Clinical Trial Protocol

	Document Number:	**c29266057-03**
EudraCT No.	2019-003389-42	
BI Trial No.	1399-0013	
BI Investigational Medicinal Product	BI 1265162	
Title	Investigation of metabolism and pharmacokinetics of BI 1265162 (C-14) after intravenous administration (Part 1) and investigation of metabolism and pharmacokinetics of BI 1265162 (C-14) after oral administration (Part 2) in healthy male subjects following a non-randomized, open-label, single-dose, single arm per trial part mass balance design	
Lay Title	A study in healthy men to test how BI 1265162 is taken up and processed by the body	
Clinical Phase	I	
Clinical Trial Leader	[redacted] Phone: [redacted] Fax:	
Principal Investigator	[redacted] Phone: [redacted] Fax:	
Status	Final Protocol (Revised Protocol (based on global amendment 2))	
Version and Date	Version: 3.0	Date: 25 February 2020

CLINICAL TRIAL PROTOCOL SYNOPSIS

Company name	Boehringer Ingelheim
Protocol date	02 January 2020
Revision date	25 February 2020
BI trial number	1399-0013
Title of trial	Investigation of metabolism and pharmacokinetics of BI 1265162 (C-14) after intravenous administration (Part 1) and investigation of metabolism and pharmacokinetics of BI 1265162 (C-14) after oral administration (Part 2) in healthy male subjects following a non-randomized, open-label, single-dose, single arm per trial part mass balance design
Principal Investigator	[redacted]
Trial site	[redacted]
Clinical phase	I
Trial rationale	To characterize the mass balance, metabolic profile and routes of elimination of BI 1265162
Trial objectives	To investigate (a) rates and routes of excretion, (b) mass balance, (c) pharmacokinetics of parent drug, any known metabolites, and total radioactivity, (d) metabolite profiling, metabolite identification, if suitable assays are available, (e) safety and tolerability
Trial design	(Part 1 & 2) Non-randomized, open-label, single-dose, single arm, mass balance design

Trial endpoints	Primary endpoints Mass balance recovery: (Part 1 & 2) Mass balance recovery of total (C-14) BI 1265162-radioactivity in urine and faeces (and vomit, if applicable): Amount of radioactivity excreted as a percentage of the administered single intravenous or oral dose of BI 1265162 (C-14) in urine ($fe_{urine, 0-t2}$),and faeces ($fe_{faeces, 0-t2}$) (and vomit ($fe_{vomit, 0-t2}$), if feasible and appropriate) Secondary endpoints Pharmacokinetics: (Part 1 & 2) Assessment of the pharmacokinetics of a single intravenous or oral dose of BI 1265162 (C-14) by calculation of the following parameters for total radioactivity and BI 1265162/ metabolite M582 (1) in plasma: AUC_{0-tz} and C_{max} Safety: Percentage of subjects with drug related adverse events (AEs)
Number of subjects	
total entered	(Part 1 & 2) 7 each, total 14
each treatment	(Part 1 & 2) 7 each, total 14
Diagnosis	Not applicable
Main criteria for inclusion	Healthy male subjects, age of 18 to 65 years (inclusive), body mass index (BMI) of 18.5 to 29.9 kg/m^2 (inclusive)
(Part 1) Test product	Intravenous solution
Dose	50 µg of BI 1265162 (C-14) consisting of 45 µg unlabelled BI 1265162 mixed with 5 µg labelled (C-14) BI 1265162 as10 mL intravenous solution (5 µg BI 1265162 (C-14)/ mL). The radioactive dose per infusion has been calculated to not exceed 0.018 MBq (0.486 µCi).
mode of admin.	Intravenous infusion of 1 hour after an overnight fast of at least 10 h.
(Part 2) Test product	Oral solution
Dose	5 mg of BI 1265162 (C-14) consisting of 4.915 mg unlabelled BI 1265162 mixed with 85.4 µg labelled (C-14) BI 1265162 as 20 mL of oral solution (0.25 mg/ mL) containing a radioactive dose of about 0.306 MBq (8.27 µCi).
mode of admin.	Oral with 240 mL of water after an overnight fast of at least 10 h.

Reference product	N/A
Dose	N/A
mode of admin.	N/A
Duration of treatments	(Part 1) Single intravenous dose of BI 1265162 (C-14) over 1 hour on Day 1. (Part 2) Single oral dose of BI 1265162 (C-14) on Day 1.
Statistical methods	(Part 1 & 2) Descriptive statistics will be calculated for all endpoints (as feasible and appropriate).

FLOW CHART 1 – INTRAVENOUS BI 1265162 (C-14)

Visit	Day[17]	Planned time (relative to drug administration [h:min]	Approximate clock time of actual day [h:min]	Event and comment	Intravenous admin.	Safety laboratory	PK blood/ plasma[2]	PK urine[6]	PK faeces[7]	Blood sampling for metabolic profiling[15]	12-lead ECG	Vital signs (BP, PR)	Questioning for AEs and concomitant therapy[9]
1	-21 to -2			Screening (SCR)[1]		A					x	x	
2	-1	-24:00	08:00						x[14]				
		-18:00	14:00	Admission to trial site		B[5]							▲
		-14:00	18:00	Light dinner (voluntary)				x					
		-10:30	21:30	Snack (voluntary)[16]									
	1	-2:00	06:00			x[3,8,19]	x[3]			x[3]	x[3]	x[3]	
		0:00	**08:00**	**Drug administration**	▲			▲	▲				
		0:05	08:05		┃		x	┃	┃				
		0:30	08:30		┃		x	┃	┃	x			
		0:59	08:59		▼		x	┃	┃	x			
		1:05	09:05				x	┃	┃				
		1:10	09:10				x	┃	┃				
		1:40	09:40				x	┃	┃				
		2:00	10:00	240 mL fluid intake		x[8]	x	┃	┃	x			
		3:00	11:00				x	┃	┃				
		4:00	12:00	240 mL fluid intake, thereafter lunch[4]		x[8]	x	┼	┃	x	x	x	
		5:00	13:00				x	┃	┃				
		7:00	15:00				x	┃	┃				
		8:00	16:00	Snack (voluntary)[4]		x[8]		┼	┃	x			
		9:00	17:00				x	┃	┃				
		11:00	19:00	Dinner			x	┃	┃				
		12:00	20:00				x	┼	┃	x	x	x	
	2	24:00	08:00				x	┼	┼	x		x	
	3	48:00	08:00			x[8]	x	┼	┼	x			
	4	72:00	08:00				x	┼	┼	x			
	5	96:00	08:00				x[20]	┼	┼	x			
	6	120:00	08:00				x[20]	┼	┼	x			
	7	144:00	08:00				x[20]	┼	┼	x			
	8	168:00	08:00				x[21]	┼	┼	x			
	9	192:00	08:00	***Discharge from trial site***		B	x[21]	▼	▼	x	x	x	
	14	312:00	08:00	Start home collection					▲				
	15	336:00	08:00	Admission to trial site[11,12]				▲	┼				
	16	360:00	08:00	Discharge from trial site[11]				▼	▼				
	21	480:00	08:00	Start home collection					▲				
	22	504:00	08:00	Admission to trial site[11,12]				▲	┼				
	23	528:00	08:00	Discharge from trial site[11]				▼	▼				
	28	648:00	08:00	Start home collection					▲				
	29	672:00	08:00	Admission to trial site[11,12]				▲	┼				
	30	696:00	08:00	Discharge from trial site[11]				▼	▼				
	35	816:00	08:00	Start home collection					▲				
	36	840:00	08:00	Admission to trial site[11,12]				▲	┼				
	37	864:00	08:00	Discharge from trial site[11]		B		▼	▼		x	x	
3	9 to 38			End-of-trial (EoT) examination[10,13]		A[18]					x	x	▼

A & B: Safety laboratory sets (see Table 5.2.3: 1)

1. Subject must be informed and written informed consent obtained prior to starting any screening procedures. Screening procedures include physical examination, check of vital signs, ECG, safety laboratory (including drug screening), demographics (including determination of body height and weight, smoking status and alcohol history), relevant medical history, concomitant therapy and review of inclusion/ exclusion criteria.
2. Pharmacokinetics (PK): BI 1265162 and its metabolite(s) in plasma (see Section 5.3.2.3); (C-14) BI 1265162 -radioactivity in whole blood and plasma (see Section 5.3.2.2). Blood sampling for an individual subject can be stopped, if (C-14) BI 1265162 -radioactivity in plasma is below limit of detection (< LLOQ 10 dpm/ mL) at two consecutive sampling time points for this subject (earliest stopping after Day 9).
3. The time is approximate; the respective procedure is to be performed and completed within 3 hours prior to drug administration.
4. If several actions are indicated at the same time point, the intake of meals will be the last action.
5. Safety laboratory including urine drug and alcohol screening.
6. Urine collection intervals (for PK/(C-14) BI 1265162 -radioactivity assessment and metabolic profiling; planned time): on Day -1 or Day 1 pre-dose (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, and 168-192 hours after administration of BI 1265162 (C-14). Thereafter 24-h collections are to be performed on Days 15-16, 22-23, 29-30, and 36-37. Urine sampling for PK/ (C-14) BI 1265162 -radioactivity will be stopped when release criteria for radioactivity recovery (see Section 3.1) have been met (earliest stopping on Day 9). "┼" means end of last collection interval, start of following collection interval. For details on sample usage, see Section 5.3.2.5.
7. All stools (for (C-14) BI 1265162 -radioactivity and metabolic profiling) will be collected quantitatively in portions up to 192 hours (sampling intervals of 0-24, 24-48, 48-72, 72-96, 96-120, 120-144, 144-168,168-192 hours) after administration of BI 1265162 (C-14). Thereafter 24-h collections are to be performed on Days 14-16, 21-23, 28-30, and 35-37. A blank sample will be collected before drug administration on Day -2, Day -1 or Day 1 (see Section 5.3.2.6). Faeces sampling for (C-14) BI 1265162 -radioactivity assessment will be stopped when the release criteria for radioactivity recovery (see Section 3.1) have been met (earliest stopping on Day 9). "┼" means end of last collection interval, start of following collection interval. For details on sample usage, see Section 5.3.2.6.
8. Measurement of haematocrit and potassium, only.
9. AEs and concomitant therapies will be recorded throughout the trial. At 1:05, 2 , 4 , 8, 24, 48, 192h after the infusion, local tolerability will be assessed according to the criteria put down in Section 2.2.2.4.
10. End-of-trial (EoT) examination to be performed after last discharge from the trial centre, or, if all once-weekly 24-hour sampling periods are needed, after discharge on Day 37. EoT examination includes physical examination, vital signs, ECG, safety laboratory, recording of AEs and concomitant therapies.
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 hours to the planned time.
12. Subjects are to collect faeces at home within 24-hour intervals before admission to once-weekly in-house collection intervals. Home collection intervals: Days 14-16, 21-23, 28-30, and 35-37. 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. Subjects will collect a pre-dose faeces sample at home or at the site in specific containers provided by [redacted]
15. Metabolic profiling sampling times may be adapted based on information obtained during the trial (e.g. levels of radioactivity in each urine and/ or plasma sample) as long as the overall blood volume stays the same. Some time points require different sample volumes; for details, see lab manual.
16. To be consumed within 30 minutes to allow 10-hour fasting prior to drug administration.
17. Days 9 to 38 are optional until release criteria are fulfilled.
18. Laboratory A, if performed on Day 9.
19. One additional blood sample for pharmacogenomics analyses will be taken.
20. Only plasma and whole blood total radioactivity samples; for details, see lab manual.
21. Only plasma total radioactivity sample; for details, see lab manual.

FLOW CHART 2 – ORAL BI 1265162 (C-14)

Visit	Day[17]	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]	PK urine[6]	PK faeces[7]	Blood sampling for metabolic profiling[15]	12-lead ECG	Vital signs (BP, PR)	Questioning for AEs and concomitant therapy[9]
1	-21 to -2			Screening (SCR)[1]	A					x	x	
2	-1	-24:00	08:00					x[14]				▲
		-18:00	14:00	Admission to trial site	B[5]							|
		-14:00	18:00	Light dinner (voluntary)			x					|
		-10:30	21:30	Snack (voluntary)[16]								|
	1	-2:00	06:00		x[3,8,19]	x[3]			x[3]	x[3]	x[3]	|
		0:00	**08:00**	**Drug administration**			▲	▲				|
		0:30	08:30			x	|	|	x			|
		0:45	08:45			x	|	|				|
		1:00	09:00			x	|	|	x			|
		2:00	10:00	240 mL fluid intake	x[8]	x	|	|	x			|
		3:00	11:00			x	|	|				|
		4:00	12:00	240 mL fluid intake, thereafter lunch[4]	x[8]	x	+	|	x	x	x	|
		6:00	14:00			x	|	|				|
		8:00	16:00	Snack (voluntary)[4]	x[8]	x	+	|	x			|
		11:00	19:00	Dinner			|	|				|
		12:00	20:00			x	+	|	x	x	x	|
	2	24:00	08:00			x	+	+	x		x	|
	3	48:00	08:00		x[8]	x	+	+	x			|
	4	72:00	08:00			x	+	+	x			|
	5	96:00	08:00			x	+	+	x			|
	6	120:00	08:00			x	+	+	x			|
	7	144:00	08:00			x[20]	+	+	x			|
	8	168:00	08:00			x[21]	+	+	x			|
	9	192:00	08:00	***Discharge from trial site***	B	x[21]	▼	▼	x	x	x	|
	14	312:00	08:00	Start home collection				▲				|
	15	336:00	08:00	Admission to trial site[11,12]			▲	+				|
	16	360:00	08:00	Discharge from trial site[11]			▼	▼				|
	21	480:00	08:00	Start home collection				▲				|
	22	504:00	08:00	Admission to trial site[11,12]			▲	+				|
	23	528:00	08:00	Discharge from trial site[11]			▼	▼				|
	28	648:00	08:00	Start home collection				▲				|
	29	672:00	08:00	Admission to trial site[11,12]			▲	+				|
	30	696:00	08:00	Discharge from trial site[11]			▼	▼				|
	35	816:00	08:00	Start home collection				▲				|
	36	840:00	08:00	Admission to trial site[11,12]			▲	+				|
	37	864:00	08:00	Discharge from trial site[11]	B		▼	▼		x	x	|
3	9 to 38			End-of-trial (EoT) examination[10,13]	A[18]					x	x	▼

A & B: Safety laboratory sets (see Table 5.2.3: 1)

1. Subject must be informed and written informed consent obtained prior to starting any screening procedures. Screening procedures include physical examination, check of vital signs, ECG, safety laboratory (including drug screening), demographics (including determination of body height and weight, smoking status and alcohol history), relevant medical history, concomitant therapy and review of inclusion/exclusion criteria.
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8. Measurement of haematocrit and potassium, only.
9. AEs and concomitant therapies will be recorded throughout the trial.
10. End-of-trial (EoT) examination to be performed after last discharge from the trial centre, or, if all once-weekly 24-hour sampling periods are needed, after discharge on Day 37. EoT examination includes physical examination, vital signs, ECG, safety laboratory, recording of AEs and concomitant therapies.
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 hours to the planned time.
12. Subjects are to collect faeces at home within 24-hour intervals before admission to once-weekly in-house collection intervals. Home collection intervals: Days 14-16, 21-23, 28-30, and 35-37. 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. Subjects will collect a pre-dose faeces sample at home or at the site in specific containers provided by [redacted]
15. Metabolic profiling sampling times may be adapted based on information obtained during the trial (e.g. levels of radioactivity in each urine and/or plasma sample) as long as the overall blood volume stays the same. Some time points require different sample volumes; for details, see lab manual.
16. To be consumed within 30 minutes to allow 10-hour fasting prior to drug administration.
17. Days 9 to 38 are optional until release criteria are fulfilled.
18. Laboratory A, if performed on Day 9.
19. One additional blood sample for pharmacogenomics analyses will be taken.
20. Only plasma and whole blood total radioactivity samples; for details, see lab manual.
21. Only plasma total radioactivity sample; for details, see lab manual.

TABLE OF CONTENTS

ABBREVIATIONS

ADME	Absorption, distribution, metabolism, and excretion
AE	Adverse event
AESI	Adverse events of special interest
[redacted]	[redacted]
ALT	Alanine transaminase
AMS	Accelerator mass spectrometry
ASL	Airway surface liquid
AST	Aspartate transaminase
[redacted]	[redacted]
$AUC_{0\text{-}tz}$	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 to the last quantifiable data point
[redacted]	[redacted]
BA	Bioavailability
BI	Boehringer Ingelheim
BMI	Body mass index (weight divided by height squared)
BP	Blood pressure
C-14	Carbon 14 labelled BI 1265162 ([^{14}C]BI 1265162)
CA	Competent authority
CF	Cystic fibrosis
CFTR	Cystic fibrosis transmembrane conductance regulator
CI	Confidence interval
CL	Total clearance of the analyte in plasma after intravascular administration
[redacted]	[redacted]
C_{max}	Maximum measured concentration of the analyte in plasma
COPD	Chronic obstructive pulmonary disease
CRF	Case Report Form, paper or electronic (sometimes referred to as ‘eCRF’)

CRO	Contract research organization
CTM	Clinical Trial Monitor
CTP	Clinical trial protocol
CTR	Clinical trial report
[redacted]	
DILI	Drug induced liver injury
DRF	Dose Range Finding
ECG	Electrocardiogram
eCRF	Electronic case report form
eDC	Electronic data capture
EDTA	Ethylenediaminetetraacetic acid
ENaC	Epithelial sodium channel
EoT	End of trial
EU	European Union
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration
$fe_{faeces,0-t2}$	Fraction of administered drug excreted in faeces from time point 0 to the last quantifiable time point
[redacted]	
$fe_{urine,\ 0-t2}$	Fraction of administered drug excreted in urine from time point 0 to the last quantifiable time point
[redacted]	
$fe_{vomit,\ 0-t2}$	Fraction of administered drug excreted in urine from time point 0 to the last quantifiable time point
FU	Follow-up
GCP	Good Clinical Practice
gCV	Geometric coefficient of variation
GI	Gastro-intestinal
gMean	Geometric mean
GMP	Good Manufacturing Practice
HED	Human Equivalent Dose
[redacted]	
HR	Heart rate
IB	Investigator's brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IH	Inhaled
iPD	Important protocol deviation
IRB	Institutional Review Board
ISF	Investigator site file

i.t.	Intra-tracheal
IV	Intravenous
[redacted]	[redacted]
LC-MS/MS	Liquid chromatography with tandem mass spectrometry
LLOQ	Lower limit of quantification
MDA	Methylenedioxyamphetamine
MDMA	Methylenedioxymethamphetamine
MedDRA	Medical Dictionary for Regulatory Activities
MRD	Multiple-rising dose
[redacted]	[redacted]
[redacted]	[redacted]
NOAEL	No observed adverse effect level
PD	Pharmacodynamics
PK	Pharmacokinetic(s)
PKS	Pharmacokinetic set
PO	Oral
PP	Polypropylene
PR	Pulse rate
QT	Time between start of the Q-wave and the end of the T-wave in an electrocardiogram
QTc	QT interval corrected for heart rate using the method of Fridericia (QTcF) or Bazett (QTcB)
REP	Residual effect period
SAE	Serious adverse event
SCR	Screening
SOP	Standard operating procedure
SRD	Single-rising dose
ss	(at) steady state
T	Test product or treatment
TMF	Trial master file
[redacted]	[redacted]
TS	Treated set
TSAP	Trial statistical analysis plan
[redacted]	[redacted]
ULN	Upper limit of normal
[redacted]	[redacted]

[redacted]	[redacted]
WHO	World Health Organization
XTC	Ecstasy

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

BI 1265162, an epithelial sodium channel (ENaC) inhibitor, is to be developed in cystic fibrosis (CF) and chronic obstructive pulmonary disease (COPD). CF and COPD are chronic respiratory disorders characterized by airflow obstruction. ENaC is expressed on airway epithelial cells and functions as an ion channel for sodium. It mediates sodium reabsorption and regulates the water content and volume of the luminal fluid, thereby maintaining airway surface liquid (ASL) and in turn regulating mucociliary clearance.

Cystic fibrosis is a lethal, inherited, multi-organ disease due to exocrine gland dysfunction that predominantly affects the lower respiratory tract and pancreas leading to chronic respiratory failure and pancreatic insufficiency. It is the most common lethal inherited disease in Caucasians [R01-1277] occurring in approximately 1 in 3000 births [R15-5503]. Pulmonary treatments include supportive care e.g. airway clearance techniques, antibacterial (including inhaled tobramycin and aztreonam), muco-active (e.g. dornase alpha and hypertonic saline) therapies and are the cornerstone of pharmacotherapy [P13-14084]. More recently, therapies are also targeting the CFTR [R17-1997]. Lung transplantation is used as well. Despite recent advances, over 90% of patients surviving the neonatal period will develop pulmonary involvement and at least 90% will die due to pulmonary complications [P96-3855]. The median age of death is below 40 years old [R15-5546].

In CF, the cystic fibrosis transmembrane conductance regulator (CFTR) gene is dysfunctional resulting in impaired epithelial chloride (Cl-) transport [R15-5486] leading, in turn, to reduced water secretion into the airway surface layer (ASL). The functional defect of the CFTR is also associated with an increase of ENaC activation, increased sodium [R15-5507] and water absorption from the airway epithelial lining fluid. These effects lead to mucus dehydration and reduction in the height of the pericilliary layer, which is normally tightly controlled to maintain optimal mucocillary clearance. The mucus becomes thickened, tenacious and adherent leading to collapsed cilia and poor mucus clearance [R15-4955]. The static mucus can, in itself, trigger an inflammatory response, but also provides an ideal environment for bacterial colonisation with bacterial infection that is often acquired in childhood and that persists throughout the patient's life [R15-4984, R15-4955]. Lung destruction is caused by a cycle of infection, inflammation, and injury, with obstruction of the airways. The dehydrated, thickened secretions, resultant endobronchial infection, and exaggerated inflammatory response lead to mucus plugging, bronchiectasis and progressive obstructive airways disease.

COPD prevalence is still rising due to increased smoking, particularly among women and adolescents. According to the 2015 estimates of the World Health Organization (WHO), 65 million people suffer from moderate to severe COPD. By 2030, COPD will be the third leading cause of death worldwide [R15-3034].

COPD is associated with significant morbidity and mortality. Smoking cessation is the only therapy known to alter the natural history of COPD. The management of stable COPD is directed towards reducing symptoms and future risk (prevention and treatment of

exacerbations and disease progression). Pharmacotherapy is based primarily on bronchodilator drugs including long acting beta agonists (LABA) and long acting-muscarinic antagonists (LAMA) and inhaled or oral corticosteroids. Other treatments include the anti-inflammatory roflumilast, influenza and pneumococcal vaccinations, and treatment of exacerbations. The mucolytic therapy N-acetylcysteine may have a small effect on exacerbations [P11-05794]. An ENaC inhibitor would be expected to have additional effect compared to mucolytic therapies given the direct effects on mucus hydration.

ENaC is expressed widely on the apical side of epithelial cells in the lung and there is increasing evidence for the role of ENaC in the pathogenesis of both, CF and COPD. Despite the differences in the underlying pathology between the two diseases, changes in the biophysical characteristics of the mucus are apparent with impaired transport of mucus (reduced mucus clearance) leading to mucus plugging, airflow obstruction and a milieu conductive to bacterial colonisation which in turn leads to worsening symptoms, lung function, and an increase in exacerbations. In both, CF and COPD, inhibition of ENaC is anticipated to reduce sodium uptake and water absorption in the airways which should translate to improvement of mucociliary clearance, pulmonary function, symptoms and quality of life whilst reducing bacterial colonization of the lower airways, and exacerbations and hospitalizations. Administration of an inhaled formulation of the potassium sparing diuretic amiloride, an ENaC inhibitor, resulted in increased mucus clearance in cystic fibrosis patients [R15-5487, R15-5485, R15-5349] but no clinical efficacy, possibly due to poor pharmacokinetic properties of administering this normally oral drug by the inhalation route [R15-5349, R15-5599, R15-5505]. The more favourable potency and kinetics demonstrated by BI 1265162 is expected to translate into clinical efficacy.

1.2 DRUG PROFILE

BI 1265162 is a potent epithelial sodium channel (ENaC) inhibitor in phase 2 for the treatment of cystic fibrosis (CF) and chronic obstructive pulmonary disease (COPD).

[redacted]

1.2.2 Safety pharmacology

For a detailed description, refer to the current 'Investigator's Brochure', c16304878.

1.2.3 Toxicology

For local tolerance, single and repeated inhaled dose toxicity, as well as genotoxicity studies, refer to the current 'Investigator's Brochure', c16304878.

Oral toxicity studies

In the pivotal 7-day oral study in *rats*, nephropathy (bilateral, widespread tubular basophilia, interstitial mononuclear cell infiltration, tubular basement membrane thickening and glomerulosclerosis) was seen in 1 out of 10 female rats at the dose of 200 mg/kg/day. A BI 1265162-related effect could not be ruled out with certainty. The finding correlated with elevated kidney weight, higher blood urea and creatinine values, and protein in the urine in the affected animal only. Based on the equivocal finding in the kidney, the NOAEL was cautiously set at 100 mg/kg/day, corresponding to the C_{max} of 19.8 and 38.9 nM and AUC_{0-24h} of 65.9 and 118 nM*h for males and females, respectively [n00264885].

Oral administration of BI 1265162 to *dogs* caused death of one male dog after 8 days given 30 mg/kg in the DRF study [n00260481]. Substantial electrolyte changes and high systemic exposure with C_{max} values of 7480 and 3000 nM were seen on Days 1 and 8, respectively, in this animal. In the pivotal 7-day repeat dose study, plasma aldosterone at all doses and changes in urine electrolytes were observed at 10 mg/kg. The NOAEL was set at 10 mg/kg/day, corresponding to the C_{max} of 874 and 565 nM and AUC_{0-24h} of 2300 and 1320 nM*h for males or females, respectively [n00261317]. The NOEL level was set at 3 mg/kg, corresponding to the C_{max} of 283 and 146 nM and AUC_{0-24h} of 670 and 415 nM*h for males or females, respectively.

Intravenous toxicity studies

In the pivotal 7-day IV study in rats, the NOAEL was set at the highest dose of 1600 µg/kg/day, corresponding to the C_{max} of 1360 nM and an AUC_{0-24h} of 616 nM*h (males & females combined) [n00264887].

An intravenous administration of BI 1265162 over 30 minutes to dogs was well tolerated up to 500 µg/kg/day in the DRF and pivotal 7 day study [n00260429, n00260959]. Pharmacodynamic related increases in plasma aldosterone were observed at 150 and 500 µg/kg/day. The IV NOAEL was set at 500 µg/kg/day, corresponding to the C_{max} of 2300 and 3520 nM and AUC_{0-24h} of 1600 and 2030 nM*h for males or females, respectively.

[redacted]

[redacted]

[redacted]

[redacted]

1.2.6 Residual Effect Period

The Residual Effect Period (REP) of BI 1265162 is 7 days. This is the period after the last dose with measurable drug levels and/ or pharmacodynamics effects is still likely to be present.

1.2.7 Drug product

BI 1265162 oral solution and concentrate for infusion

For this trial, an oral solution and a concentrate for infusion have been developed in addition to the inhalation formulation .The concentrate for infusion contains 5 µg BI 1265162/ mL (0.36 MBq/ mg).

The oral solution contains 0.25 mg BI 1265162/ mL (0.06 MBq/ mg).

For shelf-life and storage conditions, refer to the instructions on the label.

For a more detailed description of the BI 1265162 profile, refer to the current 'Investigator's Brochure', c16304878.

1.3 RATIONALE FOR PERFORMING THE TRIAL

Rationale for trial

The development of BI 1265162 was optimized for inhalation. However, as the application of inhaled radio-labelled substance is technically challenging, the intravenous application of BI 1265162 (C-14) will mimic the systemic exposure as if the compound was inhaled. The oral dose investigates the absorption and metabolism of the swallowed portion of the inhaled dose.

Therefore, this trial will be performed in 2 parts to characterize by means of mass balance

- (Part 1) basic pharmacokinetics, metabolism (metabolic profile) and routes of elimination of BI 1265162 (C-14) after intravenous administration, and
- (Part 2) the extent of gastrointestinal absorption, metabolism (metabolic profile), and routes of elimination of BI 1265162 (C-14) after oral administration.

The oral application of BI 1265162 (C-14) is intended to determine the extent of absorption of BI 1265162 and/ or its metabolites from the gastrointestinal tract. Due to the optimization of BI 1265162 for inhalation, this oral fraction is small (see also Table 1.3: 1). If metabolites will be formed in the gastro-intestinal tract and absorbed into the systemic circulation, their presence will be detected.

The data are required for future regulatory interactions, to further understand the pharmacokinetics of BI 1265162, including the quantitative determination of elimination pathways and drug metabolites.

Rationale for dose selection

The dose selection is based on previous experience with orally, inhaled and intravenously applied BI 265162 in healthy male subjects.

(i) Rationale for the intravenous dose

According to preliminary results of study 1399-0014, the single intravenous dose of 50 µg of BI 1265162 was well tolerated and safe. Comparing systemic exposures after the inhaled (trial 1399-0001, Table 1.2.4: 1) and intravenous (1399-0014, Table 1.2.4: 2) application of BI 1265162, mean C_{max} and AUC values after the intravenous application of 50 µg should correspond to those after the inhalation of 300 µg to 600 µg, and 600µg to 1200 µg, respectively. All doses were well tolerated and safe. The infusion time of 1 hour was chosen to limit the peak exposure and to better mimic the exposure after inhalation.

(ii) Rationale for the oral dose

According to preliminary results of study 1399-0014, the single oral dose of 1.25 mg of BI 1265162 seemed to be well tolerated and safe. The SAE was not assessed to be related to the oral application of BI 265162. Since the systemic exposure was lower than expected, the application of a 5 mg dose of BI 1265162 was chosen to achieve a meaningful systemic exposure in this study. For the pharmacokinetic rationale, see below.

However, an oral BI 1265162 dose of 5 mg has not been applied in humans before. A de-novo estimation of a safe starting dose was performed by applying the relevant algorisms of the FDA guidance 'Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers' [R06-1037] and the ICH guideline M3(R2) on 'Non-clinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorisation for Pharmaceuticals' [R15-0594]. The results are displayed in Table 1.3: 1 along with the relevant pharmacokinetics obtained from human studies.

Table 1.3: 1 Estimation of safe starting doses based on toxicological results in rats and dogs exposed to BI 1265162

	Rat	Dog	Human
FDA Approach			
NOAEL [mg/kg]	100	10	
NOEL[mg/kg]		3	
Conversion Factor	6.2	1.8	
HED for 60 kg Human (NOAEL) [mg]	967	333	
HED for 60 kg Human (NOEL) [mg]		99.6	
Safety Factor of 10 on HED (NOAEL) [mg]	96.7	33.3	
Safety Factor of 10 on HED (NOEL) [mg]		9.96	
ICH M3(R2) Approach			
HED for 60 kg Human (NOAEL) [mg]	967	333	
C_{max} at NOAEL [pmol/L] at Day 1		M: 927,000; F: 458,000	
AUC at NOAEL [pmol·h/L] at Day 1		M: 2,620,000; F: 1,300,000	
HED for 60 kg Human (NOEL)		99.6 mg	
C_{max} at NOEL [pmol/L] at Day 1		M: 228,000; F: 234,000	
AUC at NOEL [pmol·h/L] at Day 1		M: 655,000; F: 544,000	
Safety Factor of 50 on C_{max} (NOEL) [pmol/L]		M: 4,560; F: 4,680	
Safety Factor of 50 on AUC (NOEL) [pmol·h/L]		M: 13,100; F: 10,800	
Human pharmacokinetic parameters (gMean (gCV)) after single doses of BI 1265162			
1399-0001			
C_{max} after 1200 µg inhaled [pmol/L]			6500 (73.1)
AUC after 1200 µg inhaled [pmol·h/L]			3920 (76.4)
1399-0014 (ongoing)*			
1.25 mg PO (N=4)			
C_{max} [pmol/L]			57.7 (69.0)
$AUC_{0-\infty}$[pmol·h/L]			316 (83.5)
50 µg IV (N=4)			
C_{max} [pmol/L]			1880 (8.79)
$AUC_{0-\infty}$[pmol·h/L]			2200 (12.2)
Absolute bioavailability[%]			0.6

* **Preliminary, not validated data; subject to change!**

According to the FDA algorithm, the dog is the most sensitive species after the oral application of BI 1265162.the dog NOEL is based on urine electrolyte changes . Using a standard safety factor of 10 resulted in a maximum safe ORAL starting dose of 9.96 mg which is above the oral dose of 5 mg planned in this study.

The systemic exposures in female dogs at the HED of NOEL is 234,000 pmol/L for C_{max} at Day 1 and 544,000 pmol*h/L for AUC. The application of a safety factor of 50, as recommended by the ICH M3(R2) guideline, results in systemic exposures of 4,680 pmol/L for C_{max} and 10,800 pmol*h/L for AUC. These are well above the expected exposure to be seen with 5 mg oral dosing as referenced to the values obtained already with 1.25 mg oral administration in man.

Even though the intended oral application of 5 mg is 4-times higher than that applied in trial 1399-0014, the expected corresponding systemic exposures should be below those seen after 1200 µg inhaled and 50 µg IV as achieved safely in studies 1399-0001 and 1399-0014, respectively.

Rationale for trial population

The inclusion of male healthy subjects as a trial population in phase I studies is ideal as they provide relatively stable physiological, biochemical and hormonal conditions for studying drug effects. Healthy subjects can be tested under standardised conditions in an environment which allows repeated testing.

1.4 BENEFIT - RISK ASSESSMENT

Participation in this trial is without any (therapeutic) benefit for healthy subjects. Their participation in the trial, however, is of major importance to the development of BI 1265162. Subjects are exposed to the risks of the trial procedures and the risks related to the exposure to the trial medication.

Procedure-related risks

The use of an indwelling venous catheter or venepuncture for e.g. blood sampling may cause a syncope or result in mild bruising, and in rare cases, in transient inflammation of the wall of the vein, or nerve injury, potentially resulting in paraesthesia, reduced sensibility, and/or pain for an indefinite period. The same risks apply to venepuncture for blood sampling.

The solvent for the intravenous infusion containing a mixture of labelled and unlabelled BI 1265162 is isotonic sodium chloride solution (0.9%) adjusted to pH 4.0. Therefore, in case of inadvertent paravenous drug administration apart from local swelling, no tissue damage is expected.

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

Drug-related risks and safety measures

BI 1265162

As the nature of the target and the mechanism of action of BI 1265162 are well understood, comparable compounds have been tested internally and by other companies before, and the animal models are believed to be predictive for the effects in humans, BI 1265162 is not seen as a high risk compound. The specific mechanism of action is also well recognized for when administered systemically (orally) as a diuretic with a well-established safety profile.

The pharmacological effects of BI 1265162 seem to be dose dependent and no evidence for prolonged or irreversible effects has been observed. Both formulations, oral as well as intravenous, were used in the absolute bioavailability study 1399-0014. However, a 4-times higher oral dose of 5 mg is intended to be applied to ensure a meaningful exposure to the study drug.

A clinically relevant hyperkalaemia after the administration of a single dose of BI 1265162 is unlikely. However, safety laboratory will be performed with special focus on serum electrolytes (see Flow Chart).

BI 1265162 (C-14)

(Part 1) No therapeutic intravenous use is planned for BI 1265162. Therefore, in accordance with the guideline on non-clinical safety studies ICH-M3(R2) [R15-0594], the intravenous dose of 50 µg BI 1265162 (C-14) is considered adequately qualified by the existing oral toxicity studies. The investigation of intravenous local tolerance of drug substance is not recommended in this situation because the administered dose is very low (< 100 µg) and no novel solvent is used. BI 1265162 is labelled with the isotope (C-14) which is necessary for the purposes of this trial to identify the metabolism (metabolic profile) and routes of elimination BI 1265162.

(Part 2) BI 1265162 (C-14) is labelled with the isotope (C-14) 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 IV administration of 0.018 MBq is about 0.001 mSv. The effective dose that each subject receives from ORAL administration of 0.306 MBq is about 0.001 mSv.

Risk minimization

To mitigate the BI 1265162-related risks, the following safety measures will be applied in this trial with healthy subjects:

- Careful dose selection (see Section 1.3) for the different formulations
- Prior to starting the IV administration of trial medication there will be a function control of the venous access to prevent para-venous administration

- The IV administration will be performed as a slow infusion over 1 hour to ensure slowly rising plasma concentrations

- Hyperkalaemia after the application of a single dose of BI 1265162 seems to be unlikely. However, due to the mode of action of this compound, frequent examinations of serum potassium will be performed (see Flow Chart)

- Subjects with impaired kidney function will be excluded from the trial

- Subjects will stay at the trial site from the day prior each dosing until at least 8 days after the administration of the trial drug

Although rare, a potential for drug-induced liver injury (DILI) is under constant surveillance by sponsors and regulators. Therefore, this trial requires timely detection, evaluation, and follow-up of laboratory alterations in selected liver laboratory parameters to ensure subjects´ safety (see Section 5.2.6.1.4, adverse events of special interest).

To mitigate the radio-burden related risks, the following safety measures will be applied in this trial with healthy subjects:

- Each subject participates either in Part 1 or in Part 2 but not in both parts.

- (Part 1) The radioactive dose per infusion will be about 0.018 MBq giving a burden of 0.001 mSv and thereby falls into the ICRP 1 category (trivial level of risk) based on the calculated ICRP Category I limit for administration of (C-14) BI 1265162 of 1.8 MBq [c25192159, R15-3219].

- (Part 2) The orally applied radioactive dose is 0.306 MBq which is expected to give a radiation burden of 0.0014 mSv. This is lower than the limit proposed by ICRP Category 1, (<0.1 mSv – risk defined as trivial). For details on the radiation burden calculation, see Appendix 10.1. For clinical investigations to study the disposition, metabolism and excretion of new pharmaceutical compounds in man an effective dose of below 0.1 mSv is considered to be trivial [R15-3219].

2. TRIAL OBJECTIVES AND ENDPOINTS

2.1 MAIN OBJECTIVES, PRIMARY AND SECONDARY ENDPOINTS

2.1.1 Main objectives

The main objectives of this trial is to investigate (a) rates and routes of excretion, (b) mass balance, (c) pharmacokinetics of parent drug, any known metabolites, and total radioactivity, (d) metabolite profiling, metabolite identification, if suitable assays are available, (e) safety and tolerability in healthy male subjects.

2.1.2 Primary endpoints

The following parameters will be determined:

(Part 1 & 2) Mass balance recovery of total (C-14) BI 1265162-radioactivity in urine and faeces (and vomit, if applicable). Amount of radioactivity excreted as a percentage of the administered single intravenous or oral dose of BI 1265162 (C-14) in

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

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

- Vomit - $fe_{vomit, 0\text{-}t2}$ (fraction of (C-14)-radioactivity excreted in vomit as percentage of the administered oral dose over the time interval from 0 to the last quantifiable time point) - if feasible and appropriate

The timeframe for determination of these endpoints depends on the time of discharge of each subject, based on radioactivity excretion, and is predicted to vary between 9 and 38 days after drug administration.

2.1.3 Secondary endpoint

The following parameters will be determined:

(Part 1 & 2) Assessment of the pharmacokinetics of a single intravenous or oral dose of BI 1265162 (C-14) by means of the following parameters for total (C-14) BI 1265162-radioactivity, BI 1265162 and metabolite M582 (1) in plasma:

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

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

(Part 1 & 2) Evaluation of safety and tolerability of a single intravenous or oral dose of BI 1265162 (C-14) by means of

- Percentage of subjects with drug related adverse events (AEs) including clinically relevant findings from the physical examination

2.2 FURTHER OBJECTIVES AND FURTHER ENDPOINTS

2.2.1 Further objectives

(Part 1 & 2) The evaluation of further pharmacokinetic, mass balance and tolerability parameters after a single intravenous or oral dose of BI 1265162 (C-14).

2.2.2 Further endpoints

2.2.2.1 Further pharmacokinetic endpoints

The following pharmacokinetic endpoints after a single intravenous and oral dose of BI 1265162 (C-14) will be calculated for total (C-14) BI 265162-radioactivity, BI 1265162 and its metabolite(s) in whole blood, plasma, urine and faeces (as feasible and appropriate), and may include

- AUC_{t1-t2} (Area under the concentration-time curve of the analyte in plasma over the time interval from time point t_1 to t_2)
- $AUC_{0-\infty}$ (Area under the concentration-time curve of the analyte over the time interval from 0 extrapolated to infinity)
- $\%AUC_{tz-\infty}$ (the percentage of $AUC_{0-\infty}$ obtained by extrapolation)
- t_{max} (time from dosing to maximum measured concentration of the analyte)
- λ_z (terminal rate constant)
- $t_{1/2}$ (terminal half-life of the analyte)
- MRT_{po} (mean residence time of the analyte in the body after oral administration)
- MRT_{iv} (mean residence time of the analyte in the body after IV administration)
- CL/F (apparent clearance of the analyte in the plasma after extravascular administration)
- CL (apparent clearance of the analyte in the plasma after intravascular administration)
- V_z/F (apparent volume of distribution during the terminal phase after extravascular administration)
- $Ae_{urine, t1-t2}$ (amount of analyte that is eliminated in urine from the time interval t1 to t2)

- $Ae_{urine,\ 0\text{-}t2}$ (amount of analyte that is eliminated in urine over the time interval from 0 to the last quantifiable time point)

- $fe_{urine,\ t1\text{-}t2}$ (fraction of administered drug excreted in urine from time point t1 to t2)

- $Ae_{faeces,\ t1\text{-}t2}$ (amount of analyte that is eliminated in faeces from the time interval t1 to t2)

- $Ae_{faeces,\ 0\text{-}t2}$ (amount of analyte that is eliminated in faeces over the time interval from 0 to the last quantifiable time point)

- $fe_{faeces,\ t1\text{-}t2}$ (fraction of administered drug excreted in faeces from time point t1 to t2)

- $CLR_{,\ t1\text{-}t2}$ (renal clearance of the analyte in plasma from the time point t1 to t2)

Further pharmacokinetic parameters may be calculated as appropriate.

Determination of the metabolic pattern of BI 1265162 in plasma, urine and faeces after administration of BI 1265162 given intravenously (Part 1) and orally (Part 2) including structure elucidation of the metabolites (performed by AMS and classical methods; to be reported separately outside this report).

2.2.2.2 Further mass balance endpoints

Mass balance assessments

The following endpoints will be determined for urine:

- Ae (C-14)-radioactivity

- %Ae (fe) (C-14)-radioactivity

- Cum Ae: cumulative recovery of (C-14)-radioactivity

- Cum %Ae (fe): cumulative recovery of (C-14)-radioactivity expressed as a percentage of the dose

For faeces:

- Ae (C-14)-radioactivity

- %Ae (fe) (C-14)-radioactivity

- Cum Ae: cumulative recovery of (C-14)-radioactivity

- Cum %Ae (fe): cumulative recovery of (C-14)-radioactivity expressed as a percentage of the dose

Mass balance recovery of (C-14)-radioactivity from all excreta:

- Ae (C-14)-radioactivity
- %Ae (fe) (C-14)-radioactivity
- Cum Ae: cumulative recovery of (C-14)-radioactivity
- Cum %Ae (fe): cumulative recovery of (C-14)-radioactivity expressed as a percentage of the dose

Further pharmacokinetic parameters may be calculated as appropriate.

2.2.2.3 Determination of the blood cell/ plasma and blood/ plasma ratios of (C-14)-radioactivity

The ratio of (C-14)-radioactivity in blood cells/ plasma (C_b/ C_p) will be calculated according to the formula at those time points as indicated in the Flow Chart.

$$C_{bloodcells} / C_{plasma} = \frac{\frac{C_{blood} - C_{plasma}(1 - HC)}{HC}}{C_{plasma}}$$

$C_{blood\ cells}$ = concentration in blood cells
C_{plasma} = concentration in plasma
C_{blood} = concentration in whole blood
HC = Haematocrit in decimal

Additionally, the ratio of concentration of (C-14)-radioactivity in blood and plasma (C_{blood}/ C_{plasma}) will be calculated at all time points when (C-14)-radioactivity concentrations are quantifiable in blood and in plasma.

2.2.2.4 Local tolerability

(Part 1) Local tolerability will be assessed by the investigator on the basis of swelling, induration, heat, redness, pain, and other findings.

(Part 2) Not applicable.

2.2.2.5 Further safety and systemic tolerability endpoints

- Safety laboratory tests
- 12-lead electrocardiogram (ECG), and
- Vital signs (blood pressure [BP], pulse rate [PR])
- Physical examination

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

The overall trial design is depicted in Figure 3.1: 1 and Figure 3.1: 2.

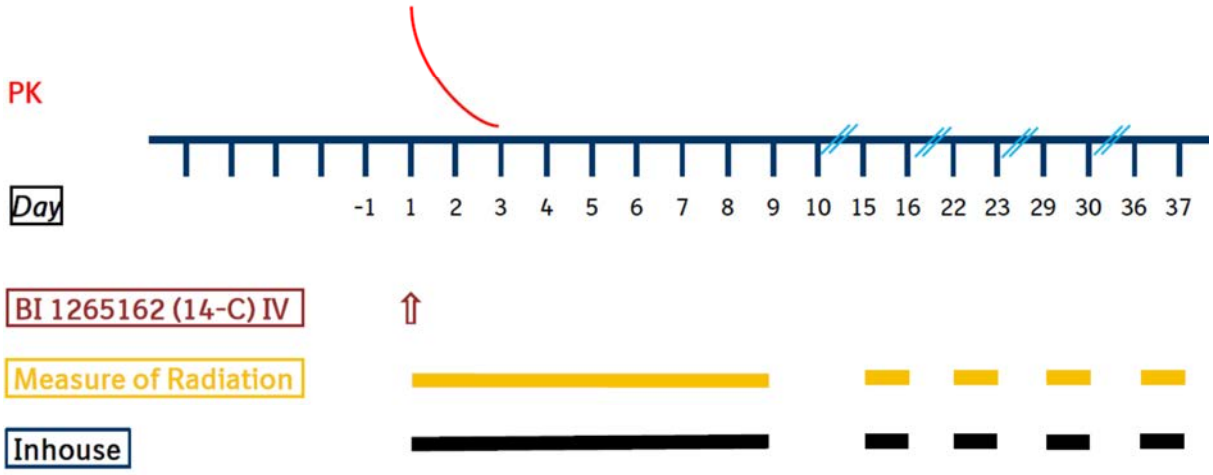


Figure 3.1: 1 Design of intravenous trial part

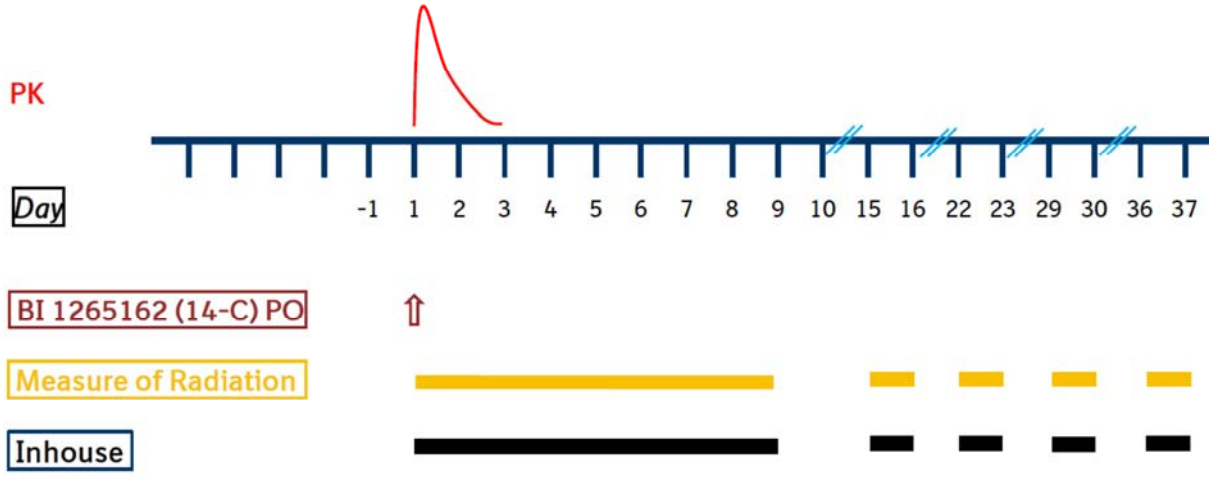


Figure 3.1: 2 Design of oral trial part

The trial will consist of two trial parts, after the BI 1265162 (C-14) administration of single (Part 1) intravenous and (Part 2) oral doses. Both parts will be performed as a non-randomized, open-label, single-dose, single arm, trial in healthy male subjects in order to investigate by means of mass balance recovery (Part 1) metabolism (metabolic profile) and routes of elimination of (C-14) BI 1265162 after intravenous administration of 50 µg BI 1265162 (C-14) and (Part 2) the extent of oral absorption, metabolism (metabolic profile),

and routes of elimination of (C-14) BI 1265162 after oral administration of 5 mg BI 1265162 (C-14). For details, see Section 4.1.

Since in both parts different subjects will take part, there will be no washout period.

On Day 1, subjects will receive the (C-14)-labelled drug substance and will then stay in the trial centre up to the morning of Day 9 for collection of blood, urine, and faeces samples. Subjects will be readmitted to the trial centre for 24 hour collection intervals of urine and faeces on Days 15, 22, 29, and 36, if release criteria as specified below have not been met on Day 9 or during any subsequent 24-h collection visits. Within 24 hours before each of these once-weekly in-house collection intervals, subjects are to collect faeces at home. This 24 hour interval home collection faeces will be used for analysis in case no defecation occurs in the subsequent 24 hours in-house collection interval. Otherwise it will be discarded.

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

If one of the following release criteria is true, 24 hour collection intervals after Days 9, 16, 23, 30, or 37, (whichever is applicable) will not be performed:

- 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 hour intervals, and
- Concentration of total radioactivity in plasma <5% of C_{max} of total radioactivity in plasma.

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

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

This is a standard design of a (C-14) human mass balance trial to determine absorption, metabolism, and excretion of BI 1265162.

The inclusion of a control group is not required for such an investigation.

The elimination of BI 1265162 is multi-exponential. The terminal mean half-life with 15.5h seems to be moderate. If drug can be absorbed all through the gastro-intestinal tract, this may result in low systemic concentrations for a longer period of time. Therefore, it cannot be excluded that prolonged sampling is necessary in humans. Hence, after8 in-house days after dosing during which excreta will be collection, subjects will return for in-house 24-h collection intervals on a weekly basis for up to 4 weeks after dosing as long as release criteria are not met (see also Section 3.1).

The open-label treatment is not expected to bias results because all subjects receive the same treatment within each trial part and the main trial endpoints are derived from measurements of plasma, urine and faeces concentrations of analytes which are provided by a bioanalytical laboratory.

3.3 SELECTION OF TRIAL POPULATION

It is planned that 7 healthy male subjects will enter each trial part, i.e. in total 14 subjects. They will be recruited from the subject-pool of the trial site.

Only male subjects will be included in the trial to reduce variability of results.

The current trial is designed to investigate the basic pharmacokinetics of BI 1265162 including absorption, metabolism, and elimination and quantitative determination of excretion by mass balance. Samples will be generated for additional metabolic profiling and structural identification. 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. who have signed informed consent) will be maintained in the ISF irrespective of whether they have been treated with investigational drug or not.

3.3.1 Main diagnosis for trial entry

The trial will be performed in healthy male subjects.

3.3.2 Inclusion criteria

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

1. Healthy male subjects according to the assessment of the investigator, as based on a complete medical history including a physical examination, vital signs (BP, PR), 12-lead ECG, and clinical laboratory tests
2. Age of 18 to 65 years (inclusive)
3. BMI of 18.5 to 29.9 kg/m^2 (inclusive)
4. Signed and dated written informed consent prior to admission to the trial, 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 3 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-child bearing potential (including homosexual men)

Subjects are required to use condoms to prevent unintended exposure of the partner to the trial 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) deviating from normal and assessed as clinically relevant by the investigator
2. Repeated measurement of systolic blood pressure outside the range of 90 to 139 mmHg, diastolic blood pressure outside the range of 45 to 89 mmHg, or pulse rate outside the range of 40 to 100 bpm
3. Any laboratory value outside the reference range that the investigator considers to be of clinical relevance
4. Any evidence of a concomitant disease assessed as clinically relevant by the investigator
5. Clinically significant gastrointestinal, hepatic, renal, respiratory, cardiovascular, metabolic, immunological or hormonal disorders
6. Cholecystectomy or other surgery of the gastrointestinal tract that could interfere with the pharmacokinetics of the trial medication (except appendectomy or simple hernia repair)
7. Diseases of the central nervous system (including but not limited to any kind of seizures or stroke), and other relevant neurological or psychiatric disorders
8. History of relevant orthostatic hypotension, fainting spells, or blackouts
9. Chronic or relevant acute infections
10. History of relevant allergy or hypersensitivity (including allergy to the trial medication or its excipients)
11. Use of drugs within 30 days of planned administration of trial medication that might reasonably influence the results of the trial (including drugs that cause QT/ QTc interval prolongation)
12. Intake of an investigational drug in another clinical trial within 60 days of planned administration of investigational drug in the current trial, or concurrent participation in another clinical trial in which investigational drug is administered
13. Smoking habit other than incidental. Incidental smoker is defined as a person who will not smoke more than 5 cigarettes per week
14. Inability to refrain from smoking in the clinical research unit

15. Alcohol abuse (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))
16. Drug abuse or positive drug screening
17. Blood donation of more than 100 mL within 30 days of planned administration of trial medication or intended blood donation during the trial
18. Intention to perform excessive physical activities within 96 hours prior to the administration of trial medication and during the trial until the discharge at Day 9
19. Inability to comply with the dietary regimen of the trial site
20. A marked baseline prolongation of QT/QTc interval (such as QTc intervals that are repeatedly greater than 450 ms) or any other relevant ECG finding at screening
21. A history of additional risk factors for *Torsade de Pointes* (such as heart failure, hypokalaemia, or family history of Long QT Syndrome)
22. Subject is assessed as unsuitable for inclusion by the investigator, for instance, because the subject is not considered able to understand and comply with trial requirements, or has a condition that would not allow safe participation in the trial

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

23. A history of chronic kidney disease
24. Participation in another ADME study with a radiation burden of 0.1-1.0 mSv in the period of 1 year prior to screening or 1.1-2.0 mSv in the past 2 years or 2.1-3.0 mSv in the past 3 years etc.
25. 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)
26. Irregular defecation pattern (less than a mean of one bowel movement every other day)

For trial restrictions, see Section 4.2.2.

3.3.4 Withdrawal of subjects from treatment or assessments

Subjects may discontinue trial treatment or withdraw consent to trial participation as a whole ('withdrawal of consent') with very different implications; see Sections 3.3.4.1 and 3.3.4.2 below.

If a subject is removed from or withdraws from the trial prior to the first administration of trial medication, the data of this subject will not be entered in the case report form (CRF) and will not be reported in the clinical trial report (CTR). If a subject is removed from or withdraws from the trial after the first administration of trial medication, this will be documented and the reason for discontinuation must be recorded in the CRF; in addition, the data will be included in the CRF 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 CRF. If the discontinuation occurs before the end of the REP (see Section 1.2.6), the discontinued subject should, if possible, be questioned for AEs and concomitant therapies at or after the end of the REP in order to ensure collection of AEs

and concomitant therapies throughout the REP, if not contrary to any consent withdrawal of the subject.

3.3.4.1 Removal of individual subjects

An individual subject will be removed from the trial if:

1. The subject wants to discontinue trial treatment, without the need to justify the decision
2. The subject has repeatedly shown to be non-compliant with important trial procedures and, in the opinion of both, the investigator and sponsor representative, is not willing or able to adhere to the trial requirements in the future.
3. The subject needs to take concomitant medication that interferes with the investigational medicinal product or other trial treatment
4. The subject can no longer receive trial treatment for medical reasons (such as surgery, adverse events [AEs], or diseases)
5. The subject has an elevation of AST and/ or ALT ≥3-fold ULN and 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

In addition to these criteria, the investigator may discontinue subjects at any time based on his or her clinical judgment.

Even if the trial treatment is discontinued, the subject remains in the trial and, given his agreement, will undergo the procedures for early treatment discontinuation and follow up as outlined in the Flow Chart and Section 6.2.3.

3.3.4.2 Withdrawal of consent to trial participation

Subjects may withdraw their consent to trial participation at any time without the need to justify the decision. If a subject wants to withdraw consent, the investigator should be involved in the discussion with the subject and explain the difference between trial treatment discontinuation and withdrawal of consent to trial participation, as well as explain the options for continued follow up after trial treatment discontinuation. For details, see Section 3.3.4.1.

3.3.4.3 Discontinuation of the trial by the sponsor

Boehringer Ingelheim reserves the right to discontinue the trial at any time for any of the following reasons:

1. Failure to meet expected enrolment goals overall or at a particular trial site
2. New toxicological findings, serious adverse events, or any safety information invalidating the earlier positive benefit-risk-assessment. More specifically, the trial will be put on hold, and only proceed after mutual consultation between the Sponsor and the Principal Investigator, if more than 50% of the subjects have drug-related and clinically relevant adverse events of moderate or severe intensity, or if 1 or more drug-related serious adverse event is reported.
3. Violation of GCP, or the CTP, or the contract with BI impairing the appropriate conduct of the trial

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

The investigator/ trial site will be reimbursed for reasonable expenses incurred in case of trial termination (except, if item 3 applies).

3.3.5 Replacement of subjects

In case subjects in either trial part do not complete the trial, the Trial Clinical Leader together with the Trial Pharmacokineticist and the Trial Statistician are to decide, if and how many subjects will be replaced. A replacement subject will be assigned a unique trial subject number, and will be assigned to the same treatment as the subject he replaces.

4. TREATMENTS

4.1 INVESTIGATIONAL TREATMENTS

Radiolabelled BI 1265162 is administered as a solution of BI 1265162 (C-14). The oral and intravenous solution contains (C-14) BI 1265162 and unlabelled BI 1265162 which is manufactured by BI Pharma GmbH & Co. KG. The final drug product oral solution and intravenous solution is made by [redacted].

4.1.1 Identity of the Investigational Medicinal Products

The characteristics of the test product are given below:

(Part 1) Intravenous BI 1265162 (C-14)

Name:	BI 1265162 (C-14) intravenous solution 5 µg/mL (10 mL; 0.018 MBq)
Substance:	BI 1265162 and (C-14) BI 1265162
Pharmaceutical formulation:	Intravenous solution
Source:	[redacted]
Unit strength:	50 µg
Posology:	1-0-0
Route of administration:	Intravenous
Duration of use:	Single dose

(Part 2) Oral BI 1265162 (C-14)

Name:	BI 1265162 (C-14) oral solution 0.25 mg/mL (20 mL; 0.306 MBq)
Substance:	BI 1265162 mixed with (C-14) BI 1265162
Pharmaceutical formulation:	Oral solution
Source:	[redacted]
Unit strength:	5 mg
Posology:	1-0-0
Route of administration:	Oral
Duration of use:	Single dose

The characteristics of the reference product are given below:

Not applicable.

4.1.2 Selection of doses in the trial

(Part 1) Intravenous BI 1265162 (C-14)

The intravenous dose of 50 µg BI 1265162 (C-14) is expected to yield exposures that will be similar to the systemic exposure which is achieved with a dose of 200 µg administered by inhalation, the highest dose being tested in phase II trials (1399-0003). This dose is below the already tested highest doses (single doses up to 1200 µg, multiple doses up to 75 µg BID (150 µg/d)) of BI 1265162 in healthy subjects. In healthy subjects, a single dose of 1200 µg was safe and well-tolerated (Section 1.3).

This dose, administered as intravenous solution, will include 0.018 MBq of BI 1265162 (C-14). The radiolabelled dose of 0.018 MBq is required for the objectives of the trial, i.e. to provide good detection limits for measurement of radioactivity in urine, faeces and plasma. The total effective dose (radiation burden) amounts to 0.001 mSv. This is below the limit of ICRP Category 1 and considered acceptable [R15-3219].

Radiation burden calculations are presented in Appendix 10.1. For risk-benefit assessment, see Section 1.4.

(Part 2) Oral BI 1265162 (C-14)

The oral dose of 5 mg BI 1265162 (C-14) was chosen on the ground of preliminary results from the ongoing absolute bioavailability trial 1399-0014 (refer to Section 1.4). Since developed for inhalative administration, BI 1265162 has not been applied in an oral fashion. An oral dose of 5 mg is considered to be adequate for the objectives of the current trial.

This dose, administered as oral solution, will include 0.306 MBq of BI 1265162 (C-14). The radiolabelled dose of 0.306 MBq is required for the objectives of the trial providing good detection limits for measurement of radioactivity in urine, faeces and plasma. The total effective dose (radiation burden) amounts to 0.0014 mSv. This is below the limit of ICRP Category 1 and considered acceptable.

Radiation burden calculations are presented in Appendix 10.1. For risk-benefit assessment, see Section 1.4.

4.1.3 Method of assigning subjects to treatment groups

This is a non-randomized, open-label, single-dose, phase I trial. All subjects will receive the same treatment per trial part: BI 1265162 (C-14), either intravenously in Part 1 or orally in Part 2. Subjects will be assigned to one of these parts based on their temporal availability. Once a subject number has been assigned, it cannot be reassigned to any other subject.

The study drug administration of one trial part will be finished prior to start of study drug administration of the other trial part.

4.1.4 Drug assignment and administration of doses for each subject

This is a non-randomised, open-label, single-dose, phase I trial. Within each trial part, all subjects receive the same treatment. Treatments to be evaluated are outlined in Table 4.1.4: 1.

Table 4.1.4: 1 Dosage and treatment schedule

Treatment	Substance	Formulation	Unit strength	Volume	Total dose	Total radioactivity
T1 (Part 1)	BI 1265162	IV solution	5 µg/mL	10 mL	50 µg over 1h	0.018 MBq
T2 (Part 2)	BI 1265162	Oral solution	0.25 mg/mL	20 mL	5 mg	0.306 MBq

Each subject is expected to participate in 1 treatment (Days -2 to 38). Intravenous (Part 1) and oral (Part 2) BI 1265162 (C-14) administrations will be applied to different subject cohorts.

Administration of trial medication will be performed after subjects have fasted overnight; fasting is to start no later than 10 hours before the scheduled dosing. The so-called four-eye principle (two-person rule) should be applied. For this, one authorised employee of the trial site should witness the administration of trial medication, and – if applicable – its preparation (e.g. reconstitution), if correct dosage cannot be ensured otherwise.

Subjects will be kept under close medical surveillance until Day 9 after drug administration. Subject should be in a semi-supine position for 4 hours after dosing of the oral drug application.

(Part 1) Intravenous BI 1265162 (C-14)

An intravenous infusion of BI 1265162 will be administered as a constant intravenous infusion over 1 hour to a subject in the semi supine position under supervision of the investigating physician or an authorised designee. Start and end time of the infusion will be recorded. For the administration an indwelling catheter is placed into an arm vein of the subject and will be kept patent with a saline infusion. A second indwelling catheter used for collection of blood samples will be placed on the contralateral arm.

(Part 2) Oral BI 1265162 (C-14)

An oral dose will be administered by the investigator (or authorised designee) together with about 240 mL of water to subjects who are in a sitting position. A part of this water can be used to rinse the vial in which the medication is provided. For drug administration, the so-called four-eye principle (two-person rule) should be applied. For this, one authorised employee of the trial site should witness the administration of trial medication, and – if applicable – its preparation (e.g. reconstitution), if correct dosage cannot be ensured otherwise.

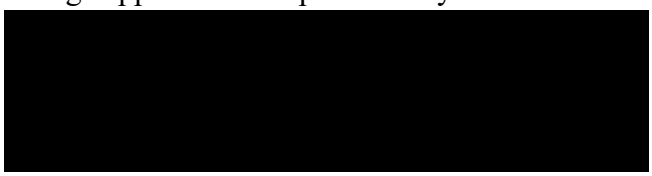
4.1.5 Blinding and procedures for unblinding

This phase I trial investigating only one treatment per trial part will be handled in an open fashion throughout (i.e., during the conduct, including data cleaning and preparation of the analysis). This is considered acceptable because the potential for bias seems to be low and does not outweigh practical considerations.

Emergency envelopes will not be provided, because the dose of trial medication is known to investigators and subjects.

4.1.6 Packaging, labelling, and re-supply

Drug supplies will be provided by the



It consists of containers holding the trial medication which is labelled with trial identification. The required information according to the Local Drug Law as well as Annex 13/ EU GMP Guideline will be provided on the containers.

Radiolabeled drug product manufacturing is done by [redacted] The final container used for administration of the radiolabeled drug product will be a syringe for intravenous infusions or a vial for oral application.

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

The telephone number of the sponsor and the name, address and telephone number of the trial site are provided in the subject information form. The EudraCT number is indicated on the title page of this protocol as well as on the subject information and informed consent forms.

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 in accordance with the recommended (labelled) storage conditions. If 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 contacted immediately.

4.1.8 Drug accountability

The investigator or designee will receive the investigational drugs delivered from the sponsor following requirements are fulfilled:

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

- Approval/ notification of the regulatory authority, e.g. competent authority
- Availability of the *curriculum vitae* of the Principal Investigator
- Availability of a signed and dated clinical trial protocol

Only authorised personnel documented in the form 'Trial Staff List' may dispense medication to trial subjects. The trial medication must be administered in the manner specified in the CTP.

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

All unused medication will be disposed of locally by the trial site upon written authorisation of the trial clinical monitor. Receipt, usage and disposal of trial medication must be documented on the appropriate 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, if adverse events require 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 results of medical evaluations are acceptable.

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

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

4.2.2.2 Restrictions on diet and life style

While admitted to the trial site, subjects will be instructed not to consume any foods or drinks other than those provided by the staff. Standardised meals will be served at the times indicated in the Flow Chart. No food is allowed for at least 4 hours after start of infusion (Part 1)/ drug intake (Part 2).

From 1 hour before start of infusion (Part 1)/ drug intake (Part 2) until lunch, fluid intake is restricted to the water administered with the drug (Part 2), and an additional 240 mL of water at 2 hours and 4 hours after start of infusion/ (Part 1) drug intake (Part 2). From lunch until 24 hours after start of infusion (Part 1)/ drug intake (Part 2), total fluid intake is restricted to 3000 mL.

Grapefruits, Seville oranges (sour or bitter oranges) and their juices, and dietary supplements and products containing St. John's wort (*Hypericum perforatum*) are not permitted starting 7 days before the first administration of trial medication until discharge at Day 9 after the last administration of trial medication.

Alcoholic beverages not permitted from 48 hours before each trial drug administration and until 24 hours after administration of trial medication.

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

Methylxanthine-containing drinks or foods (such as coffee, tea, cola, energy drinks, and chocolate) are not allowed from 24 hours before until discharge at Day 9.

Excessive physical activity (such as competitive sport) should be avoided from 96 hours before the first administration of trial medication until discharge at Day 9.

4.3 TREATMENT COMPLIANCE

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

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

5. ASSESSMENTS

5.1 ASSESSMENT OF EFFICACY

Not applicable.

5.2 ASSESSMENT OF SAFETY

5.2.1 Physical examination

At screening, the medical examination will include demographics, height and body weight, smoking and alcohol history (results not mandatory to be entered into CRF or to be reported), 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 including determination of weight.

5.2.2 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 (e.g [redacted], [redacted]) at the times indicated in the Flow Chart, after subjects have rested for at least 5 minutes in a supine position. All recordings should be made using the same type of blood pressure recording instrument on the same arm, if possible.

5.2.3 Safety laboratory parameters

For the assessment of laboratory parameters, blood and urine samples will be collected by the trial site at the times indicated in the Flow Chart after the subjects have fasted for at least 4 h. For retests, at the discretion of the investigator or designee, overnight fasting is not required.

If safety laboratory measurement is performed with other blood collection, e.g. pharmacokinetic sampling, safety laboratory measurement will always be performed first, preferably without any tourniquet.

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

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

Additional haematocrit measurements will be performed at the time points as indicated in the Flow Chart.

For electrolyte/ potassium concentration measurements, blood will be sampled without any tourniquet at time points as indicated in the Flow Chart (safety laboratory).

Table 5.2.3: 1 Routine laboratory tests

Functional lab group	BI test name [comment/ abbreviation]	A	B
Haematology	Haematocrit	X	X
	Haemoglobin	X	X
	Red Blood Cell Count/ Erythrocytes	X	X
	White Blood Cells/ Leucocytes	X	X
	Platelet Count/ Thrombocytes (quant)	X	X
Automatic WBC differential, relative	Neutrophils/ Leukocytes; Eosinophils/ Leukocytes; Basophils/ Leukocytes; Monocytes/ Leukocytes; Lymphocytes/ Leukocytes	X	X
Automatic WBC differential, absolute	Neutrophil, absol.; Eosinophils, absol.; Basophils, absol.; Monocytes, absol.; Lymphocytes, absol.	X	X
Manual differential WBC (if automatic differential WBC is abnormal and clinically relevant in the opinion of the investigator according to local procedures)	Neut. Poly (segs)/ Leukocytes; Neutrophils Bands/ Leukocytes; Eosinophils/ Leukocytes; Basophils/ Leukocytes; Monocytes/ Leukocytes; Lymphocytes/ Leukocytes	X	X
Coagulation	Activated Partial Thromboplastin Time	X	X
	Prothrombin Time – INR (International Normalization Ratio)	X	X
	Fibrinogen	X	X
Enzymes	AST [Aspartate transaminase]/ GOT, SGOT	X	X
	ALT [Alanine transaminase]/ GPT, SGPT	X	X
	Alkaline Phosphatase	X	X
	Gamma-Glutamyl Transferase	X	X
Hormones	Thyroid Stimulating Hormone	X	--
Substrates	Glucose (Plasma)	X	X
	Creatinine	X	X
	GFR/ CKD-EPI[2]	X	X
	Bilirubin, Total	X	X
	Bilirubin, Direct	X	X
	Protein, Total	X	X
	C-Reactive Protein (Quant)	X	X
Serum Electrolytes[1]	Sodium	X	X
	Potassium	X	X
	Chloride	X	X
	Calcium	X	X
Urinalysis (Stix)	Urine Nitrite (qual)	X	X
	Urine Protein (qual)	X	X
	Urine Glucose (qual)	X	X
	Urine Ketone (qual)	X	X
	Urobilinogen (qual)	X	X
	Urine Bilirubin (qual)	X	X
	Urine RBC/Erythrocytes (qual)	X	X
	Urine WBC/Leucocytes (qual)	X	X
	Urine pH	X	X
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)	X	X

A & B Safety laboratory sets (for time points, see Flow Chart)

[1] Sample tubes will be centrifuged for about 8 minutes at about 4000 g and stored at room temperature until shipment to the clinical lab.
[2] Estimated glomerular filtration rate according to CKD-EPI formula (R12-1392)

The tests listed in Table 5.2.3: 2 are exclusionary laboratory tests that may be repeated as required. The results will not be entered in the CRF/ database and will not be reported in the CTR. It is planned to perform these tests during screening only. Drug screening will be performed at screening and prior to each treatment period on Day -1.

Table 5.2.3: 2 Exclusionary laboratory tests

Functional lab group	Test name
Drug screening (urine)	Amphetamine/ MDA Barbiturates Benzodiazepine Cannabis Cocaine Methadone Methamphetamines/ MDMA/ XTC Opiates Phencyclidine Tricyclic Antidepressants
Infectious serology (blood)	Hepatitis B Surface Antigen (qualitative) Hepatitis B Core Antibody (qualitative) Hepatitis C Antibodies (qualitative) HIV-1 and HIV-2 Antibody (qualitative)

To encourage compliance with alcoholic and drug restrictions, a urine alcohol and drug test (e.g. [redacted]) will be performed prior to each treatment period, and may be repeated at any time during the trial at the discretion of an investigator or designee. The results will not be included in the CTR.

The laboratory tests listed in Tables 5.2.3: 1 and 5.2.3: 2 will be performed at [redacted]. Urinanalyis stix and drug screening tests will be performed using e.g. [redacted] respectively.

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

5.2.4 Electrocardiogram

Twelve-lead ECGs (I, II, III, aVR, aVL, aVF, V1 - V6) will be recorded using a computerised electrocardiograph ([redacted]) at the times provided in the Flow Chart.

To achieve a stable heart rate at rest and to assure high quality recordings, the site personnel will be instructed to assure a relaxed and quiet environment, so that all subjects are at complete rest.

All ECGs will be recorded for a 10 second duration after subjects have rested for at least 5 minutes in a supine position. ECG assessment will always precede all other trial procedures scheduled for the same time to avoid compromising 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. Abnormal findings will be reported as AEs (during the trial) or baseline conditions (at screening), if assessed to be clinically relevant by the investigator. Any ECG abnormalities will be carefully monitored and, if necessary, the subject will be removed from the trial and will receive the appropriate medical treatment.

ECGs may be repeated for quality reasons (for instance, due to alternating current artefacts, muscle movements, or electrode dislocation) and the repeated ECG will be used for analysis. Additional (unscheduled) ECGs may be collected by the investigator for safety reasons.

5.2.5 Other safety parameters

5.2.5.1 Local tolerability

After intravenous BI 1265162 (C-14) administration (Part 1), local tolerability will be assessed by the investigator on the basis of swelling, induration, heat, redness, pain, and other findings.

5.2.6 Assessment of adverse events

5.2.6.1 Definitions of adverse events

5.2.6.1.1 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.

The following should also be recorded as an 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.

5.2.6.1.2 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
- Requires prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly/birth defect
- 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

5.2.6.1.3 AEs considered 'Always Serious'

Cancers of new histology and exacerbations of existing cancer must be classified as a serious event regardless of the time since discontinuation of the trial medication and must be reported as described in 5.2.6.2, subsections 'AE Collection' and '**AE reporting to sponsor and timelines**'.

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

The latest list of 'Always Serious AEs' can be found in the eDC system, an electronic data capture system which allows the entry of trial data at the trial site. These events should always be reported as SAEs as described above.

5.2.6.1.4 Adverse events of special interest

The term adverse events of special interest (AESI) relates to any specific AE that has been identified at the project level as being of particular concern for prospective safety monitoring and safety assessment within this trial, e.g. the potential for AEs based on knowledge from other compounds in the same class. AESIs need to be reported to the sponsor's Pharmacovigilance Department within the same timeframe that applies to SAEs, see Section 5.2.6.2.2.

The following are considered as AESIs:

- A confirmed elevation of serum potassium > upper limit of normal (ULN) in non-haemolysed blood.
- Hepatic injury
  A hepatic injury is defined by the following alterations of hepatic laboratory parameters:
  - An elevation of AST (aspartate transaminase) and/or ALT (alanine transaminase) ≥3-fold ULN combined with an elevation of total bilirubin ≥2-fold ULN measured in the same blood sample, or
  - Aminotransferase (ALT, and/or AST) elevations ≥10 fold ULN

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

5.2.6.1.5 Intensity (severity) of AEs

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

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

5.2.6.1.6 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 reduced)

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

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

5.2.6.2 Adverse event collection and reporting

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

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

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

- From signing the informed consent onwards 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 subjects, 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 any occurrence of cancer and 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.

5.2.6.2.2 AE reporting to the 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 immediately (within 24 hours) to the sponsor's unique entry point (country specific reporting process 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 send 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.

5.2.6.2.3 Information required

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

5.2.6.2.4 Pregnancy

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

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

The ISF will contain the Pregnancy Monitoring Form for Clinical Trials (Part A and Part B) as well as non-trial specific information and consent for the pregnant partner.

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

5.3 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

5.3.1 Assessment of pharmacokinetics

For the assessment of pharmacokinetics, blood and urine samples will be collected at the time points/ time intervals indicated in the Flow Chart. The actual sampling times will be recorded and used for determination of pharmacokinetic parameters.

Pharmacokinetic sampling times may be adapted during the trial based on information obtained during trial conduct (e.g. exploratory pharmacokinetic analysis) including addition of samples as long as the total blood volume taken per subject does not exceed 500 mL. Such changes would be implemented via non-substantial CTP Amendment.

5.3.2 Methods of sample collection

5.3.2.1 Sampling of whole blood and plasma

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

- To determine (C-14)-radioactivity concentrations in whole blood and plasma
- To determine concentrations of BI 1265162 and its metabolite [redacted] (1) in plasma
- To identify further metabolites of BI 1265162 in plasma
- To determine the blood cell/ plasma and blood/ plasma ratios of (C-14)-radioactivity

Blood for pharmacokinetics of BI 1265162 and for quantification of its metabolite [redacted] will be taken from an antecubital or forearm vein into a [redacted] blood drawing tube at the times indicated in the Flow Chart.

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

5.3.2.2 Sampling of whole blood and plasma for (C-14)-radioactivity analysis in whole blood and plasma

Whole blood and plasma will be taken from an antecubital or forearm vein into a [redacted] blood drawing tube at the times indicated in the Flow Chart.

Premature stopping of blood sampling

In case (C-14)-radioactivity in plasma samples is not detectable [redacted]) at two consecutive time points for a subject, blood sampling can be stopped for this subject. However, all samples until and including the Day 9 sample have to be taken.

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

5.3.2.3 Sampling of plasma for metabolic profiling and structural elucidation

Additional [redacted]) plasma samples for the identification of drug metabolites will be investigated.

The blood samples will be drawn in parallel to pharmacokinetics (see Flow Chart).

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

5.3.2.4 Sampling of blood for haematocrit for blood cell/ plasma ratio

At each time point listed in the Flow Chart, a blood sample will be taken. This blood will be used for measurement of haematocrit which is needed for determination of blood cell/ plasma ratio (see Section 2.2.2.3).

Haematocrit will be measured at

[redacted]

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

5.3.2.5 Sampling of urine

Urine will be collected during the trial as indicated in the Flow Chart.

A blank urine sample will be collected within 14 hours prior to drug administration. All urine voided will be collected in containers, according to intervals, given in the Flow Chart.

[redacted] or 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. Volunteers will empty their bladders at the end of each sampling interval. The exact start and end times of the urine collection intervals will be recorded in the CRF.

All samples after the intake of BI 1265162 (C-14) are planned to be used for determination of (C-14)-radioactivity, BI 1265162 concentrations and its metabolites.

Samples to be used for metabolic profiling will be selected according to the levels of radioactivity in each urine sample interval.

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

5.3.2.6 Faeces sampling

Faeces will be collected during the trial as indicated in the Flow Chart.

A blank faeces sample will be collected prior to drug administration.

All stool samples will be collected quantitatively in portions up to Day 37 after drug administration. The weight of faeces and the exact times of faeces collection will be recorded in the eCRF.

All faeces samples are planned to be used for determination of (C-14)-radioactivity and metabolic profiling.

Samples to be used for metabolic profiling will be selected according to the levels of radioactivity in each faeces sample interval.

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

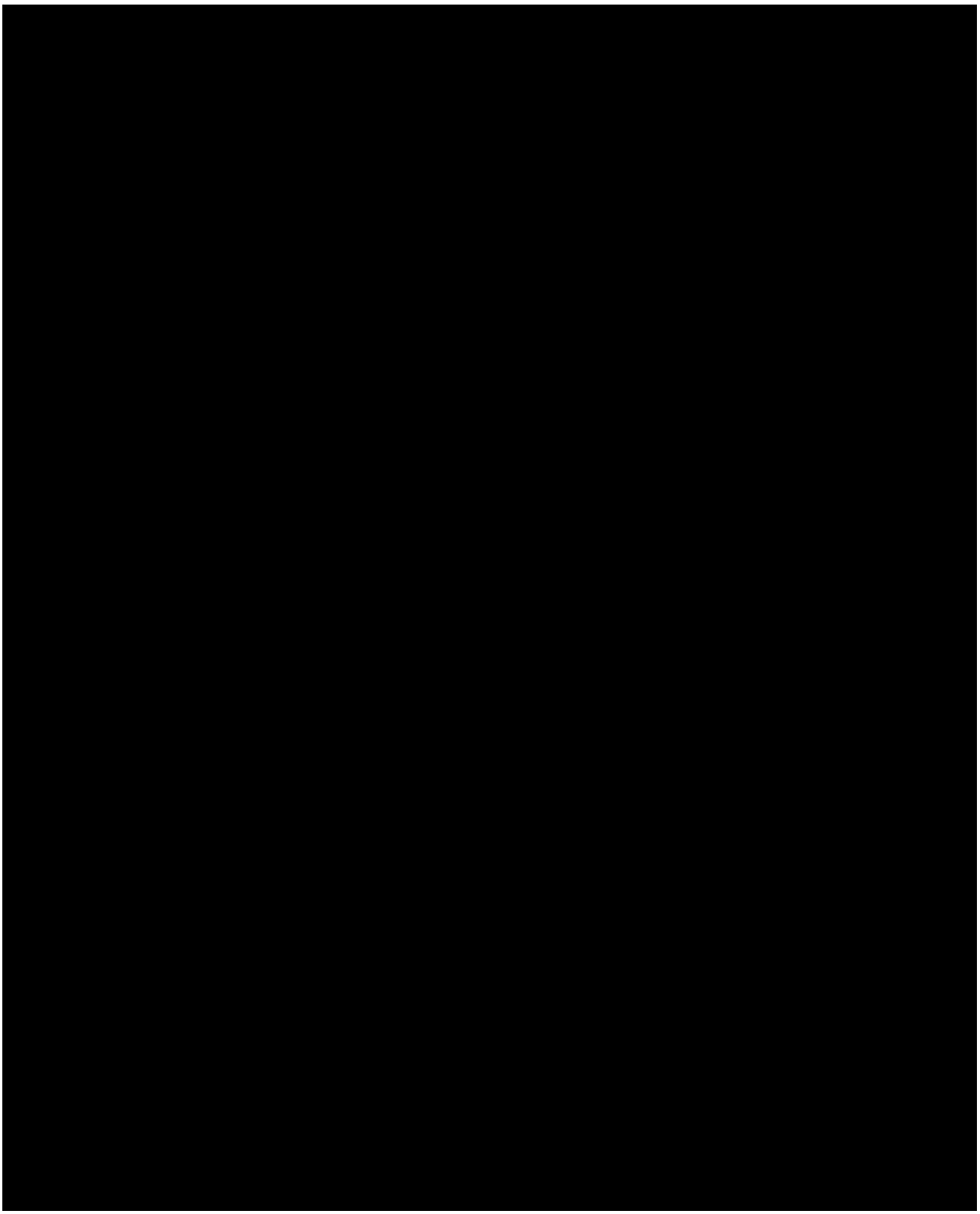
5.3.2.7 Collection of vomit

If vomiting occurs in a subject within 4 hours after drug administration, the vomit will be collected for determination of weight and (C-14)-radioactivity.

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

[redacted]

[redacted]



[redacted]

5.7 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 intravenously/ orally administered drug, and are widely used in clinical trials. The pharmacokinetic parameters and measurements outlined in Section 5.3 are generally used assessments of drug exposure in human mass-balance trials.

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 the end of trial examination are provided in the Flow Chart.

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

The acceptable deviation from the scheduled time for vital signs, ECG and laboratory tests will be ± 30 minutes for the first 4 hours after drug administration and ± 45 minutes thereafter.

In the event assessments are planned for the same scheme time in the Flow Chart, the order of the assessments should be arranged in such a way that pharmacokinetic (and pharmacodynamic) blood sampling will be done after the ECG and vital signs recordings have been conducted, with pharmacokinetic blood sampling exactly on time.

For planned blood sampling times and urine and faeces 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 the determination of pharmacokinetic parameters.

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

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

6.2.1 Screening period

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

For information regarding physical examination, vital signs, laboratory tests (including drug and virus screening), and ECG, refer to Sections 5.2.1 to 5.2.5.

6.2.2 Treatment period

Each subject is expected to participate in 1 treatment period (Days -1 to 37). Intravenous (Part 1) and oral (Part 2) BI 1265162 (C-14) administrations will be applied to different subject cohorts.

(Part 1) Intravenous BI 1265162 (C-14)

From Day -1 (prior to the application of trial medication), subjects will collect a pre-dose faeces sample at home or at the site in specific containers provided by [redacted]

On Day -1 or Day 1, subjects will collect a pre-dose (blank) urine sample prior to start of urine collection.

On Day -1, subjects will be admitted to the trial site. On Day 1, subjects will receive the (C-14)-labelled drug substance, i.e. 50 µg BI 1265162 (C-14) as a short infusion over 1 hour and will then stay in the trial centre up to the morning of Day 9 for collection of samples of blood, urine, and faeces.

Subjects will be readmitted to the trial centre for 24 hours collection intervals of urine and faeces on Days 15, 22, 29 and 36, if release criteria as described in Section 3.1 have not been met on Day 9. Within 24 hours before each of these once-weekly in-house collection intervals, subjects are to collect faeces at home. This 24 hour interval home collections will be used for analysis in case no defecation occurs in the subsequent 24 hours in-house collection interval. Otherwise it will be discarded. Once release criteria are reached, home collections will be stopped.

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 the last collection interval on Day 37, no further collections are planned.

For details on time points and procedures for collection of whole blood, plasma, urine and faeces samples for pharmacokinetic analysis, see Flow Chart and Section 5.3.2.

The safety measurements performed during the treatment period are specified in Section 5.3 of this protocol and in the Flow Chart. For details on times of all other trial procedures, see Flow Chart. AEs and concomitant therapy will be assessed continuously from screening until the end of trial examination.

(Part 2) Oral BI 1265162 (C-14)

From Day -1 to Day 1 (prior to the application of trial medication), subjects will collect a pre-dose faeces sample at home or at the site in specific containers provided by [redacted]

On Day -1 or Day 1, subjects will collect a pre-dose (blank) urine sample prior to start of urine collection.

On Day -1, subjects will be admitted to the trial site. On Day 1, subjects will receive the (C-14)-labelled drug substance, i.e. 5 mg BI 1265162 (C-14) as an oral solution together with 240 mL of water and will then stay in the trial centre up to the morning of Day 9 for collection of samples of blood, urine, and faeces.

Subjects will be readmitted to the trial centre for 24 hour collection intervals of urine and faeces on Days 15, 22, 29, and 36, if release criteria as described in Section 3.1 have not been met on Day 9. Within 24 hours before each of these once-weekly in-house collection intervals, subjects are to collect faeces at home. This 24 hour interval home collections will be used for analysis in case no defecation occurs in the subsequent 24 hours in-house

collection interval. Otherwise it will be discarded. Once release criteria are reached, home collections will be stopped.

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 the last collection interval on Day 37, no further collections are planned.

For details on time points and procedures for collection of whole blood, plasma, urine and faeces samples for pharmacokinetic analysis, see Flow Chart and Section 5.3.2.

Safety measurements performed during the treatment period are specified in Section 5.3 of this protocol and in the Flow Chart. For details on times of all other trial procedures, see Flow Chart. AEs and concomitant therapy will be assessed continuously from screening until the end of trial examination.

6.2.3 Follow-up period and trial completion

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

Subjects who discontinue before the end of the planned treatment period should undergo the EoT Visit.

All abnormal values (including laboratory parameters) that are assessed as 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 a subject's EoT Visit must be followed until they have resolved, have been sufficiently characterised, or no further information can be obtained.

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 STATISTICAL DESIGN – MODEL

The main objective of this trial is to investigate by means of mass balance recovery the metabolism (metabolic profile) and routes of elimination of (C-14) BI 1265162 after intravenous administration and the extent of gastro-intestinal absorption, metabolism (metabolic profile), and routes of elimination of (C-14) BI 1265162 after oral administration of 5 mg BI 1265162 (C-14) to healthy male subjects.

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Further objectives are to evaluate further pharmacokinetic, mass balance and tolerability parameters.

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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

Analysis sets

Statistical analyses will be based on the following analysis sets:

- Treated set (TS): The treated set includes all subjects who were entered and treated with one dose of trial drug. The treated set will be used for safety analyses.
- Pharmacokinetic parameter analysis set (PKS): This set includes all subjects from the treated set (TS) who provide at least one pharmacokinetic endpoint that was defined as primary or secondary and was not excluded due to a protocol deviation relevant to the evaluation of pharmacokinetics or due to pharmacokinetic non-evaluability (as specified in the following subsection ‘Pharmacokinetics’). Descriptive analyses of pharmacokinetic parameters will be based on the PKS.

Adherence to the protocol will be assessed by the trial team. Important protocol deviation (iPD) categories will be specified in the Integrated Quality and Risk Management Plan, iPDs will be identified no later than in the Report Planning Meeting, and the iPD categories will be updated as needed.

Pharmacokinetics

Pharmacokinetic parameters listed in Section 2.1 for drug (C-14) BI 1265162 will be calculated according to the relevant SOP of the Sponsor (001-MCS-36-472).

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

Relevant protocol deviations may be

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

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

- Missing samples/ concentration data at important phases of pharmacokinetic disposition curve

Plasma/urine concentration data and parameters of a subject which is flagged for exclusion will be reported with its individual values but will not be included in the statistical analyses. Descriptive statistics of pharmacokinetic parameters will be based on the PKS.

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).

7.3.1 Primary endpoint analyses

All parameters will be calculated and analysed descriptively.

7.3.2 Secondary endpoint analyses

Secondary endpoints (refer to Section 2.1.3) will be calculated according to the BI SOP 'Standards and processes for analyses performed within Clinical Pharmacokinetics/ Pharmacodynamics' (001-MCS-36-472) and will be assessed statistically using the same methods as described for the primary endpoints.

For the assessment of the secondary endpoint regarding safety, see Section 7.3.4.

7.3.4 Safety analyses

Safety will be analysed based on the assessments described in Section 2.2.2.2. All treated subjects (TS, refer to Section 7.2) will be included in the safety analysis. Safety analyses will be descriptive in nature and based on BI standards. No hypothesis testing is planned.

For all analyses, the treatment actually administered (= treatment at onset) to the subject will be used (any deviations from the planned treatment will be discussed in the minutes of the Report Planning Meeting).

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

Measurements (such as 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 the screening period, those between trial medication intake and discharge from study site (see Section 1.2.6) will be assigned to the treatment period. Events occurring after discharge from study site but prior to end of trial termination date will be assigned to 'follow-up'. These assignments including the corresponding time intervals will be defined in detail in the TSAP. Note that AEs occurring after the last per protocol contact but entered before final database lock will be reported to Pharmacovigilance only and will not be captured in the trial database.

Additionally, further treatment intervals (analysing treatments) may be defined in the TSAP 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 follow-up 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 5.2.6.1.4), and other significant AEs (according to ICH E3) will be listed separately.

Previous and concomitant therapies will be presented per treatment group without consideration of time intervals and treatment periods.

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

Vital signs will be assessed with regard to possible on-treatment changes from baseline.

Relevant ECG findings will be reported as AEs.

7.4 INTERIM ANALYSES

No interim analysis is planned.

7.5 HANDLING OF MISSING DATA

7.5.1 Safety

It is not planned to impute missing values for safety parameters.

7.5.2 Pharmacokinetics

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

Pharmacokinetic parameters that cannot be reasonably calculated based on the available drug concentration-time data will not be imputed.

7.6 RANDOMISATION

Randomisation is not applicable in this open-label, single arm per trial part clinical study. All subjects will receive the same treatment per trial part: BI 1265162 (C-14), either intravenously in Part 1 or orally in Part 2. Consecutive subject numbers will be assigned via the EDC system.

7.7 DETERMINATION OF SAMPLE SIZE

For this exploratory study, no prospective calculations of statistical power have been made. The sample size of at least 6 evaluable subjects per trial part has been selected to provide sufficient information on safety, tolerability and pharmacokinetics of (C-14) BI 1265162 after intravenous administration (Part 1) or oral administration (Part 2) in healthy male subjects. In order to have at least 6 evaluable subjects per trial part, the sample size will be 7 in both parts, in total 14 subjects.

8. INFORMED CONSENT, TRIAL RECORDS, DATA PROTECTION, PUBLICATION POLICY, AND ADMINISTRATIVE STRUCTURE

The trial will be carried out in compliance with the protocol, the ethical principles laid down in the Declaration of Helsinki, in accordance with the ICH Harmonized Guideline for Good Clinical Practice (GCP), relevant BI Standard Operating Procedures (SOPs) and other relevant regulations. Investigators and site staff must adhere to these principles.

Standard medical care (prophylactic, diagnostic, and therapeutic procedures) remains the responsibility of the subject's treating physician.

The investigator will inform the sponsor immediately of any urgent safety measures taken to protect the trial subjects against any immediate hazard, as well as of any serious breaches of the protocol or of ICH GCP.

The Boehringer Ingelheim transparency and publication policy can be found on the following web page: trials.boehringer-ingelheim.com. The rights of the investigator and of the sponsor with regard to publication of the results of this trial are described in the investigator contract. As a general rule, no trial results should be published prior to archiving of the CTR.

The terms and conditions of the insurance coverage are made available to investigator and subjects, and are stored in the ISF.

8.1 TRIAL APPROVAL, SUBJECT INFORMATION, 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 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 retained by the investigator as part of the trial records. A signed copy of the informed consent and any additional subject information must be given to each subject or the subject's legally accepted representative.

The subject must be given sufficient time to consider participation in the trial. The investigator or delegate obtains written consent of the subject's own free will with the informed consent form after confirming that the subject understands the contents. The investigator or [redacted] delegate must sign (or place a seal on) and date the informed consent form. If a trial collaborator has given a supplementary explanation, the trial collaborator also signs (or places a seal on) and dates the informed consent.

Re-consenting may become necessary when new relevant information becomes available and should be conducted according to the sponsor's instructions.

The consent and re-consenting process should be properly documented in the source documentation.

8.2 DATA QUALITY ASSURANCE

A risk-based approach is used for trial quality management. It is initiated by the assessment of critical data and processes for trial subject protection and reliability of the results as well as identification and assessment of associated risks. An Integrated Quality and Risk Management Plan documents the rationale and strategies for risk management during trial conduct including monitoring approaches, vendor management and other processes focusing on areas of greatest risk.

Continuous risk review and assessment may lead to adjustments in trial conduct, trial design or monitoring approaches.

A quality assurance audit/ inspection of this trial may be conducted by the sponsor, sponsor's designees, or by IRB/ IEC 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.

8.3 RECORDS

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

8.3.1 Source documents

In accordance with regulatory requirements, the investigator should prepare and maintain adequate and accurate source documents and trial records for each trial subject that include all observations and other data pertinent to the investigation. Source data as well as reported data should follow the 'ALCOA principles' and be attributable, legible, contemporaneous, original, and accurate. Changes to the data should be traceable (audit trail).

Data reported on the CRF must be consistent with the source data or the discrepancies must be explained.

Before providing any copy of subjects' source documents to the sponsor, the investigator must ensure that all subject identifiers (e.g., subject's name, initials, address, phone number, and social security number) have properly been removed or redacted to ensure subject confidentiality.

If the subject is not compliant with the protocol, any corrective action (e.g. re-training) must be documented in the subject file.

For the eCRF, data must be derived from source documents, for example:

- Subject identification: sex, year of birth (in accordance with local laws and regulations)
- Subject participation in the trial (substance, trial number, subject number, date subject was informed)
- Dates of subject's visits, including dispensing of trial medication
- Medical history (including trial indication and concomitant diseases, if applicable)
- Medication history

- AEs and outcome events (onset date [mandatory], and end date [if available])
- SAEs (onset date [mandatory], and end date [if available])
- Concomitant therapy (start date, changes)
- Originals or copies of laboratory results and other imaging or testing results, with proper documented medical evaluation (in validated electronic format, if available)
- ECG results (original or copies of printouts)
- Completion of subject's participation in the trial (end date; in case of premature discontinuation, document the reason for it, if known)
- Prior to allocation of a subject to a treatment into a clinical trial, there must be documented evidence in the source data (e.g. medical records) that the trial participant meets all inclusion criteria and does not meet any exclusion criteria. The absence of records (either medical records, verbal documented feedback of the subject or testing conducted specific for a protocol) to support inclusion/ exclusion criteria does not make the subject eligible for the clinical trial.

8.3.2 Direct access to source data and documents

The investigator/ institution will allow site trial-related monitoring, audits, IRB/ IEC review and regulatory inspections. Direct access must be provided to the CRF and all source documents/ data, including progress notes, copies of laboratory and medical test results, which must be available at all times for review by the Clinical Research Associate, auditor and regulatory inspector (e.g. FDA). They may review all CRFs and informed consents. The accuracy of the data will be verified by direct comparison with the source documents described in Section 8.3.1. The sponsor will also monitor compliance with the protocol and GCP.

8.3.3 Storage period of records

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

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 AND SUBJECT PRIVACY

Individual subject data obtained as a result of this trial is considered confidential and disclosure to third parties is prohibited with the exceptions noted in Section 8.7.

Data protection and data security measures are implemented for the collection, storage and processing of patient data in accordance with the principles 6 and 12 of the WHO GCP handbook.

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

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

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

- Sample and data usage has to be in accordance with the informed consent
- The BI-internal facilities storing biological samples from clinical trial participants as well as the external banking facility are qualified for the storage of biological samples collected in clinical trials
- An appropriate sample and data management system, incl. audit trail for clinical data and samples to identify and destroy such samples according to ICF is in place
- A fit for the purpose documentation (biomarker proposal, analysis plan and report) ensures compliant usage
- If applicable, a fit for purpose approach will be used for assay/ equipment validation depending on the intended use of the biomarker data

Samples and/ or data may be transferred to third parties and other countries as specified in the ICF

8.6 TRIAL MILESTONES

The **start of the trial** is defined as the date of the enrolment of the first subject in the trial.

The **end of the trial** is defined as the 'date of the last visit of the last subject in whole trial' ('Last Subject Completed') 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.

Early termination of the trial is defined as the premature termination of the trial for any reason before the end of the trial as specified in this protocol.

Temporary halt of the trial is defined as any unplanned interruption of the trial by the sponsor with the intention to resume it.

Suspension of the trial is defined as an interruption of the trial based on a Health Authority request.

The EC/ competent authority in each participating EU member state will be notified about the trial milestones according to the laws of each member state.

A final report of the clinical trial data will be written only after all subjects have completed the trial in all countries (EU or non-EU), so that all data can be incorporated and considered in the report.

8.7 ADMINISTRATIVE STRUCTURE OF THE TRIAL

The trial is sponsored by Boehringer Ingelheim (BI).

The trial will be conducted at [redacted] s, under the supervision of the Principal Investigator. Relevant documentation on the participating (Principal) Investigators (e.g. their curricula vitae) will be filed in the ISF.

BI has appointed a Trial Clinical Monitor, responsible for coordinating all required trial 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 clinical trial monitors (CTM), Clinical Research Associates, and investigators of participating trial sites.

The non-labelled trial medication will be provided by the [redacted]

The radiolabelled trial medication (intravenous and oral solution) will be provided by [redacted]

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

The analyses of unlabelled BI 1265162 concentrations in plasma will be performed at the Department of [redacted] or at a suitable contract research organisation.

The analyses of labelled BI 1265162 [redacted] will be conducted at [redacted]

Metabolic identification will be performed at the Department of [redacted]

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

Data management and statistical evaluation will be done by BI or a contract research organisation appointed by BI according to BI SOPs. Tasks and functions assigned in order to organise, manage, and evaluate the trial are defined according to BI SOPs. A list of responsible persons and relevant local information can be found in the ISF.

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10. APPENDICES

10.1 RADIO BURDEN CALCULATION

[redacted]

Radiation Burden Calculation Report [redacted]

Title (provisional):	A phase I, single center, open-label, non-randomized, non-placebo-controlled study to investigate the metabolism, excretion pattern, mass balance, safety, tolerability and pharmacokinetics of intravenously and orally administered BI 1265162 in healthy volunteers
Sponsor:	Boehringer Ingelheim
Protocol No:	1399-0013
[redacted] **Project Id:**	[redacted]
Version Date:	20 June 2019

■Calculation of Radiation Burden after intravenous administration

BI 1265162 is a small-molecule inhibitor of the epithelial sodium channel to be administered via oral inhalation. The target indications are cystic fibrosis and chronic obstructive pulmonary disease.
As a study using radiolabeled compounds administered via inhalation is technically challenging, this administration route is investigated by the combination of an intravenous and an oral administration in two parallel cohorts of volunteers, to characterize the absorption, metabolism and excretion of respectively the part deposited in and resorbed from the lungs, and the part which is deposited in the oral cavity and upper airways and ends up in the gastro-intestinal system.
Excretion and pharmacokinetic studies using BI 1265162 were conducted on rats[1,2], and quantitative tissue distribution studies on pigmented rats[3,4]. A radiation dose assessment was made based on these studies. In addition, data from studies in human volunteers[5] were taken into consideration.

The following assumptions, based on the data from these experiments, and taking the worst case scenario, were made to be able to estimate the effective radiation dose:

- After intravenous dosing, BI 1265162 and possible metabolites are considered to be distributed more or less homogeneously throughout the body, with the exception of higher exposure of uveal tract and in a lesser degree the liver, which are calculated separately.
- The major part of the administered amount of ^{14}C-radiolabeled BI 1265162 and possible metabolites show reasonably fast elimination from the body, mostly via fecal and for a smaller part via urinary excretion.
- Using the data of the BI 1265162 study in rats after intravenous and intratracheal administration a half-life of total ^{14}C-activity of 30 hours is estimated, with a half-life of the parent compound of 7.4 hours; in humans a terminal phase half-life of BI 1265162 of approximately 15.5 hours is assumed[5]. In the current estimation a half-life of total BI 1265162-derived radioactivity of 15.5 / 7.4 x 30 = 63 hours is used.
- The absorbed fraction is 1, as it is administered intravenously.
- Based on the excretion study in rats ^{14}C-radiolabeled BI 1265162 is found to be excreted both in feces and in urine. For the calculation is assumed: 85% of the intravenously administered radioactivity is excreted via the gastrointestinal tract in feces and 15% is excreted via the kidneys.

Based on these assumptions the estimated effective radiation burden after a single intravenous radioactivity dose of ^{14}C-radiolabeled BI 1265162 is approximately **0.05 mSv/MBq**.

As the radiolabeled dose which can be given intravenously is limited by the pharmacological dose (maximum dose planned 200 µg) and the specific activity (approximately 2.8 MBq/mg) the maximum possible label dose to be given intravenously in this study is 0.56 MBq. The estimated effective radiation burden of this dose is **0.028 mSv**.

For biomedical investigations in small groups of human volunteers an effective dose below 0.1 mSv is considered to be trivial[6].

[redacted]

Appendix A1: Radiation burden of the gastrointestinal tract after intravenous administration of 1.0 MBq ^{14}C BI 1265162

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 intravenous = 1.0 MBq; Excretion via GI tract: 85% of the dose, excretion via urine: 15% of the dose. These assumptions give:

H_{ST}, H_{IS}, H_{RC}, H_{LC} and H_{RS} are all 0.000 mSv.

total GI: = 0.0000 mSv

The total contribution of the GI tract to the effective dose (body radiation burden) amounts to 0.000 mSv.

Appendix A2: Radiation burden of the central compartment after intravenous administration of 1.0 MBq ^{14}C BI 1265162

Average body weight = 70 kg; SEE = 7.1905 x 10-7; 100% of the dose administered intravenously and excreted with a half-life of 63 hours. Total number of disintegrations in the central compartment after intravenous dosing is 268 x 10^9 with a tissue weighting factor of 0.95 (1 minus the weighting factors for the liver and uveal tract) giving a H_{tw} of 0.0285 mSv.

Appendix A3: Radiation burden of the uveal tract and the liver after intravenous administration of 1.0 MBq ^{14}C BI 1265162

For the liver SEE = 2.72 x 10-5; 17.2% of the dose administered iv excreted from the liver with a half-life of 9 hours with a weighting factor of 0.04 giving a contribution to the radiation burden of 0.0014 mSv.

For the uveal tract SEE = 0.884477; 0.004% of the dose administered iv excreted from this tissue with a half-life of 840 hours with a weighting factor of 0.01 giving a contribution to the radiation burden of 0.0245 mSv.

The contribution to the radiation burden for these two organs/tissues is 0.0259 mSv

The total effective dose (radiation burden), based on the above-mentioned worst case scenario for intravenous administration of 1.0 MBq ^{14}C-labeled BI 1265162 amounts to 0.0285 + 0.0259 = 0.05 mSv.

[redacted]

[redacted]

■Calculation of Radiation Burden after oral administration

The planned dose range for oral dosing is from 1.25 to 5 mg. With a specific activity of approximately 2.8 MBq/mg a dose of 3.7 MBq would probably be feasible.
This radiation burden consists of the contribution from the gastro-intestinal tract plus the contribution to the rest of the body caused by the systemically absorbed fraction after oral dosing.

For the contribution of the whole body plus the liver and uveal tract after oral dosing the contribution to the radiation burden of these systems after intravenous administration is used, corrected for the estimated absorption from the gastro-intestinal system, and multiplied by the dose of radioactivity.
The highest absorption after oral administration has been seen in a study in rats 7.6% of the dose (dogs: 7% of the dose). F= 0.076.

Appendix A4: Radiation burden of the gastrointestinal tract after oral administration of 3.7 MBq ^{14}C BI 1265162

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 orally = 3.7 MBq; systemic absorption = 7.6%; excretion via GI tract: 99% of the dose (92.4% unabsorbed fraction plus 0.85 x 7.6%); excretion via urine: 1% of the dose. These assumptions give:

H_{ST} = 0.0030; H_{SI}, H_{RC}, H_{LC} and H_{RS} are all 0.000 mSv.

total GI: = 0.0030 mSv

The total contribution of the GI tract to the effective dose (body radiation burden) amounts to 0.0030 mSv.

The contribution of the whole body and the liver and uveal tract is 3.7 MBq x 0.05 mSv/MBq x 0.076 = 0.014 mSv.

The total effective dose (radiation burden), based on the above-mentioned worst case scenario for oral administration of 3.7 MBq ^{14}C-labeled BI 1265162 amounts to 0.014 + 0.0030 = 0.017 mSv.

For biomedical investigations in small groups of human volunteers an effective dose below 0.1 mSv is considered to be trivial[6].

[redacted]

[redacted]

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5.: Investigator's brochure Version 3.0, dated 25 February 2019.

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Name: [redacted]	Signature: [redacted] Signed by: [redacted] Reason: I am the author of this document Date & Time: 20 Jun 2019 04:56 PM +02:00 DocuSign

[redacted]

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

11.1 GLOBAL AMENDMENT 1

Date of amendment		10 Feb 2020
EudraCT number **EU number**		2019-003389-42
BI Trial number		1399-0013
BI Investigational Medicinal Product(s)		BI 1265162
Title of protocol		Investigation of metabolism and pharmacokinetics of BI 1265162 (C-14) after intravenous administration (Part 1) and investigation of metabolism and pharmacokinetics of BI 1265162 (C-14) after oral administration (Part 2) in healthy male subjects following a non-randomized, open-label, single-dose, single arm per trial part mass balance design

To be implemented only after approval of the IRB / IEC / Competent Authorities	☐
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval	☐
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only	☒

Section to be changed		Synopsis Flow Chart 1 and foot note 9 Flow Chart 2 and foot note 10 Section 1.2.5 Section 2.2.2.3 Section 3.3.3 Section 5.2.3, Table 5.2.3: 1 Section 5.3.2.1 Section 5.3.2.2
Description of change		Correction of typographical and factual errors as well as inconsistencies
Rationale for change		Correction of typographical and factual errors as well as inconsistencies

11.2 GLOBAL AMENDMENT 2

Date of amendment		25 February 2020
EudraCT number **EU number**		2019-003389-42
BI Trial number		1399-0013
BI Investigational Medicinal Product(s)		BI 1265162
Title of protocol		Investigation of metabolism and pharmacokinetics of BI 1265162 (C-14) after intravenous administration (Part 1) and investigation of metabolism and pharmacokinetics of BI 1265162 (C-14) after oral administration (Part 2) in healthy male subjects following a non-randomized, open-label, single-dose, single arm per trial part mass balance design

To be implemented only after approval of the IRB / IEC / Competent Authorities	☐
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval	☐
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only	☒

Section to be changed		Flow Chart 1 Flow Chart 2 Section 5.3.2 Section 5.3.3 Section 5.6.1
Description of change		Logistical updates regarding PK, total radioactivity and metabolic samples. Typological correction in Flow Chart 2: Safety Lab Panel B, ECG and vital signs moved from day 30 to day 37 (identically to Flow Chart 1).
Rationale for change		Logistical reasons as well as typological and stylistic corrections.

APPROVAL / SIGNATURE PAGE

Document Number: c29266057 **Technical Version Number:3.0**

Document Name: clinical-trial-protocol-version-03

Title: Investigation of metabolism and pharmacokinetics of BI 1265162 (C-14) after intravenous administration (Part 1) and investigation of metabolism and pharmacokinetics of BI 1265162 (C-14) after oral administration (Part 2) in healthy male subjects following a non-randomized, open-label, single-dose, single arm per trial part mass balance design

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Author-Trial Clinical Pharmacokineticist	[redacted]	26 Feb 2020 09:39 CET
Author-Trial Statistician		26 Feb 2020 10:16 CET
Author-Clinical Trial Leader		26 Feb 2020 14:58 CET
Approval-Therapeutic Area Head		27 Feb 2020 11:43 CET
Verification-Paper Signature Completion		27 Feb 2020 14:31 CET
Approval-Team Member Medicine		27 Feb 2020 22:27 CET

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed