Clinical Trial Protocol

	Document Number:	**c25000855-04**
EudraCT No.	2018-002689-38	
BI Trial No.	1399-0014	
BI Investigational Medicinal Product	BI 1265162	
Title	Absolute bioavailability of BI 1265162 following oral and inhaled administration in healthy male volunteers (an open-label, randomised, single-dose, three-period, three-sequence crossover study followed by a fixed treatment)	
Lay Title	A study in healthy men that tests if taking BI 1265162 by mouth, intravenously, or inhaled influences the amount of BI 1265162 in the blood	
Clinical Phase	I	
Trial Clinical Leader	Phone: Fax:	
Principal Investigator	Phone: Fax:	
Status	Final Protocol (Revised Protocol (based on global amendment 3))	
Version and Date	Version: 4.0	Date: 20 August 2019

CLINICAL TRIAL PROTOCOL SYNOPSIS

Company name	Boehringer Ingelheim
Protocol date	30 Jan 2019
Revision date	20 Aug 2019
BI trial number	1399-0014
Title of trial	Absolute bioavailability of BI 1265162 following oral and inhaled administration in healthy male volunteers (an open-label, randomised, single-dose, three-period, three-sequence crossover study followed by a fixed treatment)
Principal Investigator:	
Trial site	
Clinical phase	I
Trial rationale	This study will generate pharmacokinetic information on the absolute bioavailability following inhaled (with and without charcoal) and oral dosing versus intravenous infusion to support the planned human ADME trial and future development of BI 1265162 in patients.
Trial objective	To investigate the absolute bioavailability of BI 1265162 following oral and inhaled (with and without charcoal) administration
Trial design	Randomised, open-label, three-way crossover followed by a fixed treatment design
Trial endpoints:	Primary endpoints: $AUC_{0-\infty}$ of BI 1265162
Number of subjects **total entered** **each treatment**	 12 12
Diagnosis	Not applicable
Main criteria for inclusion	Healthy male subjects, age of 18 to 50 years (inclusive), body mass index (BMI) of 18.5 to 29.9 kg/m^2 (inclusive)
Test product 1 **dose** **mode of admin.**	Drug formulation BI 1265162 oral solution *Doses are tentative and may be adapted after first period (cf. 7.4) Oral with 240 mL of water after an overnight fast of at least 8 h (T1)

Test product 2	Drug formulation BI 1265162 solution for inhalation
dose	
mode of admin.	Inhaled by Respimat after an overnight fast of at least 8 h in combination with activated charcoal (T2) and without activated charcoal (T3).
Reference product	Drug formulation (R) BI 1265162 concentrate for infusion
dose	* Doses are tentative and may be adapted after first period (cf. 7.4)
mode of admin.	Intravenous over 1h after an overnight fast of at least 8 h
Duration of treatment	One day (single dose) for each treatment with a wash out period of at least 6 days between each treatment period
Statistical methods	Absolute bioavailability (F) will be estimated by the ratios of the geometric means (Ti/R, i=1,2, 3) for the dose-normalized primary endpoint following oral and inhaled administrations. Additionally, their two-sided 90% confidence intervals (CIs) will be provided. This method corresponds to the two one-sided t-test procedure, each at a 5% significance level. Since the main focus is on estimation and not testing, a formal hypothesis test and associated acceptance range is not specified. The statistical model will be an analysis of variance (ANOVA) on the logarithmic scale including effects for sequence, subjects nested within sequences, period and treatment. CIs will be calculated based on the residual error from the ANOVA. Descriptive statistics will be calculated for all endpoints.

FLOW CHART – ORAL ADMINISTRATION (T1)

Period	Visit	Day	Planned time (relative to drug administration) [h:min]	Approximate clock time of actual day [h:min]	Event and comment	PK/Metabolites $_{blood}$	Safety laboratory	12-lead ECG	Vital signs (BP, PR)	Questioning for AEs and concomitant therapy [6]
SCR	1	-21 to -1			Screening (SCR)[1]		x	x	x	
1/2/3/4 (four periods separated by a wash-out of at least 6 days)	2/3/4	-1	-12:00	20:00	Admission to trial site (Device training if needed)		x[5]			x
		1	-1:00	07:00	Allocation to treatment[2] (visit 2 only) (Device training if needed)	x[2]	x[2]	x[2]	x[2]	x[2]
			0:00	08:00	BI 1265162 administration + 240 mL fluid intake					
			0:30	08:30		x				
			0:45	08:45		x				
			1:00	09:00		x				
			2:00	10:00	240 mL fluid intake	x	x[7]	x	x	x
			3:00	11:00		x				
			4:00	12:00	240 mL fluid intake, thereafter lunch[3]	x				
			6:00	14:00		x				
			8:00	16:00	Snack (voluntary)[3]	x				
			11:00	19:00	Dinner					
			12:00	20:00		x				x
		2	24:00	08:00	Breakfast (voluntary)[3], discharge from trial site	x	x	x	x	x
FU	6	3 to 7			End of trial (EOS) examination[4]		x	x	x	x

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. Pharmacogenetic samples will be collected if needed.
2. The time is approximate; the procedure is to be performed and completed within the 3 h prior to drug administration.
3. If several actions are indicated at the same time, the intake of meals will be the last action.
4. At the end of trial visit the End of trial (EoTrial) examination includes physical examination, vital signs, ECG, safety laboratory, recording of AEs and concomitant therapies.
5. Only urine drug screening and alcohol breath test will be done at this time
6. AEs and concomitant therapies will be recorded throughout the trial, but will be specifically asked for at the times indicated in the Flow Chart above.
7. Serum electrolytes only

FLOW CHART – INHALED ADMINISTRATION (T2 AND T3)

Period	Visit	Day	Planned time (relative to drug administration) [h:min]	Approximate clock time of actual day [h:min]	Event and comment	PK/Metabolites blood	Safety laboratory	12-lead ECG	Vital signs (BP, PR)	Questioning for AEs and concomitant therapy [6]
SCR	1	-21 to -1			Screening (SCR)[1]		x	x	x	
1/2/3/4 (four periods separated by a wash-out of at least 6 days)	2/3/4/5*	-1	-12:00	20:00	Admission to trial site (Device training if needed)		x[5]			x
		1	-1:00	07:00	Allocation to treatment[2] (visit 2 only) (Device training if needed)	x[2]	x[2]	x[2]	x[2]	x[2]
			-0:15	07:45	Active charcoal administration (T2 only)					
			0:00	08:00	BI 1265162 administration					
			0:02	08:02		x				
			0:03	08:03	Active charcoal administration (T2 only)					
			0:05	08:05		x				
			0:10	08:10		x				
			0:15	08:15		x				
			0:40	08:40		x				
			1:00	09:00		x				
			1:05	09:05	Active charcoal administration (T2 only)					
			2:00	10:00	240 mL fluid intake	x	x[7]	x	x	x
			4:00	12:00	240 mL fluid intake, thereafter lunch[3]	x				
			8:00	16:00	Snack (voluntary)[3]	x				
			10:00	18:00		x				
			11:00	19:00	Dinner					
			12:00	20:00		x				x
		2	24:00	08:00	Breakfast (voluntary)[3], discharge from trial site	x	x	x	x	x
FU	6	3 to 7			End of trial (EOS) examination[4]		x	x	x	x

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. Pharmacogenetic samples will be collected if needed.
2. The time is approximate; the procedure is to be performed and completed within the 3 h prior to drug administration.
3. If several actions are indicated at the same time, the intake of meals will be the last action.
4. At the end of trial visit the EoTrial examination includes physical examination, vital signs, ECG, safety laboratory, recording of AEs and concomitant therapies.
5. Only urine drug screening and alcohol breath test will be done at this time
6. AEs and concomitant therapies will be recorded throughout the trial, but will be specifically asked for at the times indicated in the Flow Chart above.
7. Serum electrolytes only

* At Visit 5/period 4 all subjects receive treatment T3

FLOW CHART – INTRAVENOUS ADMINISTRATION (R)

Period	Visit	Day	Planned time (relative to drug administration) [h:min]	Approximate clock time of actual day [h:min]	Event and comment	Intravenous admin.	PK/Metabolites blood	Safety laboratory	12-lead ECG	Vital signs (BP, PR)	Questioning for AEs and concomitant therapy [6]
SCR	1	-21 to -1			Screening (SCR)[1]			x	x	x	
1/2/3/4 (four periods separated by a wash-out of at least 6 days)	2/3/4	-1	-12:00	20:00	Admission to trial site (Device training if needed)			x[5]			x
		1	-1:00	07:00	Allocation to treatment[2] (visit 2 only) (Device training if needed)		x[2]	x[2]	x[2]	x[2]	x[2]
			0:00	08:00	Start of BI 1265162 administration + 240 mL fluid intake	▲					
			0:05	08:05			x				
			0:30	08:30			x				
			0:59	08:59			x				
			1:00	09:00		▼			x	x	
			1:05	09:05			x				
			1:10	09:10			x				
			1:20	09:20			x				
			1:40	09:40			x				
			2:00	10:00	240 mL fluid intake		x	x[7]	x	x	x[8]
			2:30	10:30			x				
			3:00	11:00			x				
			3:30	11:30			x				
			4:00	12:00	240 mL fluid intake, thereafter lunch[3]		x				
			5:00	13:00			x				
			7:00	15:00			x				
			8:00	16:00	Snack (voluntary)						
			9:00	17:00			x				
			11:00	19:00	Dinner[3]		x				
			13:00	21:00			x				x
		2	24:00	08:00	Breakfast (voluntary)[3], discharge from trial site		x	x	x	x	x[8]
FU	6	3 to 7			End of trial (EOS) examination[4]			x	x	x	x

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. Pharmacogenetic samples will be collected if needed.
2. The time is approximate; the procedure is to be performed and completed within the 3 h prior to drug administration.
3. If several actions are indicated at the same time, the intake of meals will be the last action.
4. At the end of trial visit the EoTrial examination includes physical examination, vital signs, ECG, safety laboratory, recording of AEs and concomitant therapies.
5. Only urine drug screening and alcohol breath test will be done at this time
6. AEs and concomitant therapies will be recorded throughout the trial, but will be specifically asked for at the times indicated in the Flow Chart above.
7. Serum electrolytes only
8. Includes assessment of local tolerability

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ABBREVIATIONS

ADME	Absorption, distribution, metabolism, and excretion
AE	Adverse event
AESI	Adverse events of special interest
ANOVA	Analysis of variance
$AUC_{0-\infty}$	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity
$\%AUC_{tz-\infty}$	Percentage of $AUC_{0-\infty}$ obtained by extrapolation
AUC_{t1-t2}	Area under the concentration-time curve of the analyte in plasma over the time interval t_1 to t_2
AUC_{0-tz}	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 to the last quantifiable data point
BA	Bioavailability
BI	Boehringer Ingelheim
BID	Three times daily
BMI	Body mass index (weight divided by height squared)
BP	Blood pressure
CA	Competent authority
CI	Confidence interval
CL	Total clearance of the analyte in plasma after intravascular administration
CL/F	Apparent clearance of the analyte in plasma after extravascular administration
C_{max}	Maximum measured concentration of the analyte in plasma
CML	Clinical Monitor Local
CRF	Case Report Form, paper or electronic (sometimes referred to as ‘eCRF’)
CTP	Clinical trial protocol
CTR	Clinical trial report
CV	Arithmetic coefficient of variation
DILI	Drug induced liver injury
ECG	Electrocardiogram
eCRF	Electronic case report form
eDC	Electronic data capture
EDTA	Ethylenediaminetetraacetic acid
EoTrial (EOS)	End of trial
EudraCT	European Clinical Trials Database
F	Absolute bioavailability factor
FU	Follow-up

GCP	Good Clinical Practice
gCV	Geometric coefficient of variation
GI	Gastro-intestinal
gMean	Geometric mean
HPC	Human Pharmacology Centre
HR	Heart rate
IB	Investigator's brochure
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ISF	Investigator site file
IV	Intravenous
λ_z	Terminal rate constant of the analyte in plasma
LC-MS/MS	Liquid chromatography with tandem mass spectrometry
MDA	Methylenedioxyamphetamine
MDMA	Methylenedioxymethamphetamine
MedDRA	Medical Dictionary for Regulatory Activities
$MRT_{,in(ex)}$	Mean residence time of the analyte in the body after intravascular (extravascular) administration
PD	Pharmacodynamic(s)
PE	Polyethylene
PK	Pharmacokinetic(s)
PKS	Pharmacokinetic set
PP	Polypropylene
PR	Pulse rate
QD	Twice daily
QT	Time between start of the Q-wave and the end of the T-wave in an electrocardiogram
QTc	QT interval corrected for heart rate using the method of Fridericia (QTcF) or Bazett (QTcB)
R	Reference treatment
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
$t_{\lambda z,start(end)}$	Lower (upper) limit on time for values to be included in the calculation of λ_z

$t_{1/2}$	Terminal half-life of the analyte in plasma
t_{max}	Time from (last) dosing to the maximum measured concentration of the analyte in plasma
TS	Treated set
t_z	Time of last measurable concentration of the analyte in plasma
TSAP	Trial statistical analysis plan
ULN	Upper limit of normal
V_{ss}	Apparent volume of distribution at steady state after intravascular administration
V_z	Apparent volume of distribution during the terminal phase after intravascular administration
V_z/F	Apparent volume of distribution during the terminal phase after extravascular administration
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 are the cornerstone of pharmacotherapy [P13-14084], and more recently therapies targeting the CFTR [R17-1997]. Lung transplantation is also used. 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 periciliary 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 anti-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 the 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 not 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 are expected to translate into clinical efficacy.
ENaC is also located on the apical side of the epithelial layer in the kidney and the colon as well as being expressed in the brain, eye, vascular endothelial, and smooth muscle cells and in the tongue. Inhibition of ENaC in the kidney leads to reduced absorption of sodium with a concomitant reduction in potassium excretion from/ into the urine. As demonstrated by the reference oral compound amiloride, increases in serum potassium or reduction in serum sodium/ chloride may be expected based on mechanism in case of excessive systemic exposure. This is not expected with therapeutic inhalational administration of BI 1265162. Based on preclinical in vitro and in vivo models, BI 1265162 administered by the inhalational route may be beneficial.

2. TRIAL OBJECTIVES AND ENDPOINTS

2.1 MAIN OBJECTIVES, PRIMARY AND SECONDARY ENDPOINTS

2.1.1 Main objectives

The main objective of this trial is to investigate the absolute bioavailability of BI 1265162 following administration of oral solution and inhaled (with and without charcoal) via Respimat.

2.1.2 Primary endpoint

The following pharmacokinetic parameter will be determined for BI 1265162:

- $AUC_{0-\infty}$ (area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity)

2.1.3 Secondary endpoint

Not applicable.

Safety and tolerability of BI 1265162 will be assessed based on:

- Adverse events (including clinically relevant findings from the physical examination)

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

The study will be performed as a randomised, open-label, three-way crossover trial followed by a fixed treatment in healthy male subjects in order to compare BI 1265162 given as oral solution (T1) and inhaled via Respimat with activated charcoal(T2) and without activated charcoal (T3) compared to BI 1265162 given intravenous (Reference, R). The subjects will be randomly allocated to one of the treatment sequences (T1-T2-R-T3 or R-T1-T2-T3 or T2-R-T1-T3). For details, refer to Section 4.1.

For logistical reasons, subjects may receive the treatments on Day 1 e.g. first all subjects with oral, followed by all subjects with inhaled and last all subjects with intravenous administration. All 12 subjects will be dosed on Day 1 in a staggered fashion, e.g. 10 min in between intravenous administration. From a safety perspective it is acceptable to treat all subjects on the same calendar day: Low doses BI 1265162 have been selected to ensure that, even in case of a higher bioavailability of the planned oral dose, the expected plasma concentrations of BI 1265162 are in the range of plasma concentrations observed in First-in-Man trial 1399-0001. In that previous trial, all single doses of BI 1265162, up to 1200µg inhaled, were safe and well tolerated. No safety concerns were identified.

The doses for intravenous and/or oral administration might be adapted for PK purposes after the first treatment period (see Section 7.4). In case this is needed, this will be implemented via a non-substantial amendment.

There will be a washout period of at least 6 days between the treatments, i.e. the dose in the previous treatment period and the dose in the current treatment period are separated by at least 6 days.

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

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

For this absolute bioavailability trial, the crossover design is required as the assessment is within a subject.

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

3.3 SELECTION OF TRIAL POPULATION

It is planned that 12 healthy male subjects will enter the study. They will be recruited from the volunteers' pool of the trial site.

Only male subjects will be included in the study because no data on reproductive toxicology are available at this time.

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 study will be performed in healthy 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
2. Age of 18 to 50 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 study, in accordance with GCP and local legislation

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 140 mmHg, diastolic blood pressure outside the range of 50 to 90 mmHg, or pulse rate outside the range of 45 to 90 bpm
3. Any laboratory value outside the reference range that the investigator considers to be of clinical relevance
4. Any evidence of a concomitant disease assessed as clinically relevant by the investigator
5. 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. Smoker (more than 10 cigarettes or 3 cigars or 3 pipes per day)
14. Inability to refrain from smoking on specified trial days
15. Alcohol abuse (consumption of more than 30 g per day)
16. Drug abuse or positive drug screening
17. Blood donation of more than 100 mL within 30 days of planned administration of trial medication or intended blood donation during the trial
18. Intention to perform excessive physical activities within one week prior to the administration of trial medication or during the trial
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 study requirements, or has a condition that would not allow safe participation in the study

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

23. The subject has a diagnosis history of pulmonary hyperreactivity
24. A history of chronic kidney disease
25. Cannot use Respimat® appropriately

For study restrictions, refer to 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; please 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, 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 Discontinuation of trial treatment

An individual subject will discontinue trial treatment if:
The subject wants to discontinue trial treatment, without the need to justify the decision
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.
The subject needs to take concomitant medication that interferes with the investigational medicinal product or other trial treatment
The subject can no longer receive trial treatment for medical reasons (such as surgery, adverse events [AEs], or diseases)
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/her 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, please see Section 3.3.4.1 above.

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:

Failure to meet expected enrolment goals overall or at a particular trial site

New toxicological findings, serious adverse events, or any safety information invalidating the earlier positive benefit-risk-assessment. More specifically, the trial will be terminated if more than 50% of the subjects have drug-related and clinically relevant adverse events of moderate or severe intensity, or if at least 1 drug-related serious adverse event is reported

Violation of GCP, or the CTP impairing the appropriate conduct of the trial-

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

3.3.5 Replacement of subjects

In case subjects 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 sequence as the subject he replaces.

4. TREATMENTS

4.1 INVESTIGATIONAL TREATMENTS

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

4.1.1 Identity of the Investigational Medicinal Products

4.1.2 Method of assigning subjects to treatment groups

The randomisation list will be provided to the trial site in advance.

Subjects will be allocated to treatment sequences prior to the first administration of trial medication in the morning of Day 1 (Visit 2). For this purpose, numbers of the randomisation list will be allocated to the subjects by drawing lots. Subjects are then assigned to a treatment sequence according to the randomisation list.

Once a randomisation number has been assigned, it cannot be reassigned to any other subject. The randomisation procedure is described in Section 7.6.

4.1.3 Drug assignment and administration of doses for each subject

This trial is a 3-way crossover study. All subjects will receive the 3 treatments in randomised order. The treatments to be evaluated are outlined in Table 4.1.4: 1 below.

Table 4.1.4: 1 Dosage and treatment schedule

*At the time points given in the flow chart, 10 g activated charcoal will be taken by the respective subjects to avoid possible gastrointestinal absorption of BI 1265162

** Doses are tentative and may be adapted after first period (cf. 7.4)

Administration of all trial medications will be performed after subjects have fasted overnight; fasting is to start no later than 8 h before the scheduled dosing / start of infusion.

The oral medication will be administered as a single dose together with about 240 mL of water to a subject in the sitting or standing position under supervision of the investigating physician or an authorised designee.

During the first 4 h after oral drug administration, they are not allowed to lie down (i.e. no declination of the upper body of more than 45 degrees from upright posture).

The intravenous medication will be administered as a continuous intravenous infusion over 60 minutes under supervision of the investigating physician or an authorised designee. Start and end time of the infusion will be recorded. Subjects will receive 240 mL of water upon start of infusion.

The inhaled medication will be administered with the RESPIMAT in a sitting or standing position under supervision of the investigating physician or an authorised designee. Planned time 0:00h will always be the first actuation. To avoid any contamination (e.g PK tubes), administration of trial medication should be performed in a separate room; subject and staff should wear e.g. gloves and protective wear. Subjects will receive some water after the 2nd actuation to rinse the mouth.

For all drug administrations, 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 – not applicable for assembling of RESPIMAT), if correct dosage cannot be ensured otherwise.

Subjects will be kept under close medical surveillance until 24 h after drug administration.

The treatments will be separated by a wash-out phase of at least 6 days.

4.1.4 Blinding and procedures for unblinding

This open-label Phase I trial will be handled in an open fashion throughout (that is, during the conduct, including data cleaning and preparation of the analysis).

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

4.1.5 Packaging, labelling, and re-supply

The investigational medicinal products will be provided by BI. They will be packaged and labelled in accordance with local law and the principles of Good Manufacturing Practice.

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.

4.1.6 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.

4.1.7 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
- 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 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 Clinical Trial Leader. 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 study days) on the appropriate pages of the CRF.

4.2.2.2 Restrictions on diet and life style

While admitted to the trial site, the 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 h after drug intake / start of infusion.

From 1 h before drug intake until lunch, fluid intake is restricted to the water administered with the drug (for intravenous treatment after start of infusion), and an additional 240 mL of water at 2 h and 4 h post-dose / start of infusion. From lunch until 24 h post-dose, subjects should be instructed not to exceed a total fluid intake of 3000 mL.

Grapefruits, Seville oranges (sour or bitter oranges) and their juices, and dietary supplements and products including St. John's wort (Hypericum perforatum) are not permitted starting 7 days before the first administration of trial medication until 24 h after last administration of trial medication.

Alcoholic beverages, consumption of seafood and dried fruits are not permitted from 48 hours before each study drug administration and until 24 h 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 10 h before until 24 h after administration of trial medication.

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

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

4.3 TREATMENT COMPLIANCE

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

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 (Dinamap Pro 100,) at the times indicated in the Flow Chart, after subjects have rested for at least 5 min in a supine position. All recordings should be made using the same type of blood pressure recording instrument on the same arm, if possible.

5.2.3 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 10 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. PK 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.

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
Manual differential WBC (if automatic differential WBC is abnormal)	Neut. Poly (segs); Neut. Poly (segs), absol.; Neutrophils Bands; Neutrophils Bands, absol.; Eosinophils/Leukocytes; Eosinophils, absol.; Basophils/ Leukocytes; Basophils, absol.; Monocytes/ Leukocytes; Monocytes, absol.; Lymphocytes/Leukocytes; Lymphocytes, absol.		
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[3]	X	X
	Bilirubin, Total	X	X
	Bilirubin, Direct	X	X
	Protein, Total	X	X
	C-Reactive Protein (Quant)	X	X
Serum Electrolytes[2]	Sodium	X	X
	Potassium	X	X
	Chloride	X	X
	Calcium	X	X
Urinalysis[1] (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[1] (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: parameters to be determined at Visit 1 (screening examination)
B: parameters to be determined at Visit 2,3,4,5 and Visit 6 (end of trial examination) (for time points refer to Flow Chart)

1 if erythrocytes, leukocytes nitrite or protein are abnormal in urinalysis

2 Sample tubes will be centrifuged for about 8 minutes at about 4000 g and stored at room temperature until shipment to the clinical lab.
3 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 restrictions, a breath alcohol test (e.g. Alcotest® 7410,) will be performed prior to each treatment, and may be repeated at any time during the study at the discretion of an investigator or designee. The results will not be included in the CTR

The laboratory tests listed in Tables 5.2.3: 1 and 5.2.3: 2 will be performed at , with the exception of drug screening tests. These tests will be performed at the trial site using Drogenschnelltest Multidrogen-Pipettiertest M-10/14-PDT, or comparable test systems.

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

5.2.4 Electrocardiogram

Twelve-lead ECGs (I, II, III, aVR, aVL, aVF, V1 - V6) will be recorded using a computerised electrocardiograph (CardioSoft EKG System,) 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 sec duration after subjects have rested for at least 5 min in a supine position. ECG assessment will always precede all other study procedures scheduled for the same time to avoid compromising ECG quality.

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

All locally printed ECGs will be evaluated by the investigator or a designee. 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 assessment. 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 iv administration, local tolerability will be assessed by the investigator on the basis of swelling, induration, heat, redness, pain, and other findings at the times provided in the Flow Chart.

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 subject 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 subject 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, please see Section 5.2.6.2.2.
The following are considered as AESIs:

- Hepatic injury

A hepatic injury is defined by the following alterations of hepatic laboratory parameters:

- o 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
- o Aminotransferase (ALT, and/or AST) elevations ≥10 fold ULN

These lab findings constitute a hepatic injury alert and the subjects showing these lab abnormalities need to be followed up according to the 'DILI checklist' provided in the 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 volunteers, when subjects discontinue from the trial due to screening failures prior to administration of any trial medication. In these cases, the subjects' data must be collected at trial site but will not be entered in the CRF or trial database and will not be reported in the CTR.
- After the individual subject's end of trial:

- The investigator does not need to actively monitor the subject for AEs but should only report 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 via fax immediately (within 24 hours) to the sponsor's unique entry point (country specific contact details will be provided in the ISF). The same timeline applies if follow-up information becomes available. In specific occasions the Investigator could inform the sponsor upfront via telephone. This does not replace the requirement to complete and fax the BI SAE form.

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

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.

5.3 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

5.3.1 Assessment of pharmacokinetics

For the assessment of pharmacokinetics, blood samples will be collected at the time points indicated in the Flow Chart. The actual sampling times will be recorded and used for determination of pharmacokinetic parameters. PK sampling times may be adapted during the trial based on information obtained during trial conduct (e.g. exploratory PK 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 Blood sampling for pharmacokinetic analysis

For quantification of analyte concentrations in plasma, 2.7 mL of blood will be drawn from an antecubital or forearm vein into an K_2-EDTA (dipotassium ethylenediaminetetraacetic acid)-anticoagulant blood drawing tube at the times indicated in the Flow Chart. Blood will be withdrawn by means of either an indwelling venous catheter or by venepuncture with a metal needle.

The EDTA-anticoagulated blood samples will be centrifuged for approximately 10 min at approximately 2000 g to 4000 g and at 4 to 8 °C. Two plasma aliquots will be obtained and

stored in polypropylene tubes. The first aliquot should contain at least 0.7 mL of plasma. The process from blood collection until transfer of plasma aliquots into the freezer should be completed in less than 90 min. The time each aliquot was placed in the freezer will be documented. Until transfer on dry ice to the analytical laboratory, the aliquots will be stored upright at approximately -20°C or below at the trial site. The second aliquot will be transferred to the analytical laboratory after the bioanalyst has acknowledged safe arrival of the first aliquot. At the analytical laboratory, the plasma samples will be stored at approximately -20°C or below until analysis.

At a minimum, the sample tube labels should list BI trial number, subject number, visit, and planned sampling time.

5.3.2.2 Plasma sampling for metabolism analysis

Additional K_3-EDTA plasma samples for the identification of drug metabolites will be investigated.

The blood samples will be drawn in parallel to PK samples (see Flow Chart). At each of these time points specified in Flow Chart, 4.9 mL blood will be needed for metabolite analysis. The blood samples will be processed in the same way as the PK samples described in Section 5.3.2.1 However, obtained plasma (approximately 2 mL) will be transferred into a single polypropylene tube. Samples should be stored from blood collection until transfer of plasma aliquots in ice water or on ice. Samples will be stored at about -20°C or below until transfer to the metabolism laboratory.

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

Plasma samples dedicated to metabolism investigation can be transferred together with the PK samples to (but packed separately):

These plasma samples may be used for further methodological investigations (e.g. for stability testing or assessment of metabolites. However, only data related to the analyte and/or its metabolite(s) will be generated by these additional investigations. The investigation results will not be reported as part of this study. The study samples will be discarded after completion of the additional investigations but not later than 5 years after the CTR is archived.

5.3.3 Analytical determinations

5.3.3.1 Analytical determination of analyte plasma concentration

BI 1265162 concentrations in plasma will be determined by a validated LC-MS/MS (liquid chromatography tandem mass spectrometry) assay. The analysis will be performed at

All details of the analytical method will be available prior to the start of sample analysis.

5.3.4 Pharmacokinetic - pharmacodynamic relationship

Not applicable.

5.4 ASSESSMENT OF BIOMARKER(S)

Not applicable.

5.5 BIOBANKING

Not applicable.

5.6 OTHER ASSESSMENTS

5.6.1 Pharmacogenomic evaluation

Pharmacogenomic investigations explore the role of genetic variation in determining an individual's response to drugs. For this purpose, a sample of at most 10 mL of blood will be obtained at the screening examination from each subject whose genotype has not been previously determined. Separate informed consent for genotyping will be obtained from each volunteer prior to sampling.

DNA will be extracted from the blood sample in order to sequence genes coding for proteins that are involved in the absorption, distribution, metabolism, and excretion (ADME) of drugs. The gene sequences to be determined include known and likely functional variations of key ADME genes and incorporate more than 90% of ADME-related genetic markers identified by the PharmaADME group (weblink.pharmaadme.org). It is not intended to include the pharmacogenomic data in the CTR. However, the data may be part of the CTR, if necessary.

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 orally, IV or inhaled 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.

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.

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

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

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

For planned blood sampling times, refer to the Flow Chart. While these nominal times should be adhered to as closely as possible, the actual sampling times will be recorded and used for 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 study.

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

Genotyping will be performed in those volunteers whose genotypes have not been previously determined (for details, see Section 5.3).

6.2.2 Treatment period

Each subject is expected to participate in 4 treatment periods (Days -1, 1 and 2 in each period). At least 6 days will separate drug administrations in the first, second, third and fourth treatment periods.

On Day -1 of each treatment period, study participants will be admitted to the trial site and kept under close medical surveillance for at least 24 h following drug administration/start of infusion. The subjects will then be allowed to leave the trial site after formal assessment and confirmation of their fitness.

For details on time points and procedures for collection of plasma samples for PK analysis, refer to Flow Chart and Section 5.3.2.

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

6.2.3 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 Section 5.2.
Subjects who discontinue treatment before the end of the planned treatment period should undergo the EoTrial 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 EoTrial 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 absolute bioavailability (F) of BI 1265162 following oral administration (T1) and inhalation with activated charcoal (T2) and without charcoal (T3) on the basis of the primary pharmacokinetic endpoint, as listed in Section 2.1.2. Therefore the primary endpoint obtained after T1,T2 and T3 will be compared to the primary endpoint obtained after intravenous administration of BI 1265162 (R). For details regarding treatments R, T1, T2 and T3 see Section 4.1.1. The trial is designed to allow intra-subject comparisons and will be evaluated statistically by use of a linear model for logarithmically transformed PK endpoint.

Further objectives include the evaluation of the proportion of the absolute bioavailability of BI 1265162 that is absorbed from the GI tract following inhalation without charcoal by comparison to the absolute bioavailability following inhalation with charcoal and to evaluate and compare further pharmacokinetic parameters, as listed in Section 2.2.2.1 between all treatments. These pharmacokinetic parameters will be assessed by descriptive statistics. Furthermore, the assessment of safety and tolerability is a further objective of this trial, and will be evaluated by descriptive statistics for the parameters specified in Section 2.2.2.2 and Section 2.2.2.3.

7.2 NULL AND ALTERNATIVE HYPOTHESES

The absolute bioavailability (F) of BI 1265162 following oral (T1), inhaled with activated charcoal (T2) and without charcoal (T3) administration will be estimated by the ratios of the geometric means (Ti/R, i=1,2, 3) of the primary endpoint, and their corresponding 2-sided 90% confidence intervals (CIs) will be provided. This method corresponds to the two one-sided t-test procedure, each at the 5% significance level. Since the main focus is on estimation and not testing, a formal hypothesis test and associated acceptance range is not specified.

To evaluate the proportion of the absolute bioavailability of BI 1265162 after inhalation that is absorbed by the GI tract, the intra-individual difference between the absolute bioavailability of BI 1265162 inhaled with activated charcoal (T2) and without charcoal (T3) will be estimated using an analysis of variance model and a 2-sided 90% CI will be provided. Since the main focus is on estimation and not testing, a formal hypothesis test is not specified.

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 randomized and treated with at least one dose of study drug. The treated set will be used for disposition and safety analyses.
- Pharmacokinetic parameter analysis set (PKS): This set includes all subjects in the treated set (TS) who provide at least one PK endpoint that was defined as primary or further and was not excluded due to a protocol deviation relevant to the evaluation of PK or due to PK non-evaluability (as specified in the following subsection 'Pharmacokinetics'). Thus, a subject will be included in the PKS, even if he contributes only one PK parameter value for one period to the statistical assessment. Descriptive and model based analyses of PK 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 suggested in the IQRM Plan. Important protocol deviations will be identified no later than in the Report Planning Meeting, and the IPD categories will be updated as needed.

Pharmacokinetics

The pharmacokinetic parameters listed in Section 2.1.2 and 2.2.2.1 for drug BI 1265162 will be calculated according to the relevant SOP of the Sponsor (001-MCS-36-472).

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

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

- After oral administration, the subject experienced emesis that occurred at or before two times median t_{max} of the respective treatment (Median t_{max} is to be determined excluding the subjects experiencing emesis),
- A predose concentration is >5% C_{max} value of that subject
- Missing samples/concentration data at important phases of PK disposition curve

Plasma 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 and inferential statistics of PK 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

The primary and further pharmacokinetic endpoints (refer to Section 2.1.2 and 2.2.2.1) will be calculated according to the BI SOP ‘Standards and processes for analyses performed within Clinical Pharmacokinetics/ Pharmacodynamics’ (001-MCS-36-472). The non-compartmental analysis will be performed using a validated software program such as Phoenix WinNonlin™ software (version 6.3 or higher, Certara USA Inc., Princeton, NJ, USA) or SAS® Version 9.4 (or later version).

Primary analyses

The absolute bioavailability (F) will be estimated based on different administration methods of BI 1265162. As different doses are investigated among the administration methods, the primary endpoint (see Section 2.1.2) will be dose normalized for the statistical analysis. The statistical model used for the analysis of the primary endpoint will be an analysis of variance (ANOVA) model on the logarithmic scale. That is, the dose normalized PK endpoint will be log-transformed (natural logarithm) prior to fitting the ANOVA model. This model will include effects accounting for the following sources of variation: ‘sequence’, ‘subjects within sequences’, ‘period’ and ‘treatment’. The effect 'subjects within sequences' will be considered as random, whereas the other effects will be considered as fixed. The model is described by the following equation:

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

y_{ijkm} = logarithm of dose normalized $AUC_{0-\infty}$ measured on subject m in sequence i receiving treatment k in period j,

μ = the overall mean,

ζ_i = the i^{th} sequence effect, i = 1, 2, 3

s_{im} = the effect associated with the m^{th} subject in the i^{th} sequence, m = 1, 2, 3, 4

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

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

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

where $s_{im} \sim N(0, \sigma_B^2)$ i.i.d., $e_{ijkm} \sim N(0, \sigma_W^2)$ i.i.d. and s_{im}, e_{ijkm} are independent random variables.

Point estimates for the ratios of the geometric means (Ti/R, i=1, 2), i.e. for the absolute bioavailability F, and their two-sided 90% confidence intervals (CIs) will be provided.

The difference between the expected means for log(Ti)-log(R), i=1, 2, will be estimated by the difference in the corresponding adjusted means (Least Squares Means). Additionally their two-sided 90% confidence intervals will be calculated based on the residual error from the ANOVA and quantiles from the t-distribution. These quantities will then be back-transformed to the original scale to provide the point estimate and 90% CIs for each comparison of interest.

7.3.2 Secondary endpoint analyses

Not applicable.

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 7.3) 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 randomised 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 ECG, vital signs, or laboratory parameters) or AEs will be assigned to treatments (see Section 4.1) based on the actual treatment at the planned time of the measurement or on the recorded time of AE onset (concept of treatment emergent AEs). Therefore, measurements planned or AEs recorded prior to first intake of trial medication will be assigned to the screening period, those between first trial medication intake and end of REP (see Section 1.2.6) will be assigned to the treatment period. Events occurring after the REP but prior to next intake or 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), 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.

For safety assessments such as ECG, vital signs, or laboratory parameters, the baseline value is defined as the last measurement prior to drug administration on Day 1 of the respective treatment period.

Laboratory data will be compared to their reference ranges. A normalisation of lab values will not be performed as this is a single site with one local laboratory. 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 or other safety-relevant data will be assessed with regard to possible on-treatment changes from baseline.

Relevant ECG findings will be reported as AEs.

7.4 EXPLORATORY PK ANALYSES

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

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

7.6 RANDOMISATION

Subjects will be randomised to one of the 3 treatment sequences (T1-T2-R-T3 or R-T1-T2-T3 or T2-R-T1-T3) in a 1:1:1 ratio. The block size will be documented in the CTR.

The sponsor will arrange for the randomisation as well as packaging and labelling of trial medication. The randomisation list will be generated using a validated system that uses a pseudo-random number generator and a supplied seed number so that the resulting allocation is both reproducible and non-predictable.

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

7.7 DETERMINATION OF SAMPLE SIZE

It is planned to enter a total of 12 subjects in the trial, because this sample size is considered sufficient to achieve the aims of this exploratory trial. With this sample size, the following precision in estimating the ratio of geometric means (Ti/R, i=1, 2, 3), i.e. the respective absolute bioavailability F, can be expected with 95% probability. Precision is defined as the

ratio of upper CI limit to the absolute BA estimate. Note that the precision is independent of the actual ratio of geometric means.

Table 7.7: 1 Precision that can be expected with 95% probability and illustrative two-sided 90% confidence intervals around the ratios of geometric means (Ti/R, i=1,2,3) for different gCVs in a 3x3 crossover trial (N=12)

gCV [%]	Precision upper CL / absolute BA estimate	Ratio [%]*	Lower CI limit [%]	Upper CI limit [%]
15.0	1.14	5	4.38	5.70
15.0	1.14	50	43.83	57.03
15.0	1.14	75	65.75	85.55
15.0	1.14	100	87.67	114.07
20.0	1.19	5	4.20	5.95
20.0	1.19	50	41.98	59.55
20.0	1.19	75	62.97	89.32
20.0	1.19	100	83.97	119.10
25.0	1.24	5	4.02	6.21
25.0	1.24	50	40.24	62.13
25.0	1.24	75	60.35	93.20
25.0	1.24	100	80.47	124.27

*Ratio of geometric means (Ti/R, i=1,2,3) for a PK endpoint is defined by $\exp(\mu_{Ti})/\exp(\mu_R)$.

The expected 90% confidence interval limits in the table were derived by

$$\text{CI limit}_{\text{upper,lower}} = \exp(\ln(\theta) \pm \omega),$$

with θ being the ratio (Ti/R, i=1, 2, 3) on original scale and ω the distance from the estimate θ to either confidence interval limit on the log-scale, which was obtained from the achievable precision on the original scale.

The calculation was performed as described by Julious [R11-5230] using R Version 3.5.1.

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), the EU regulation 536/2014, 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. 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 the investigator and the 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 (or the subject's legally accepted representative) according to ICH-GCP and to the regulatory and legal requirements of the participating country. Each signature must be personally dated by each signatory and the informed consent and any additional subject-information form 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 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, refer to Section 4.1.7.

ClinBase™
In the Phase I unit – the validated ClinBase system is used for processing information and controlling data collected in clinical studies. In addition to its function as a procedure control system, ClinBase™ serves as data base. Instead of being entered into CRFs, selected data are directly entered into the system.

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 CRF, 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.

Data directly entered into ClinBase™ (that is, without prior written or electronic record) are considered to be source data. The place where data are entered first will be defined in a trial specific Source Data Agreement. The data in ClinBase™ are available for inspection at any time.

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(s) must retain the source and essential documents (including ISF) according to the local requirements valid at the time of the end of the trial.

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

8.4 EXPEDITED REPORTING OF ADVERSE EVENTS

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

8.5 STATEMENT OF CONFIDENTIALITY 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
- 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.

The sponsor will submit to the EU database a summary of the final trial results within one year from the end of a clinical trial as a whole, regardless of the country of the last patient (EU or non-EU).

8.7 ADMINISTRATIVE STRUCTURE OF THE TRIAL

The trial is sponsored by Boehringer Ingelheim (BI).

The trial will be conducted at the 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 local clinical monitors (CML), Clinical Research Associates, and investigators of participating trial sites

The trial medication will be provided by the

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

Analyses of BI 1265162 concentrations in plasma will be performed at the .

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

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

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

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10. APPENDICES

10.1 HANDLING INSTRUCTIONS BI 1265162 ORAL SOLUTION

10.1.1 Overview

The BI 1265162 oral solution 20 mL (0.25 mg/mL) is ready to use. Prior to oral drug administration, the needed volume of the oral solution is withdrawn from the vials into a syringe. The oral solution can be stored for up to 24 hours at room temperature in the syringe.

Finally, the oral solution is administered directly into the mouth of the person.

The following description provides a list of required consumables and a step by step instruction.

10.1.2 List of Consumables

Table 10.1.2: 1 Material for withdrawal and administration of the BI 1265162 oral solution (0.25 mg/mL)

Material	Manufacturer	Process Step
Vial Adapter, 20 mm diameter		Withdrawal of solution from glass vial
Injekt® syringe, 5/10/20 mL / Luer Solo		Withdrawal of solution from glass vial, storage, administration
Combi Stopper		Capping of syringe

10.1.3 Preparation for administration of the BI 1265162 oral solution (0.25 mg/mL)

- **Step 1:** Remove the flip-off seal from the glass vial containing BI 1265162 oral solution 20 mL (0.25 mg/mL)
- **Step 2:** Attach a new Vial Adapter on the vial and mount the Injekt® syringe
- **Step 3:** Withdraw the required volume (adding a little surplus) from the vial
- **Step 4:** Disconnect the syringe from the Vial Adapter
- **Step 5:** Holding the syringe upright, push the plunger to the exact volume needed, thereby removing any air bubbles from the syringe
- **Step 6:** Put a Combi Stopper to the Injekt® syringe for safe storage of the system until administration
- **Step 7:** Before administration, remove the Combi Stopper from the Injekt® syringe

10.1.4 In-use stability

After withdrawal of the BI 1265162 oral solution (0.25 mg/mL) from the vial into the syringe, storage of the solution in the capped syringe is allowed for up to 24 hours at room temperature. Vial and syringe shall be protected from direct sun exposure. No additional light protection measures are required.

10.1.5 Mode of application

The vials are for single use only.

10.2 HANDLING INSTRUCTIONS FOR BI 1265162 CONCENTRATE FOR SOLUTION FOR INFUSION

10.2.1 Overview

Prior to intravenous drug administration, the needed volume of the concentrate for solution for infusion is withdrawn from the vials into a syringe. This is diluted by a factor of five with 0.9 % saline. Subsequently, the application system is flushed with the solution for infusion.

Finally, the needed volume of solution for infusion is administered over 60 minutes. Residual solution for infusion is discarded.

The following description provides a list of required consumables and a step by step instruction.

10.2.2 List of Consumables

Table 10.2.2: 1 Material for withdrawal of solutions and preparation and administration of the BI 1265162 solution for infusion (5 µg/mL)

Material	Manufacturer	Process Step
Mini-Spike®		Withdrawal of solution from glass vial
Omnifix® syringe, 20 mL / Luer Lock Solo		Withdrawal of solutions from glass vial, mixing, infusion
Original Perfusor® Syringe 50 mL, Luer Lock		Withdrawal of solutions from glass vial, mixing, infusion
Original Perfusor® Line IV-Standard – PE, Luer Lock		Infusion
Combi Stopper		Capping of infusion line after priming
Introcan Safety® iv catheter		Infusion
Octeniderm®		Desinfection

10.2.4 In-use stability

After mixing the BI 1265162 concentrate for solution for infusion and the 0.9 % saline to obtain the BI 1265162 solution for infusion (5 µg/mL) and priming of the Original Perfusor® Line, storage of the solution before start of infusion is allowed for 2 hours at room temperature. Vial and syringe shall be protected from direct sun exposure. No additional light protection measures are required.

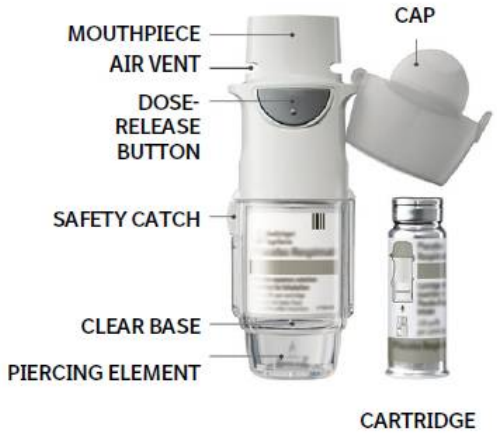
10.2.5 Mode of application

The vials are for single use only.

10.3 HANDLING INSTRUCTIONS FOR RESPIMAT INHALER

These instructions explain generally the use of BI 1265162 RESPIMAT inhaler. Depending on the clinical study, the product is administered under direct medical supervision or used by patients at home. Depending on the situation, the Instructions can be adapted to the specific situation as need may be.

Read these Instructions for Use before you start demonstrating or using RESPIMAT.



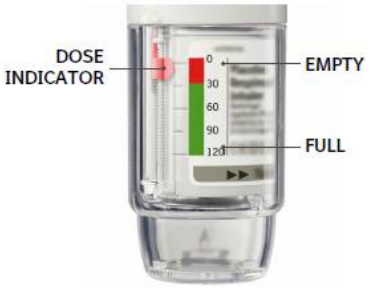
How to store BI 1265162 RESPIMAT

Keep BI 1265162 RESPIMAT out of the sight and reach of children.
Do not freeze BI 1265162 RESPIMAT. For further storage conditions, please refer to product label.
If BI 1265162 RESPIMAT has not been used for more than 7 days, repeat steps 4 to 6 (turn, open, press) under ‘Prepare for first Use’ until a cloud is visible. Then repeat steps 4 to 6 three more times.
Do not use BI 1265162 RESPIMAT after the expiry date.

How to care for BI 1265162 RESPIMAT

Clean the mouthpiece including the metal part inside the mouthpiece with a damp cloth or tissue, at least once a week. Cleaning on a daily basis or daily disinfection with an alcoholic tissue is also possible.
Any minor discoloration in the mouthpiece does not affect BI 1265162 RESPIMAT inhaler performance.

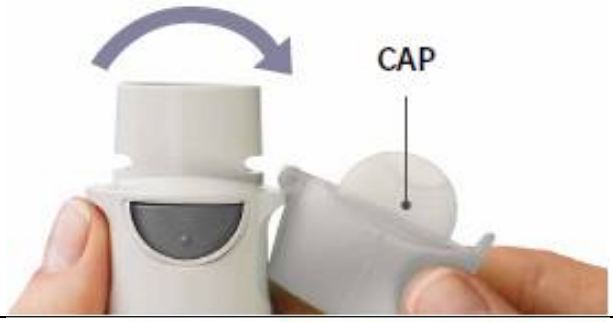
When to get a new BI 1265162 RESPIMAT



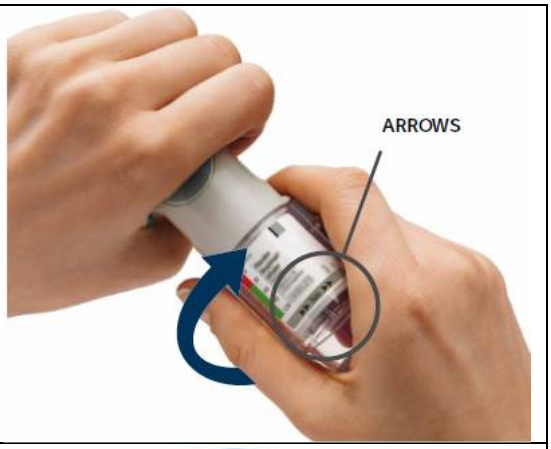
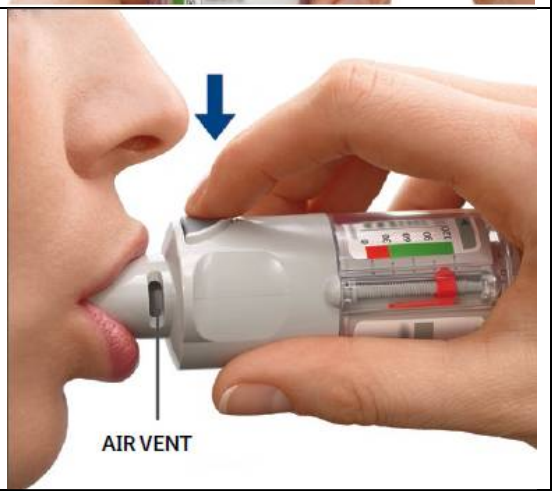
- BI 1265162 RESPIMAT inhaler contains 120 puffs if used as indicated.
- The dose indicator shows approximately how much medication is left.
- When the dose indicator enters the red area of the scale, get a new BI 1265162 RESPIMAT from the investigational site; there are approximately 30 puffs left.
- Once the dose indicator reaches the end of the red scale, BI 1265162 RESPIMAT locks automatically – no more doses can be released. At this point, the clear base cannot be turned any further. The inhaler should not be discarded; it should be returned to investigational site.

Prepare for first use

Remove clear base Keep the cap closed. Press the safety catch while firmly pulling off the clear base with your other hand.	

Insert cartridge Insert the narrow end of the cartridge into the inhaler. Place the inhaler on a firm surface and push down firmly until it snaps into place.	
Replace clear base Put the clear base back into place until it clicks.	
Turn Keep the cap closed. Turn the clear base in the direction of the arrows on the label until it clicks (half a turn).	
Open Open the cap until it snaps fully open.	
Press Point the inhaler toward the ground Press the dose-release button. Close the cap. Repeat steps 4-6 until a cloud is visible. After a cloud is visible, repeat steps 4-6 three more times.	

Daily use

TURN Keep the cap closed. TURN the clear base in the direction of the arrows on the label until it clicks (half a turn).	
OPEN OPEN the cap until it snaps fully open.	
PRESS Breathe out slowly and fully. Close your lips around the mouthpiece without covering the air vents. While taking a slow, deep breath through your mouth, PRESS the dose-release button and continue to breathe in. Hold your breath for 10 seconds or for as long as comfortable. Repeat Turn, Open, Press for a total of puffs required by the clinical trial protocol. Close the cap until you use your BI 1265162 RESPIMAT inhaler again.	

Answers to Common Questions

It is difficult to insert the cartridge deep enough.

Did you accidentally turn the clear base before inserting the cartridge? Open the cap, press the dose-release button, then insert the cartridge.
Did you insert the cartridge with the wide end first? Insert the cartridge with the narrow end first.

I cannot press the dose-release button.

Did you turn the clear base? If not, turn the clear base in a continuous movement until it clicks (half a turn).
Is the dose indicator on BI 1265162 RESPIMAT pointing to zero?
BI 1265162 RESPIMAT inhaler is locked after 120 puffs. Prepare and use a new BI 1265162 RESPIMAT inhaler.

I cannot turn the clear base.

Did you turn the clear base already? If the clear base has already been turned, follow steps "OPEN" and "PRESS" under "Daily Use" to get your medicine.
Is the dose indicator on the BI 1265162 RESPIMAT pointing to zero? The BI 1265162 RESPIMAT inhaler is locked after 120 puffs. Prepare and use your new RESPIMAT inhaler.

The dose indicator on the BI 1265162 RESPIMAT reaches zero too soon.

Did you turn the clear base before you inserted the cartridge? The dose indicator counts each turn of the clear base regardless whether a cartridge has been inserted or not.
Did you spray in the air often to check whether the BI 1265162 RESPIMAT is working? Once you have prepared BI 1265162 RESPIMAT, no test-spraying is required if used daily.
Did you insert the cartridge into a used RESPIMAT? Always insert a new cartridge into a **NEW** RESPIMAT.

BI 1265162 RESPIMAT sprays automatically.

Was the cap open when you turned the clear base? Close the cap, then turn the clear base.
Did you press the dose-release button when turning the clear base? Close the cap, so the dose-release button is covered, then turn the clear base.
Did you stop when turning the clear base before it clicked? Turn the clear base in a continuous movement until it clicks (half a turn).

BI 1265162 RESPIMAT doesn't spray.

Did you insert a cartridge? If not, insert a cartridge.

Did you repeat Turn, Open, Press less than three times after inserting the cartridge?
Repeat Turn, Open, Press three times after inserting the cartridge as shown in the steps 4 to 6 under “Prepare for first Use”.

Is the dose indicator on BI 1265162 RESPIMAT pointing to 0? If the dose indicator points to 0, you have used up all your medication and the inhaler is locked.
Once BI 1265162 RESPIMAT is assembled, do not remove the clear base or the cartridge.
Always insert a new cartridge into a **NEW** RESPIMAT.

Further information

BI 1265162 RESPIMAT inhaler must not be disassembled after inserting the cartridge and replacing the clear base.
Do not touch the piercing element inside the base.

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

APPROVAL / SIGNATURE PAGE

Document Number: c25000855 **Technical Version Number:4.0**

Document Name: clinical-trial-protocol-revision-3

Title: Absolute bioavailability of BI 1265162 following oral and inhaled administration in healthy male volunteers (an open-label, randomised, single-dose, three-period, three-sequence crossover study followed by a fixed treatment)

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Approval-Therapeutic Area		20 Aug 2019 14:03 CEST
Author-Clinical Trial Leader		20 Aug 2019 14:07 CEST
Approval-Team Member Medicine		20 Aug 2019 14:09 CEST
Author-Trial Clinical Pharmacokineticist		20 Aug 2019 21:16 CEST
Verification-Paper Signature Completion		21 Aug 2019 12:08 CEST
Author-Trial Statistician		22 Aug 2019 08:16 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed