration of use:	Single dose

Test product 2

Substance:	BI 1467335
Pharmaceutical formulation:	Film-coated tablet
Source:	BI Pharma GmbH & Co. KG
Unit strength:	5 mg

Posology: 2-0-0

Route of administration: p.o.

Duration of use: up to 40 days

4.1.2 Method of assigning subjects to treatment groups

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

Subject numbers are - for the eight planned subjects assigned to the single dose treatment and - in case volunteer replacement is necessary (see Section 3.3.5). If assigned to the multiple dose treatment respective subject numbers are - for the eight planned subjects and - in case of required volunteer replacement.

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

The randomisation procedure is described in Section 7.5.

4.1.3 Selection of doses in the trial

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

The dose on Day 1 (SD) or Day 28 (MD) administered as oral solution will include 2.0 MBq (54 µCi) of [^{14}C]-radiolabelled BI 1467335. The radiolabeled dose of 2.0 MBq is required to provide sufficient analytical sensitivity to enable metabolite quantification in a sufficiently low range. The total effective dose (radiation burden) amounts to 0.56 mSv. This is below the limit of 1.0 mSv and considered acceptable. Radiation burden calculations are presented in Appendix 10.1. For risk-benefit assessment, see Section 2.3.

4.1.4 Drug assignment and administration of doses for each subject

Subjects assigned to the multiple dose part will receive a preceding treatment of unlabeled 10 mg BI 1467335 as film-coated tablet once daily from Day 1 to Day 27. Subjects assigned to the single dose part receive only one dose on Day 1 of [^{14}C]-radiolabelled 10 mg BI 1467335 as oral solution as described below.

In the morning of Day 1 (single dose) or Day 28 (multiple dose), following an overnight fast of at least 10 h, all subjects will receive one single oral dose of the radiolabelled trial drug ([^{14}C]BI 1467335 oral solution 0.5 mg/mL (20 mL; 2.0 MBq)). Treatment with non-radiolabelled compound (film-coated tablets) will continue from Day 29 up to Day 40, but may be stopped earlier in case release criteria have been met (see Section 3.1).

The radiolabelled medication will be administered to a subject in the sitting position under supervision of the investigator or an authorised designee (administration directly out of the glass bottle the solution is contained in). Thereafter, the bottle will be rinsed 2 times with

25 mL each of non-sparkling water, and the volunteer will drink this additional amount. Thereafter, the volunteer will drink an additional amount of 190 mL of non-sparkling water (total volume of oral solution + rinsing water + additional water: 260 mL).

After administration, will determine for each volunteer the residual amount of [^{14}C]-radioactivity in the bottle used for administration. will determine both the weight of drug product and the total dose of [^{14}C]-radioactivity administered for each volunteer.

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

On Day 1 (SD) and Day 28 (MD) lunch will be given 4 h postdose. During the first 4 h after drug administration (only on Day 1 [SD part] and Day 28 [MD part]), subjects are not allowed to lie down (i.e., no declination of the upper body of more than 45 degrees from upright posture) except for medical examinations or if necessary for any medical reasons (e.g., adverse events). For restrictions with regard to diet and fluid intake during the investigational period see Section 4.2.2.2.

4.1.5 Blinding and procedures for unblinding

This is an open-label study.

4.1.6 Packaging, labelling, and re-supply

Non-labelled drug supplies will be provided by
Boehringer Ingelheim Pharma GmbH & Co. KG

Radiolabeled drug product manufacturing is provided by

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

Examples of the labels will be available in the ISF.

No re-supply is planned.

4.1.7 Storage conditions

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

4.1.8 Drug accountability

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

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

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

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

4.2 OTHER TREATMENTS, EMERGENCY PROCEDURES, RESTRICTIONS

4.2.1 Other treatments and emergency procedures

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

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

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

any concomitant 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

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 (SD part) or Day 28 (MD part), starting from 1 hour before drug administration until 2 h after drug intake fluid intake is not allowed except from the 240 mL water administered with the drug intake (20 mL oral solution) and an additional 240 mL of water served on Day 1 (SD) or Day 28 (MD) at 2 h and 4 h post-dose (mandatory for all subjects). From 2 hours until 22 hours post-dose fluid intake should be within about 1000 to 3000 mL.

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

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

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

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

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

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

4.3 TREATMENT COMPLIANCE

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

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

5. VARIABLES AND THEIR ASSESSMENT

5.1 EFFICACY - CLINICAL PHARMACOLOGY

5.1.1 Endpoints of efficacy

No efficacy endpoints will be evaluated in this trial.

5.1.2 Assessment of efficacy

Not applicable.

5.2 SAFETY

5.2.1 Endpoints of safety

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

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

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

5.2.2 Assessment of adverse events

5.2.2.1 Definitions of adverse events

Adverse event

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

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

Serious adverse event

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

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

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

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

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

AEs considered 'Always Serious'

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

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

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

Adverse events of special interest (AESIs)

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

The following are considered as AESIs in this trial:

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

  These lab findings constitute a hepatic injury alert and the 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 (severity) of AEs

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

Causal relationship of AEs

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

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

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

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

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

5.2.2.2 Adverse event collection and reporting

AE collection

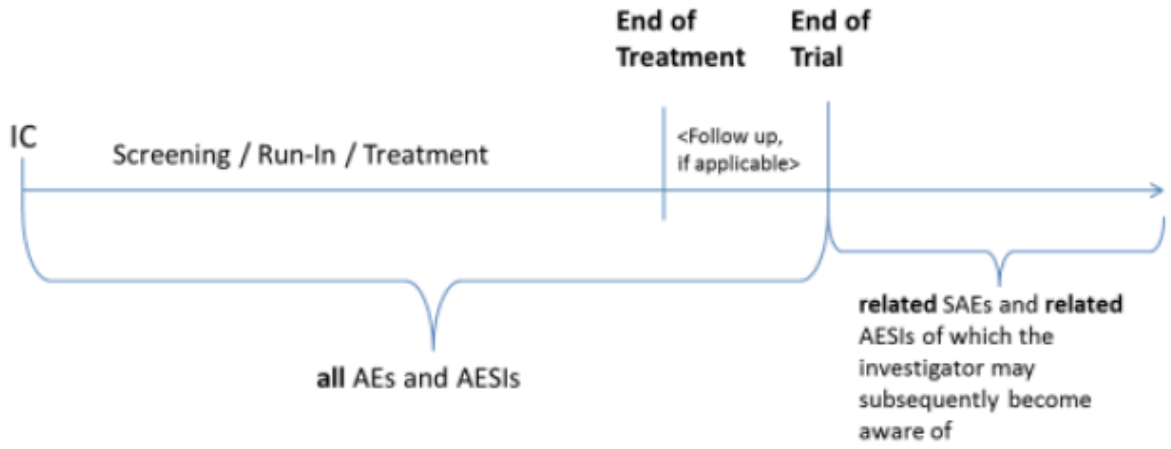
Upon enrolment into a trial, the subject's baseline condition is assessed (for instance, by documentation of medical history/concomitant diagnoses), and relevant changes from baseline are noted subsequently.

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

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

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

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



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

AE reporting to sponsor and timelines

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

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

Information required

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

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

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

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

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

5.2.3 Assessment of safety laboratory parameters

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

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

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

Table 5.2.3: 1 Routine laboratory tests

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

1 Hormones only at screening and end of trial.

Table 5.2.3: 1 Routine laboratory tests (cont).

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

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

Table 5.2.3: 2 Exclusionary laboratory tests

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

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

5.2.4 Electrocardiogram

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

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

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

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

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

5.2.5 Assessment of other safety parameters

5.2.5.1 Vital signs

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

5.2.5.2 Medical examinations

At the screening visit, the medical examination will include documentation of subject information, informed consent, demographics including height and body weight, smoking and alcohol history, relevant medical history and concomitant therapy, review of inclusion and exclusion criteria, review of vital signs (BP, PR), 12-lead ECG, laboratory tests, and a physical examination. At the end of trial examination, it will include review of vital signs, 12-lead ECG, laboratory tests, and a physical examination.

5.4 APPROPRIATENESS OF MEASUREMENTS

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

5.5 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

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

5.5.1 Pharmacokinetic endpoints

5.5.1.1 Primary endpoints

Primary endpoints will be the mass balance recoveries of [^{14}C]-radioactivity in urine and faeces after single and multiple doses:

- $fe_{urine,\ 0\text{-}t2}$ (fraction of [^{14}C]-radioactivity excreted in urine as percentage of the administered oral dose over the time interval from 0 to the last quantifiable time point)

- $fe_{faeces,\ 0\text{-}t2}$ (fraction of [^{14}C]-radioactivity excreted in faeces as percentage of the administered oral dose over the time interval from 0 to the last quantifiable time point)

Timeframe: The timeframe for determination of these endpoints depends on discharge of radioactivity from each individual subject and is predicted to vary between 2-7 weeks after drug administration.

5.5.1.2 Secondary endpoints

The following secondary endpoints will be evaluated for [^{14}C]-radioactivity: in the single and multiple doses treatment groups:

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

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

The following secondary endpoints will be evaluated for BI 1467335 in plasma in the single dose treatment group:

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

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

The following secondary endpoints will be evaluated for BI 1467335 in plasma in the repeated doses treatment group:

- $C_{max,ss}$ (maximum measured concentration of the analyte at steady state)

- $AUC_{0\text{-}\tau}$ (area under the concentration-time curve of the analyte over the time interval from τ)

5.5.2 Methods of sample collection

5.5.2.1 Sampling of whole blood and plasma

Whole blood and plasma will be collected at time points shown in the Flow Chart:

- to determine [^{14}C]-radioactivity concentrations in whole blood and plasma
- to determine concentrations of BI 1467335
  in plasma
- to determine the blood cell/ plasma and blood/ plasma ratios of [^{14}C]-radioactivity

5.5.2.2 Sampling of whole blood and plasma for [^{14}C]-radioactivity analysis in whole blood and plasma and quantification of BI 1467335 in plasma

Single dose

At each time point listed in the Flow Chart, 8 mL blood will be taken from a forearm vein using a commercial vacutainer or monovette collection tube with K2-EDTA as anticoagulant. Withdrawal of blood will be done via an indwelling cannula.

Multiple dose

From Day 1 up to and including Day 21, 3 mL, from Day 28 each time point listed in the Flow Chart, 6 mL (for time points pre-dose – 12 h (inclusive) or 8 mL (for time points 24 h - 36 h) or 4 mL (for time points 48 h – last) blood will be taken from a forearm vein using a commercial vacutainer or monovette collection tube with K2-EDTA as anticoagulant.

It is planned that from Day 28 all aliquots of all time points are prepared for determination of [^{14}C]-radioactivity in whole blood and plasma.

Withdrawal of blood will be done via an indwelling cannula.

Single dose

Aliquots for bioanalysis of BI 1467335 in plasma are planned to be prepared as long as PK blood sample are collected for total radioactivity after 336 h.

Multiple dose

Aliquots for bioanalysis of BI 1467335 in plasma are planned to be prepared for up to 24 h after last drug administration, and at predose on days specified in the Flow Chart in order to assess steady state on through plasma concentrations.

Premature stopping of blood sampling

In case [^{14}C]-radioactivity in plasma samples is not detectable (<LLOQ 10 dpm/mL) at two consecutive time points for a subject, blood sampling can be stopped for this subject. However, all samples until and including the 336 h sample for single dose and until 24 h for multiple dose have to be taken.

Laboratory manual

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

5.5.2.5 Urine sampling

During the trial urine will be collected at time points or in intervals as indicated in the Flow Chart:

- to determine [^{14}C]-radioactivity concentrations in urine
- to determine concentrations of BI 1467335 in urine

A blank sample will be taken prior to drug administration.

For urine collection, the weight of the empty containers has to be determined prior to and at the end of the collection interval. The urine 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. The exact start and end times of the urine collection intervals will be recorded in the CRF.

All samples after intake of [^{14}C]BI 1467335 are planned to be used for determination of [^{14}C]-radioactivity.

Single dose:

Samples until and including the collection interval 312-336 h are planned to be used for analysis of BI 1467335

Multiple doses:

On Day 28 samples until and including the collection interval 12-24 h are planned to be used for analysis of BI 1467335

Laboratory Manual

For a detailed description of urine sampling, preparation of collection containers, sample storage, sample handling, labelling, and sample shipment refer to the laboratory manual.

5.5.2.6 Faeces sampling

Faeces will be collected for the analysis of [^{14}C]-radioactivity in intervals as indicated in the Flow Chart. A blank sample will be taken prior to drug administration.

All faeces samples after intake of [^{14}C]BI 1467335 are planned to be used for determination of [^{14}C]-radioactivity.

Laboratory Manual

For a detailed description of faeces sampling, sample preparation, sample storage, labelling, and sample shipment refer to the laboratory manual.

5.5.2.7 Collection of vomit

If after trial drug administration vomiting occurs in a volunteer within 12 h after radioactive drug administration, the vomit will be collected for determination of weight and [^{14}C]-radioactivity.

5.5.3 Analytical determinations

5.5.3.1 Analytical determination of BI 1467335 plasma and urine concentrations

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

Since this is an open study, the bioanalyst will be unblinded during sample analysis.

5.5.3.3 Radiokinetic and Excretion Balance

Determination of [^{14}C]-radioactivity concentrations in plasma, whole blood, urine, and faeces (and vomit, if applicable) will be done by means of validated liquid scintillation counting methods at

The blood, plasma, urine and faeces concentrations of radioactivity will be determined in agreement with relevant Standard Operating Procedures (SOPs).

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 (SD and MD) and on Day 28 (MD) are to be performed and completed within a 3 h-interval prior to the trial drug administration.

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

The planned times for admission, discharge, start and end of the urine and faeces collection intervals are approximate. The procedures are to be performed within a time window of +/- 4 h to the planned time.

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

For planned individual plasma and blood concentration sampling times and urine/faeces sampling times/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 parameters. If beginning or end of a urine/faeces collection interval and a blood sample are scheduled for the same time point, urine/faeces collection should be done first, with withdrawal of the blood sample as closely to the planned time point as possible.

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

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

6.2.1 Screening period

Screening visit is defined as Visit 1.

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

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

6.2.2 Treatment period

Each subject assigned to the SD group will receive a single dose of [^{14}C]BI 1467335 on Day 1. Each subject assigned to the MD group will receive a single dose of BI 1467335 from Day 1 up to Day 27 and from day 29 up to Day 40 and a single dose of [^{14}C]BI 1467335 on Day 28.

On Day -1 (SD) or Day 27 (MD) participants will be admitted to the trial site and kept under close medical surveillance as indicated in the Flow Chart and Section 5.2.5.

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

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

6.2.3 End of trial period

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

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

All abnormal values (including laboratory parameters) that are judged clinically relevant by the investigator will be monitored using the appropriate tests until a return to a medically acceptable level is achieved. (S)AEs persisting after subject's end of trial must be followed up until they have resolved, have been sufficiently 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 basic pharmacokinetics of BI 1467335, [^{14}C]-radioactivity, including mass balance, following a single oral dose of 10 mg [^{14}C]BI 1467335 given to healthy male subjects.

7.1.2 Endpoints

Primary endpoints are pharmacokinetic endpoints as listed in Section 5. Safety and tolerability will be determined on the basis of the parameters listed in Section 5.2.

7.1.3 Model

No statistical model will be used.

7.2 NULL AND ALTERNATIVE HYPOTHESES

No confirmatory analysis will be conducted for this study. Data will be reported with descriptive statistics only.

7.3 PLANNED ANALYSES

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

7.3.1 Primary analyses

The primary and secondary parameters (refer to Section 5.5.1) will be calculated according to the relevant corporate procedure of the sponsor 'Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics' (001-MCS-36-472, current version). Analyses will be performed for parent drug and for total radioactivity.

Pharmacokinetic endpoint values of a subject will be included in the analysis if they are not flagged for exclusion, e.g. due to PK non-evaluability or a protocol violation relevant to the evaluation of PK endpoints, which will be decided no later than in the Report Planning Meeting.

Relevant protocol violations may be

- Study drug not administered or wrong drug administered
- Administered dose (amount of drug) is not in compliance with the protocol, i.e. is too low or too high

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

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

The primary analysis of primary and secondary endpoints will be based on descriptive statistics only using PKS. Descriptive analyses will be described in more detail in the TSAP.

7.3.2 Secondary analyses

Refer to Section 7.3.3 for a description of the analysis of safety.

7.3.3 Safety analyses

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

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

Measurements (such as ECG, vital signs, or laboratory parameters) or AEs will be assigned to treatments (see Section 4.1) based on the actual treatment at the planned time of the measurement or on the recorded time of AE onset (concept of treatment emergent AEs).

Therefore, measurements planned or AEs recorded prior to first intake of trial medication will be assigned to 'screening', those between first trial medication intake until the trial termination date will be assigned to treatment. 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.

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

Relevant ECG findings will be reported as AEs

More details will be described in TSAP.

7.3.4 Interim analyses

No interim analysis is planned.

7.3.5 Pharmacokinetic analyses

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

If a predose concentration value is greater than 5% of C_{max}, the subject's pharmacokinetic data will be not included in any statistical evaluations, in accordance with international guidances. The individual pharmacokinetic parameters of such a subject will be calculated and listed separately. If a predose concentration is above BLQ, but less than or equal to 5% of the subject's C_{max} value, the subject's data without any adjustments will be included in all pharmacokinetic measurements and calculations.

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 Corporate Procedure of the Sponsor (001-MCS-36-472).

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

7.4.3 Pharmacokinetic parameters

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

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

7.5 RANDOMISATION

Randomisation is not applicable in this open-label single arm study. All subjects will receive the same treatment. A list of consecutive subject numbers for SD and MD subjects separately will be provided (see Section 4.1.2 for details of allocation of subject numbers to subjects).

7.6 DETERMINATION OF SAMPLE SIZE

For this exploratory study, no prospective calculations of statistical precision or power have been made. The planned sample size of 8 subjects per treatment group has been selected for practical reasons and is judged as being adequate to get reliable results regarding the trial objectives.

8. INFORMED CONSENT, DATA PROTECTION, TRIAL RECORDS

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

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

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

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

8.1 STUDY APPROVAL, SUBJECT INFORMATION, AND INFORMED CONSENT

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

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

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

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

8.2 DATA QUALITY ASSURANCE

A quality assurance audit/inspection of this trial may be conducted by the sponsor or sponsor's designees, by IRBs/IECs, or by regulatory authorities. The quality assurance

auditor will have access to all medical records, the investigator's trial-related files and correspondence, and the informed consent documentation of this clinical trial.

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

8.3 RECORDS

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

8.3.1 Source documents

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

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

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

8.3.2 Direct access to source data and documents

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

8.3.3 Storage period of records

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

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

8.4 EXPEDITED REPORTING OF ADVERSE EVENTS

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

8.5 STATEMENT OF CONFIDENTIALITY

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

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

8.6 COMPLETION OF TRIAL

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

9. REFERENCES

9.1 PUBLISHED REFERENCES

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

R10-4848 Common terminology criteria for adverse events (CTCAE): version 4.0 (NIH publication no. 09-5410, published: May 28, 2009 (v4.03: June 14, 2010), revised June 2010, reprinted June 2010). http://evs.nci.ni h.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_ QuickReference_8.5x11.pdf; 2010.

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

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

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

9.2 UNPUBLISHED REFERENCES

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

c04751792 Investigator's Brochure: BI 1467335 in NASH. 27 Mar 2017.

c08854973 Safety, tolerability, pharmacokinetics and pharmacodynamics of multiple rising oral doses of BI 1467335 in healthy male and female subjects (double-blind, randomised, placebo-controlled within dose groups). Study 1386.8. 05 Oct 2016.

10. APPENDICES

10.1 RADIATION BURDEN CALCULATION

Radiation Burden Calculation Report

Title:	A phase I, open-label, single and multiple dose trial to investigate metabolism and pharmacokinetics of [14C]-BI 1467335 administered as oral solution in healthy male volunteers
Sponsor:	Boehringer Ingelheim
Protocol No:	1386-0011
Project Id:	BID546EC-175461
Version Date:	09 November 2017 (final version)

Calculation of Radiation Burden (Dosimetry)

Appendix A1: Radiation burden of the gastrointestinal tract after oral administration of 2.0 MBq ^{14}C BI1467335

Using SEE-values, an organ-specific radiation burden can be estimated. The SEE-value is dependent, among other factors, on the mass of the target organ and the type of radiation.
With these SEE-values and the number of disintegrations U in the target organ, the organ dose equivalent H_t is calculated:
H_t= constant x U x SEE (mSv); using a target organ-related weight factor, the contribution of the organ burden to the body burden is translated as: $H_{wb,t} = H_t$ x weight factor (mSv)

In order to be able to calculate the radiation burden of the GI tract, this has been divided in five sections, i.e., the stomach (st), the small intestines (si), the right part of the large intestines, the left part of the large intestines (lc) and the rectum / sigmoid (rs).
The SEE-values for these organs are:

ST:	1.0 x 10 -5,	(weight factor = 0.12)
SI:	3.2 x 10 -7,	(weight factor = 0.01)
RC:	2.3 x 10 -10,	(weight factor = 0.048)
LC:	2.9 x 10 -10.	(weight factor = 0.045)
RS:	9.2 x 10 -10.	(weight factor = 0.027)

The number of disintegrations U in each target organ depends on the amount of radioactivity excreted, or any metabolites that are eliminated via the gall bladder that is standardised for the various compartments of the GI tract (constant). I0 = 2.0 MBq; Excretion via GI tract: 23% of the dose, excretion via urine: 77% of the dose. These assumptions give:

Hst=	0.0016 mSv
Hsi=	0.0000 mSv
HRC=	0.0000 mSv
HLC=	0.0000 mSv
HRS=	0.0000 mSv
total GI:	0.0016 mSv

The total contribution of the GI tract to the effective dose (body radiation burden) amounts to 0.0016 mSv.

Appendix A2: Radiation burden of the central compartment after oral administration of 2.0 MBq ^{14}C BI1467335

Average body weight = 70 kg; SEE = 7.1905 x 10-7; 100% of the orally administered dose is absorbed and 85.9% (100% minus the percentages of the separately calculated organs/tissues) of the dose is excreted with a half-life of 80 hours. Total number of disintegrations in the central compartment after oral administration of 2.0 MBq [^{14}C]BI1467335 is 707 x 10^9 with a tissue weighting factor of 0.77 giving a Htw of 0.0610 mSv.

Appendix A3: Radiation burden of the liver and kidneys after oral administration of 2.0 MBq ^{14}C BI1467335

For the liver SEE = 2.72 x 10^{-5}; 8.5% of the dose administered orally, excreted with a half-life of 73 h, with a tissue weighting factor of 0.05 giving a Htw of 0.0139 mSv.

For the kidney SEE= 1.58 x 10^{-4} ; 2.2% of the dose administered orally, excreted with a half-life of 100 h, with a tissue weighting factor of 0.05 giving a Htw of 0.0286 mSv.

For the uveal tract SEE = 8.84 x 10^{-2}; 0.22% of the dose administered orally, excreted with a half-life of 140 h, with a tissue weighting factor of 0.01 giving a Htw of 0.45 mSv.

For the stomach SEE= 1.0 x 10^{-5} ; 3.2% of the dose administered orally, excreted with a half-life of 150 h, with a tissue weighting factor of 0.12 giving a Htw of 0.01 mSv.

The contribution to the radiation burden of these four organs/tissues is 0.0139 + 0.0286 + 0.45 + 0.01 = 0.5025 mSv

The total effective dose (radiation burden) of a single oral dose of ^{14}C-labeled BI1467335 containing 2.0 MBq ^{14}C-activity, based on the above-mentioned worst case scenario amounts to 0.56 mSv.

Name and Date:	**Signature:**
09 November 2017	

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

Number of global amendment		1
Date of CTP revision		26 February 2018
EudraCT number		2017-002879-26
BI Trial number		1386-0011
BI Investigational Product(s)		BI 1467335
Title of protocol		A phase I, open-label, single and multiple dose trial to investigate metabolism and pharmacokinetics of [^{14}C]BI 1467335 administered as oral solution in healthy male volunteers
To be implemented only after approval of the IRB / IEC / Competent Authorities		☐
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		☐
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		☒
Section to be changed		1. Synopsis 2. Section 4.2.2 Restrictions 3. Section 5.2.2 Methods of sample collection
Description of change		1. Inconsistency in description of PK sampling. During multiple dose, samples for ^{14}C radioactivity not before Day 28, instead of “at all time points”. 2. Restriction of poppy seeds. 3. During multiple dose, samples for ^{14}C radioactivity not before Day 28 and sampling procedures accordingly modified.

Number of global amendment		1
Rationale for change		Minor inconsistencies in the methods of PK sampling required a protocol revision. To avoid false positive drug screens during the treatment period, the restrictions were amended to include a restriction on poppy-seed containing products. In the context of this amendment, a few further inconsistencies have been corrected.

Number of global amendment		2
Date of CTP revision		14 March 2018
EudraCT number		2017-002879-26
BI Trial number		1386-0011
BI Investigational Product(s)		BI 1467335
Title of protocol		A phase I, open-label, single and multiple dose trial to investigate metabolism and pharmacokinetics of [^{14}C]BI 1467335 administered as oral solution in healthy male volunteers
To be implemented only after approval of the IRB / IEC / Competent Authorities		☐
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		☒
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		☐
Section to be changed		Flow Chart 1.2 Drug profile 4.2.2 Restrictions
Description of change		Flow Chart: Elimination of inconsistencies Section 1.2: Implementation of new *in vitro* data classifying BI 1467335 Section 4.2.2: Addition of prohibited foods to mitigate the risk of relevant adverse reactions.
Rationale for change		

Number of global amendment		2
		In the context with this amendment we have also included missing ticks in the flow chart as already described in the foot note # 10.

APPROVAL / SIGNATURE PAGE

Document Number: c17932132 **Technical Version Number:3.0**

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

Title: A phase I, open-label, single and multiple dose trial to investigate metabolism and pharmacokinetics of [14C]BI 1467335 administered as oral solution in healthy male volunteers

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Approval-Therapeutic Area		15 Mar 2018 15:25 CET
Author-Trial Statistician		15 Mar 2018 15:26 CET
Approval-Team Member Medicine		15 Mar 2018 15:29 CET
Author-Trial Clinical Pharmacokineticist		15 Mar 2018 16:04 CET
Author-Trial Clinical Monitor		15 Mar 2018 16:19 CET
Approval-Biostatistics		15 Mar 2018 16:21 CET
Verification-Paper Signature Completion		16 Mar 2018 14:50 CET

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed