Clinical Trial Protocol

	Document Number: c15848245-01
EudraCT No.:	2017-001106-15
BI Trial No.:	1399-0001
BI Investigational Product:	BI 1265162
Title:	Safety, tolerability and pharmacokinetics of single rising inhaled doses of BI 1265162 in healthy male volunteers in a partially randomised, single blind, placebo-controlled trial
Lay Title	This study tests the safety, tolerability and how different doses of BI 1265162 are taken up in the body of healthy men.
Clinical Phase:	I
Trial Clinical Monitor:	Phone: Fax:
Principal Investigator:	Phone: Fax:
Status:	Final Protocol
Version and Date:	Version: 1.0 Date: 19 September 2017

Page 1 of 80

CLINICAL TRIAL PROTOCOL SYNOPSIS

Name of company: Boehringer Ingelheim		**Tabulated Trial Protocol**	
Name of finished product: Not applicable			
Name of active ingredient: BI 1265162			
Protocol date: 19 September 2017	**Trial number:** 1399-0001		**Revision date:** Not applicable

Title of trial:	Safety, tolerability and pharmacokinetics of single rising inhaled doses of BI 1265162 in healthy male volunteers in a partially randomised, single blind, placebo-controlled trial
Principal Investigator:	
Trial site:	
Clinical phase:	I
Objectives:	To investigate safety, tolerability and pharmacokinetics, following single doses of BI 1265162
Methodology:	Single-blind, partially randomised within dose groups, placebo-controlled, parallel-group design
No. of subjects:	
total entered:	56*
each treatment:	8 per dose group (6 on active drug and 2 on placebo) * Additional subjects may be entered to allow testing of additional doses on the basis of experience gained during the trial conduct (e.g. preliminary PK data), provided the planned and approved highest dose will not be exceeded. Thus, the actual number of subjects entered may exceed 56, but will not exceed 72 subjects entered.
Diagnosis:	Not applicable
Main criteria for inclusion:	Healthy male subjects, age of 18 to 50 years, body mass index (BMI) of 18.5 to 29.9 kg/m^2
Test product:	BI 1265162
dose:	
mode of admin.:	Inhalation by RESPIMAT
Comparator product:	Placebo
dose:	Not applicable
mode of admin.:	Inhalation by RESPIMAT
Duration of treatment:	Single dose

Name of company: Boehringer Ingelheim		**Tabulated Trial Protocol**	
Name of finished product: Not applicable			
Name of active ingredient: BI 1265162			
Protocol date: 19 September 2017	**Trial number:** 1399-0001		**Revision date:** Not applicable
Criteria for pharmacokinetics:	Secondary endpoints: AUC_{t1-t2} and C_{max}		
Criteria for safety:	Primary endpoint to assess safety and tolerability of BI 1265162 is the number [N (%)] of subjects with drug-related adverse events. <u>Further criteria of interest:</u> AEs including clinically relevant findings from the physical examination, safety laboratory tests, 12-lead electrocardiogram (ECG), continuous ECG monitoring, vital signs (blood pressure [BP], pulse rate [PR])		
Statistical methods:	Descriptive statistics will be calculated for all endpoints.		

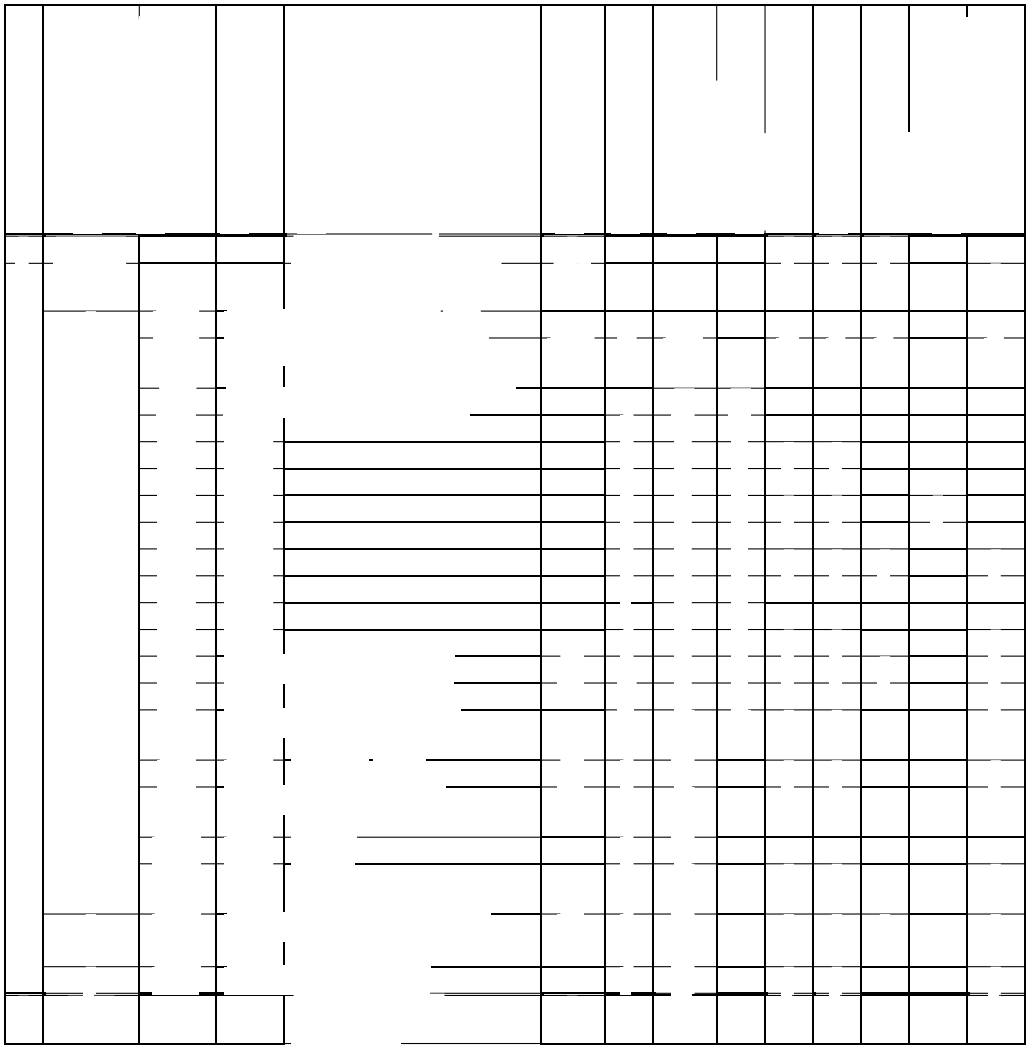


TABLE OF CONTENTS

ABBREVIATIONS

AE	Adverse event
AESI	Adverse events of special interest
AMG	Arzneimittelgesetz (German drug law)
ANCOVA	Analysis of covariance
AUC_{t1-t2}	Area under the concentration-time curve of the analyte in plasma over the time interval t_1 to t_2
BI	Boehringer Ingelheim
b.i.d.	*Bis in die*, twice daily
BLQ	Below limit of quantification
BMI	Body mass index (weight divided by height squared)
BP	Blood pressure
CA	Competent authority
CF	Cystic fibrosis
CI	Confidence interval
C_{max}	Maximum measured concentration of the analyte in plasma
COPD	Chronic obstructive pulmonary disease
CRF	Case report form
CTP	Clinical trial protocol
CTR	Clinical trial report
CV	Arithmetic coefficient of variation
DILI	Drug induced liver injury
ECG	Electrocardiogram
EDTA	Ethylenediaminetetraacetic acid

EOT	End of trial
gCV	Geometric coefficient of variation
gMean	Geometric mean
HR	Heart rate
IB	Investigator's brochure
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ISF	Investigator site file
LC-MS/MS	Liquid chromatography with tandem mass spectrometry
MedDRA	Medical Dictionary for Regulatory Activities
NC	Not calculated
NOA	Not analysed
NOAEL	No observed adverse effect level
NOR	No valid result
NOS	No sample available
NOTEL	No toxic effect level
PK	Pharmacokinetic(s)
PKS	Pharmacokinetic set
PR	Pulse rate
q.d.	*Quaque die*, once daily
QT	Time between start of the Q-wave and the end of the T-wave in an electrocardiogram
QTc	QT interval corrected for heart rate using the method of Fridericia (QTcF) or Bazett (QTcB)
RDC	Remote data capture
REP	Residual effect period
SAE	Serious adverse event
SCR	Screening
SRD	Single-rising dose
SUSAR	Suspected Unexpected Serious Adverse Reaction

TMF	Trial master file
TDMAP	Trial Data Management and Analysis Plan
TSAP	Trial statistical analysis plan
ULN	Upper limit of normal

2.2 TRIAL OBJECTIVES

The primary objective of this trial is to investigate the safety and tolerability of BI 1265162 in healthy male subjects following inhalative administration of single rising doses.

Secondary objective is the exploration of the pharmacokinetics (PK) of BI 1265162 after single dosing.

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

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

This single-rising dose trial is designed as single-blind, partially randomised, and placebo-controlled within parallel dose groups.

Partially randomised means that the subjects will be treated in two equally sized cohorts per dose group, with the first cohort being treated in a fixed sequence and the second cohort being treated in a randomised order.

A total of 56 healthy male subjects is planned to participate in the trial, according to 7 sequential groups comprising 8 subjects per group. However, additional subjects may be entered to allow testing of intermediate doses within the planned and approved dose range on the basis of experience gained during trial conduct (e.g. preliminary PK data), i.e. the actual number of subjects entered may exceed 56. Such changes may be implemented via non-substantial CTP Amendments.

Within each dose group, 6 subjects will receive the active drug and 2 will receive placebo. Only one dose is tested within each dose group

The dose groups to be evaluated are outlined in Table 3.1: 1 below.

On the first study day of each dose level, the first cohort will be treated in the following order: first subject (active) followed at least 1 h later by the second subject (placebo) followed at least 1 h later by the third subject (active) followed at least 10 min later by the fourth subject (active). If BI 1265162 treatment is safe and showed acceptable tolerability in the first cohort, the subjects in the second cohort will be treated not earlier than 2 days later than the first treated volunteer in the first cohort. In the second cohort, a time interval of at least 10 min will be maintained between dosing of individual subjects in a random order. The dose groups will be investigated consecutively in ascending order of doses. A time interval of at least 6 days will be maintained between the administration of the study drug to the first cohort in a dose group and the first cohort in the next dose group. The decision to proceed to the next dose group will be based upon the safety, tolerability data of the preceding dose groups and explorative PK data in some dose groups (see Section 7.3.4).

The next dose will only be given if, in the opinion of the investigator, no safety concerns arose in the preceding dose group (i.e. no dose-limiting events occurred) and if none of the pre-specified trial-specific stopping criteria were met (refer to Section 3.3.4.2).

A documented Safety Review must take place prior to each dose escalation. Furthermore, an unscheduled safety review meeting can be requested anytime for any reasonable cause by the Principal Investigator (or an authorised deputy) or the sponsor of the study, e.g. because of any unforeseen adverse events, etc. Dose escalation will only be permitted if no safety concerns exist in the opinion of the Principal Investigator (or an authorised deputy) and the Trial Clinical Monitor (or an authorised deputy).

The minimum data set for review consists of the following data:

- AEs in the current and preceding dose groups up to at least 48h post dosing (including clinically relevant findings from ancillary safety testing listed below) (Note: AEs may be ongoing at the time of Safety Reviews and AE information may be subject to change prior to Database Lock)
- Results from 12-lead ECG and continuous ECG monitoring in the current and preceding dose groups.
- Vital signs in the current and preceding dose groups
- Clinical laboratory tests in the current and preceding dose groups
- Preliminary PK data as per Section 7.3.4
- Check of criteria for stopping subject treatment as per Section 3.3.4.1

The decision to escalate the dose will be made jointly by the Principal Investigator (or an authorised deputy) and the Trial Clinical Monitor (or an authorised deputy) after in-depth analysis of all available safety data, especially SAEs (if occurred), AEs and out-of-range laboratory results (if considered clinically significant). Safety Reviews can be conducted face-to-face or by video/telephone conference. The Trial Clinical Monitor is responsible for organization and minutes of the reviews. Minutes will be signed off by the Principal Investigator (or an authorised deputy) and filed in the ISF and TMF.

The investigator (after consultation with the sponsor) is allowed to alter the scheduled dose levels (e.g. add low and/or intermediate dose levels) on the basis of experience gained during the study, provided the planned and approved highest dose is not exceeded. In this case, the total number of subjects in this trial might increase. The investigator and/or the sponsor should stop dose escalation in case the safety evaluation leads to concerns that would not allow higher dosing.

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

3.1.1 Administrative structure of the trial

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

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

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

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

Safety laboratory tests will be performed by the local laboratory of the trial site (Medizinisches Versorgungszentrum Dr. Klein, Dr. Schmitt & Partner, Kaiserslautern, Germany).

The analyses of BI 1265162 concentrations in plasma and urine will be performed at the Department of Drug Metabolism and Pharmacokinetics, BI Pharma GmbH & Co. KG, Biberach, Germany.

The digitally recorded 12-lead ECGs will be sent to a specialised contract research organisation for evaluation.

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

Data management and statistical evaluation will be done by BI or a contract research organisation appointed by BI according to BI SOPs.

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

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

For single -rising dose trials, the design described in Section 3.1 is viewed favourable under the provision not to expose the subjects involved to undue risks since the main study objective is to investigate safety and tolerability of BI 1265162.

With the rising dose design, single-blind conditions regarding the subject's treatment (active or placebo) are maintained within each dose group. However, the current dose level will be known to subjects and investigators. The disadvantage of this trial design is a possible observer bias with regard to the dose-depending effects as well as time effects, but it has the virtue of minimizing subject risk by sequentially studying ascending doses. As time-effects

are expected to be small relative to the differences between the doses in the broad range investigated, unbiased comparisons between treatments can still be expected.

It is standard in trials involving healthy volunteers to include a placebo group as control for the evaluation of safety and tolerability. Each dose group consists of 8 subjects with 6 on active treatment, and 2 on placebo. The placebo control group includes all subjects of all dose groups treated with placebo. 6 subjects per active treatment group are in general considered as sufficient for the exploratory evaluation of pharmacokinetics.

3.3 SELECTION OF TRIAL POPULATION

It is planned that 56 healthy male will enter the study. The actual number of subjects entered may exceed the total of 56 if additional intermediate doses will be tested (see Section 3.1). Subjects will be recruited from the volunteers' pool of the trial site.

Only male subjects will be included into the study because hitherto no data on reproductive toxicology are available.

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

3.3.1 Main diagnosis for study entry

The study will be performed in healthy subjects.

3.3.2 Inclusion criteria

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

1. Healthy male subjects according to the assessment of the investigator, based on a complete medical history including a physical examination, vital signs (BP, PR), 12-lead ECG, and clinical laboratory tests
2. Age of 18 to 50 years (incl.)
3. BMI of 18.5 to 29.9 kg/m^2 (incl.)
4. FEV_1 and FVC of equal or greater than 80% of predicted normal, at screening and prior to randomisation
5. 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) is deviating from normal and judged as clinically relevant by the investigator

2. Repeated measurement of systolic blood pressure outside the range of 90 to 140 mmHg, diastolic blood pressure outside the range of 50 to 90 mmHg, or pulse rate outside the range of 50 to 90 bpm
3. Any laboratory value outside the reference range that the investigator considers to be of clinical relevance
4. Any evidence of a concomitant disease judged as clinically relevant by the investigator
5. Gastrointestinal, hepatic, renal, respiratory, cardiovascular, metabolic, immunological or hormonal disorders
6. Cholecystectomy and/or surgery of the gastrointestinal tract that could interfere with the pharmacokinetics of the trial medication (except appendectomy and simple hernia repair)
7. Diseases of the central nervous system (including but not limited to any kind of seizures or stroke), and other relevant neurological or psychiatric disorders
8. History of relevant orthostatic hypotension, fainting spells, or blackouts
9. Chronic or relevant acute infections
10. History of relevant allergy or hypersensitivity (including allergy to the trial medication or its excipients)
11. Use of drugs within 30 days prior to administration of trial medication if that might reasonably influence the results of the trial (incl. QT/QTc interval prolongation)
12. Participation in another trial where an investigational drug has been administered within 60 days prior to planned administration of trial medication, or current participation in another trial involving administration of investigational
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 30 g per day for males)
16. Drug abuse or positive drug screening
17. Blood donation of more than 100 mL within 30 days prior to administration of trial medication or intended donation during the trial
18. Intention to perform excessive physical activities within one week prior to administration of trial medication or during the trial
19. Inability to comply with dietary regimen of trial site
20. A marked baseline prolongation of QT/QTc interval (such as QTc intervals that are repeatedly greater than 450 ms in males) or any other relevant ECG finding at screening
21. A history of additional risk factors for Torsades de Pointes (such as heart failure, hypokalemia, or family history of Long QT Syndrome)
22. A history of chronic kidney disease (EGFR $\underline{<59}$ mls/min including corrections as per ethnicity)
23. Subject is assessed as unsuitable for inclusion by the investigator, for instance, because considered not able to understand and comply with study requirements, or has a condition that would not allow safe participation in the study
24. The subject has a diagnosis history of pulmonary hyperreactivity

25. Male subjects with WOCBP partner who are unwilling to use male contraception (condom or sexual abstinence) from the first administration of trial medication until 14 days after last administration of trial medication (BI 1265162 or placebo)

For study restrictions, refer to Section 4.2.2.

3.3.4 Removal of subjects from therapy or assessments

3.3.4.1 Removal of individual subjects

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

- The subject withdraws consent for trial treatment or trial participation, without the need to justify the decision
- The subject needs to take concomitant drugs that interfere with the investigational product or other trial medication
- The subject is no longer able to participate for other medical reasons (such as surgery, adverse events (AEs), or diseases)

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

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

If a subject is removed from or withdraws from the trial prior to first administration of trial medication, the data of this subject will not be entered in the case report form (CRF) or trial database and will not be reported in the clinical trial report (CTR). If a subject is removed from or withdraws from the trial after first administration of trial medication, this will be documented and the reason for discontinuation must be recorded in the CRF. In this case, the data will be included in the CRF/trial database and will be reported in the CTR. At the time of discontinuation a complete end of trial examination will be performed if possible and the information will be recorded in the CRFs. If the discontinuation occurs before the end of the REP (see Section 5.2.2.2), the discontinued subject should if possible be questioned for AEs and concomitant therapies at or after the end of the REP in order to ascertain collection of AEs and concomitant therapies throughout the REP, if not contrary to any consent withdrawal of the subject. These discontinuations will be discussed in the CTR.

3.3.4.2 Discontinuation of the trial by the sponsor

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

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

- The expected enrolment goals overall or at a particular trial site are not met
- Violation of GCP, or the CTP, or the contract with BI by a trial site or investigator, disturbing the appropriate conduct of the trial
- The sponsor decides to discontinue the further development of the investigational product.
- Dose escalation will be stopped as soon as at least 2 subjects at one dose level on active drug showed relevant individual QT prolongation, i.e. a QTc increase of greater 60 ms from baseline in connection with absolute QT or QTc greater than 500 ms, which has been confirmed by a repeat ECG recording (e.g. follow-up ECG).

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

3.3.5 Replacement of subjects

In case that more than 2 subjects on active per dose group do not complete the trial, the trial clinical monitor together with the trial pharmacokineticist and the trial statistician are to decide if and how many subjects will be replaced. A replacement subject will be assigned a unique study subject number, and will be assigned to the same treatment as the subject he replaces.

4. TREATMENTS

4.1.2 Method of assigning subjects to treatment groups

Prior to the screening visit, subjects will be contacted in writing and informed about the planned visit dates. The subjects willing to participate will be recruited to dose groups according to their temporal availability. As soon as enough subjects have been allocated to 1 of the 14 dose cohorts (2 cohorts per dose group), the following subjects will be allocated to one of the other dose cohorts. Therefore, the allocation of subjects to dose cohorts is not influenced by trial personnel, but only by the subjects' temporal availability. As the study

includes healthy subjects from a homogenous population, relevant imbalances between the dose groups are not expected.

The randomization list with study subject numbers and allocated treatments will be provided to the trial site and the sponsor (TCM) in advance. The allocation of subjects to study subject numbers will be performed prior to the first administration of trial medication. For this purpose, the subjects will be allocated to a study subject number by the method 'first come first served'. Once a subject number has been assigned, it cannot be reassigned to any other subject.

The randomisation procedure is described in Section 7.5.

4.1.3 Selection of doses in the trial

The doses selected for this trial cover the subtherapeutic as well as the estimated therapeutic range and include a safety margin (see Section 1.2).

4.1.4 Drug assignment and administration of doses for each subject

The treatments to be evaluated are outlined in Table 4.1.4: 1 below. The number of actuations for placebo corresponds to the number of actuations of the respective dose level.

Each newly assembled RESPIMAT Inhaler (has to be done on the day of application) has to be primed by qualified medical/pharmaceutical study personnel at the trial site under the responsibility of the investigator. To avoid contamination, except those devices used for training, priming should NOT take place in the same room where the subject is inhaling trial medication or the trial will be performed or samples will be processed. The inhaler should be primed under e.g. hood/outside by actuating it until an aerosol is visible plus three additional actuations. All priming actuations should be directed to the ground. For detailed priming instructions please refer to the RESPIMAT Inhaler handling instructions in Appendix 10.1.

Both the study drug as well as the placebo treatment (depending on randomisation) will be inhaled with the RESPIMAT in a sitting or standing position under supervision of the investigating physician or an authorised designee. If more than one actuation is needed, planned time 0:00h will always be the first actuation. If more than one actuation will be needed, the duration from first to last actuation will be recorded. 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. After study drug inhalation, subjects will drink 240 mL of water.

The so-called four-eye principle (two-person rule) should be applied for administration of trial medication and – if applicable – its preparation (e.g. assembling of device), otherwise correct dosage cannot be ensured.

Subjects will be kept under close medical surveillance until 24 h following drug administration. During the first 4 h after 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 except for medical examination), or to sleep. For restrictions with regard to diet see Section 4.2.2.2.

4.1.5 Blinding and procedures for unblinding

4.1.5.1 Blinding

The treatments administered (active or placebo) will be single-blind (blinded to subjects only). However, the current dose level will be known to the subjects.

Within the ECG laboratory, the staff involved with interval measurements and assessments will be blinded with respect to the treatment and also with regard to the recording date and time as well as the time points of the ECGs. The interval measurements for a given subject will be performed in a random and blinded sequence by a single technician. No more than two different blinded readers will evaluate the ECGs of the study.

In addition, the trial pharmacokineticist, trial pharmacometrician and bioanalyst may receive the randomisation codes prior to official unblinding to perform the interim / preliminary PK analysis. He or she will confirm in writing that the codes will be treated confidentially.

In addition, the drug metabolism scientist may receive the randomisation codes prior to official unblinding to perform metabolites in safety testing analysis (MIST). He or she will confirm in writing that the codes will be treated confidentially.

The database of this trial will be handled open-label, because no bias with regard to data cleaning of safety measures is expected.

4.1.5.2 Procedures for emergency unblinding

As this trial will be conducted single-blinded, the treatment information will be known. Therefore, no emergency envelopes will be provided.

4.1.6 Packaging, labelling, and re-supply

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

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

- BI trial number
- Name of product and strengths or identification code
- Pharmaceutical dosage form, quantity of dosage units

- Route and mode of administration
- Term 'For Clinical Trial Use' (domestic language)
- Sponsor name and address
- Storage conditions
- Use-by date
- Subject or medication number
- Batch Number

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

No re-supply is planned.

4.1.7 Storage conditions

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

4.1.8 Drug accountability

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

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

Only authorised personnel as documented in the form 'Trial Staff List' may dispense medication to trial subjects. The trial medication must be administered in the manner specified in the CTP. All unused medication will be disposed locally by the trial site upon written authorisation by the clinical monitor. Receipt, usage and disposal must be documented on the respective forms. Account must be given for any discrepancies.

The investigator must maintain records of the product's delivery to the trial site, the inventory at the site, the use by each subject, and the disposal of unused products.

These records will include dates, quantities, batch / serial numbers, expiry ('use-by') dates, and the unique code numbers assigned to the investigational products and trial subjects. The

investigator will maintain records that document adequately that the subjects were provided the doses specified by the CTP, and that reconcile all investigational products received from the sponsor.

4.2 OTHER TREATMENTS, EMERGENCY PROCEDURES, RESTRICTIONS

4.2.1 Other treatments and emergency procedures

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

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

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

From 1 h before drug intake until lunch, fluid intake is restricted to 240 mL of water served at 2 h and 4 h post-dose (mandatory for all subjects). From lunch onwards, liquid intake is restricted to an additional 3000 mL. Subjects will be asked to drink the additional amount till one hour prior to the stop of urine collection on day 2. The total amount of liquid intake will be documented.
Standardised meals (identical for each dose group) will be served at the time points described in the study Flow Chart. Use of table salt is not allowed during in-house confinement at the trial site.

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

Alcoholic beverages, consumption of seafood and dried fruits are not permitted from 48 hours before the study drug administration and until last blood sampling.

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

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

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

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

4.3 TREATMENT COMPLIANCE

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

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

5. VARIABLES AND THEIR ASSESSMENT

5.1 EFFICACY - CLINICAL PHARMACOLOGY

5.1.1 Endpoints of efficacy

No efficacy endpoints will be evaluated in this trial.

5.1.2 Assessment of efficacy

Not applicable.

5.2 SAFETY

5.2.1 Endpoints of safety

Primary endpoint to assess safety and tolerability of BI 1265162 is the number [N (%)] of subjects with drug-related adverse events.

Further criteria of interest:

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

5.2.2 Assessment of adverse events

5.2.2.1 Definitions of adverse events

Adverse event

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

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

Serious adverse event

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

- results in death,

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

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

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

AEs considered 'Always Serious'

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

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

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

Adverse events of special interest (AESIs)

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

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

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

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

Intensity (severity) of AEs

The intensity (severity) of 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

Causal relationship of AEs

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

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

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

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

- No plausible time to onset of the event relative to the time of drug exposure is evident (e.g. pre-treatment cases, diagnosis of cancer or chronic disease within days / weeks of drug administration; an allergic reaction weeks after discontinuation of the drug concerned)
- Continuation of the event despite the withdrawal of the medication, taking into account the pharmacological properties of the compound (e.g. after 5 half-lives). Of note, this criterion may not be applicable to events whose time course is prolonged despite removing the original trigger.

- Additional arguments amongst those stated before, like alternative explanation (e.g. situations where other drugs or underlying diseases appear to provide a more likely explanation for the observed event than the drug concerned).
- Disappearance of the event even though the trial drug treatment continues or remains unchanged.

5.2.2.2 Adverse event collection and reporting

AE collection

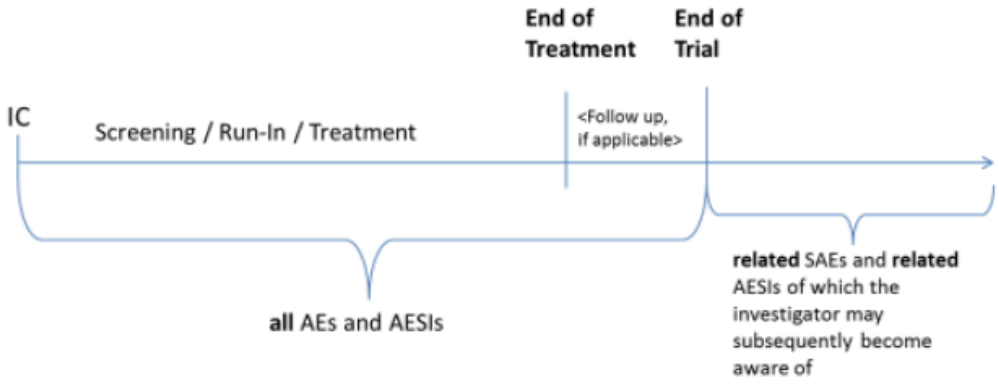
Upon enrolment into a trial, the subject's baseline condition is assessed (for instance, by documentation of medical history/concomitant diagnoses), and relevant changes from baseline are noted subsequently.

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

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

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

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



The REP for BI 1265162, when measurable drug levels or PD effects are still likely to be present after the last administration, is not known for this first-in-human trial. Therefore, all AEs reported until the end of trial examination (last per protocol contact) will be considered on treatment; please see Section 7.3.3.

AE reporting to sponsor and timelines

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

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

Information required

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

The following should also be recorded as an (S)AE in the CRF and 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 CRF only.

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

5.2.3 Assessment of safety laboratory parameters

For the assessment of laboratory parameters, blood and urine samples will be collected by the trial site at the time points indicated in the Flow Chart after the subjects have fasted for at least 8 h (excluding sample at 06:00h post administration).

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

Category	**Test name**	A[1]	B[2]	C[3]
Haematology	Haematocrit	X	X	X
	Haemoglobin	X	X	X
	Red blood cells (RBC)	X	X	X
	White blood cells (WBC)	X	X	X
	Platelets	X	X	X
	Reticulocyte count	X	X	X
Automatic WBC differential (relative and absolute)	Neutrophiles	X	X	X
	Eosinophils	X	X	X
	Basophils	X	X	X
	Monocytes	X	X	X
	Lymphocytes	X	X	X
Manual differential WBC (if automatic differential WBC is abnormal and clinically relevant in the opinion of the investigator)	Polymorphnuclear neutrophils (segs), band neutrophils (stabs), eosinophils, basophils, monocytes, lymphocytes			
Coagulation	Activated partial thromboplastin time (aPTT)	X	X	X
	Prothrombin Time (Quick and INR)	X	X	X
Enzymes	Aspartate aminotransferase (AST/GOT, SGOT)	X	X	X
	Alanine aminotransferase (ALT/GPT, SGPT)	X	X	X
	Alkaline phosphatase	X	X	X
	Gammaglutamyl transferase (GGT)	X	X	X
	Lactate dehydrogenase	X	X	X
	Amylase	X	X	X
	Lipase	X	X	X

Table 5.2.3: 1 Routine laboratory tests (cont'd)

Category	**Test name**	A[1]	B[2]	C[3]
Substrates	Glucose (plasma)	X	-	-
	Creatinine	X	X	X
	eGFR, calculated from serum creatinine using CKD-EPI formula	X	X	X
	Bilirubin, total	X	X	X
	Bilirubin, direct	X	X	X
	Cholesterol, total	X	X	X
	Triglycerides	X	X	X
	C-reactive protein	X	X	X
	Urea	X	X	X
Electrolytes	Calcium	X	X	X
	Sodium	X	X	X
	Potassium	X	X	X
	Chloride	X	X	X
Hormones	Thyroid stimulating hormone (TSH)	X	-	-
	*Aldosterone	-	X	-
24h collection Urine**	Urine potassium	-	X	-
	Urine sodium	-	X	-
	Urine chloride	-	X	-
	Urine creatinine	-	X	-
Urinalysis (Stix) [Urin-Sediment will be performed , if urinalysis abnormal]	Urine nitrite	X	X	X
	Urine protein	X	X	X
	Urine glucose	X	X	X
	Urine ketone	X	X	X
	Urobilinogen	X	X	X
	Urine bilirubin	X	X	X
	Urine RBC	X	X	X
	Urine WBC	X	X	X
	Urine pH	X	X	X
Urine sediment (microscopic examination if erythrocytes, leukocytes nitrite or protein are abnormal in urine)	Only positive findings will be reported (for instance, the presence of sediment bacteria, casts in sediment, squamous epithelial cells, erythrocytes, leukocytes)			

[1]A: parameters to be determined at screening examination
[2]B: parameters to be determined during the study (for time points refer to Flow Chart)
[3]C: parameters to be determined during the Follow-up-examination

* Aldosterone (after a 15-minute resting period in supine position) samples may be stored at about -20C in case shipment/analytics on the same day is not possible

** For baseline from blank urine sample and all Urine collected from 0-24h. These will be stored intermittent in a refrigerator. After processing the 12-24h PK urine fraction (cf. Section 5.5.2.3), all collected fractions (0-24h) will be mixed for the 24h urine electrolyte measurement. Mixing should be done by transferring the entire content of all collection containers into a single PE/PP or glass container, and stirring the mixed fractions for about 1 min (manually or using a stir bar or other stirring device out of PE, PP, Teflon or glass).

The tests listed in Table 5.2.3: 2 are exclusionary laboratory tests which may be repeated as required. The results will not be entered in the CRF/database and will not be reported in the CTR. It is planned to perform these tests during screening only. Drug screening will be performed at screening and 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/p24-antigen (qualitative)

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

The laboratory tests listed in Table 5.2.3: 1 and 5.2.3: 2 will be performed at Medizinisches Versorgungszentrum Dr. Klein, Dr. Schmitt & Partner, Kaiserslautern, Germany with the exception of the urinalysis stix and drug screening tests. These tests will be performed at the trial site using Combur 9 Test (Roche Diagnostics, GmbH, Mannheim, Germany) and AccuSign® DOA 10 test (Diagnostik Nord GmbH, Schwerin, Germany).

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

5.2.4 Electrocardiogram

5.2.4.1 12-lead resting ECG

Recording

Twelve-lead resting ECGs (I, II, III, aVR, aVL, aVF, V1 - V6) will be recorded using a computerised electrocardiograph (CardioSoft EKG System, GE Medical Systems, Freiburg, Germany) at the time points given in the Flow Chart. Electrode placement will be performed according to the method of Wilson, Goldberger and Einthoven modified by Mason and Likar (hips and shoulders instead of ankles and wrists). Precise electrode placement will be marked with an indelible mark on the skin to allow reproducible placement throughout the study.

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 recording will always precede all other study procedures scheduled for the same time (except for blood drawing from an intravenous cannula that is already in place) to avoid compromising ECG quality.

ECGs will be recorded as single ECGs or as triplicate ECGs (i.e. three single ECGs recorded within 180 sec) as indicated in the Flow Chart. Three triple ECGs will be recorded at baseline as indicated in the Flow Chart.

ECGs may be repeated for quality reasons for instance due to alternating current artefacts, muscle movements, or electrode dislocation. For repetition within triplicate ECGs the time window of 180 sec applies as well. The repeat ECGs are assigned to the respective scheduled time point. For the repeats due to quality reasons, only the repeated ECG recordings will be sent to the central ECG lab, whereas the initially recorded ECGs will be discarded.

Additional (unscheduled) ECGs may be collected by the Investigator for safety reasons. These ECGs are assigned to the prior scheduled time point. Unscheduled ECGs will not be included into the statistical analysis of interval lengths.

Data transfer

ECGs will be transferred electronically to the central ECG lab
for evaluation.

In case of repeat ECGs due to quality reasons, only the repeated ECG recordings will be transferred to the central ECG lab, whereas the initially recorded ECGs will be discarded. Unscheduled ECGs (for safety reasons) will be transferred to the central ECG lab but will not be included into the statistical analysis of interval lengths.

Data transfer from the central ECG lab to the sponsor is described in the ECG data transfer agreement (see TMF).

Evaluation

a) Central ECG lab

Central ECG lab evaluation (of visit 2 ECGs only) will be performed for the first of three replicate ECGs per time point given in the Flowchart. For baseline, where 3 triplicate ECGs are recorded, only the first triplicate ECG (i.e. 3 single ECGs) will be evaluated.
RR and QT intervals will be determined semi-automatically, whereas PR, QRS intervals and QRS-axis are measured automatically by a validated GE 12-SL-algorithm or equivalent.

Heart rate (HR) and the QT interval corrected for HR (QTc e.g. QTcF and QTcB) will be determined by the sponsor (see TSAP for details).
All semi-automatic interval measurements in one subject will be performed on the

same lead. The intervals will be measured from four cardiac cycles (beats) in lead II. If lead II shows a flat T wave or is not measurable for any reason, lead V5 will be used, or if that lead is not measurable, then lead I will be used. The lead actually used will be reported in the CTR.
For automatic interval measurements no lead will be provided

For blinding arrangements see Section 4.1.5.1. No more than two blinded readers will evaluate all ECGs of the study. ECGs from a particular subject should be evaluated by a single reader. Evaluation of ECGs will comply with the ICH E14 guidance document and supplements [R07-4722, R16-0366] as well as the FDA requirements for annotated digital ECGs [R09-4830].

b) Trial site

All local ECGs will be evaluated by the investigator or a designee.

For the inclusion or exclusion (see Section 3.3) of a subject and for the assessment of cardiac safety during the study, the QT and QTcB values generated by the computerised ECG system or their manual corrections by the investigators will be used.
In doubtful cases, ECGs may be sent upfront (i.e. prior to the regular data transfer) for cardiologic assessment by the central lab. In this case, these centrally measured results would overrule any other results obtained.

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

5.2.4.2 Continuous ECG monitoring

Cardiac rhythm (including heart rate) will be monitored by means of continuous 3-lead ECG recording for at least 15 min before (for baseline assessment) until 4 h following drug administration using patient monitors (e.g. ApexPro Telemetry System, GE Medical Systems, Freiburg, Germany).

5.2.5 Assessment of other safety parameters

5.2.5.1 Vital signs

Systolic and diastolic blood pressures (BP) as well as pulse rate (PR) or heart rate (heart rate is considered to be equal to pulse rate) will be measured by a blood pressure monitor (e.g. Dash 3000, GE Medical Systems, Freiburg, Germany) at the times indicated in the Flow Chart, after subjects have rested for at least 5 min in a supine position. All recordings should be made using the same type of blood pressure recording instrument on the same arm if possible.

5.2.5.2 Medical examinations

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

5.4 APPROPRIATENESS OF MEASUREMENTS

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

5.5 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

Date and clock time of drug administration and pharmacokinetic sampling will be recorded in the CRFs. Planned sampling times should be adhered to as close as possible. However, these sampling times only represent guidance; thus, deviations which may occur especially shortly after inhalation are not regarded as protocol violations.

PK sampling times and periods may be adapted during the trial based on information obtained during trial conduct (e.g. preliminary PK data) including addition of samples and visits as long as the total blood volume taken per subject does not exceed 500 mL. Such changes would be implemented via non-substantial CTP Amendments.

5.5.1 Pharmacokinetic endpoints

The following pharmacokinetic parameters will be determined if feasible:

5.5.1.1 Secondary endpoints

- AUC_{t1-t2} (area under the concentration-time curve of the analyte in plasma over the time interval t_1 to t_2)

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

5.5.2 Methods of sample collection

5.5.2.1 Plasma sampling for pharmacokinetic analysis

For quantification of BI 1265162 plasma concentrations, 4.9 mL of blood will be taken from an antecubital or forearm vein into an K_3-EDTA (tripotassium ethylenediaminetetraacetic acid)-anticoagulant blood drawing tube at the times indicated in the Flow Chart. Blood will be withdrawn by means of either an indwelling venous catheter or by venipuncture with a metal needle.

The EDTA-anticoagulated blood samples will be centrifuged for about 10 min at about 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 1.0 mL plasma. The process from blood collection until transfer of plasma aliquots into the freezer should be completed within 60 min, with interim storage of blood samples and aliquots in ice water or on ice. For each aliquot the time when the sample was placed in the freezer will be documented. Until transfer on dry ice to the analytical laboratory, the aliquots will be stored upright at about -20°C or below at the trial site. 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 about -20°C or below until analysis.

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

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

5.5.3 Analytical determinations

5.5.3.1 Analytical determination of analyte plasma concentration

BI 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 Drug Metabolism and Pharmacokinetics Germany, Boehringer Ingelheim Pharma GmbH & Co KG, Biberach, Germany. All details of the analytical method will be available prior to the start of sample analysis.

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

5.6 BIOMARKER

Not applicable.

5.7 PHARMACODYNAMICS

Not applicable.

5.8 PHARMACOKINETIC - PHARMACODYNAMIC RELATIONSHIP

Not applicable.

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

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

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

The acceptable deviation from the scheduled time for vital signs, spirometry, ECG and laboratory tests will be ± 30 min for the first 4 h after trial 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 venipuncture are scheduled for the same time, venipuncture should be the last of the measurements (if at the same time point as spirometry, spirometry should be last measurement) due to its inconvenience to the subject and possible influence on physiological parameters.

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

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

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

6.2.1 Screening period

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

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

6.2.2 Treatment period

Each subject will receive one dose of the respective trial medication (BI 1265162 or placebo) at Visit 2.

Trial medication will be administered by each subject under direct supervision of the investigator or [redacted] designee. Details on treatments and procedures of administration are described in Section 4.1.4.

Study participants will be admitted to the trial site in the morning of Day 1 and kept under close medical surveillance for at least 24 h following drug administration. The subjects will then be allowed to leave the trial site after formal assessment and confirmation of their fitness by the investigator or [redacted] designee. On all other study days, the study will be performed in an ambulatory fashion.

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

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

6.2.3 End of trial period

For AE assessment, laboratory tests, recording of ECG and vital signs, and physical examination during the end of trial period, see Sections 5.2.2 to 5.2.5.
Subjects who discontinue treatment before the end of the planned treatment period should undergo the end of trial visit.

All abnormal values (including laboratory parameters) that are judged clinically relevant by the investigator will be monitored using the appropriate tests until a return to a medically acceptable level is achieved. Adverse events persisting after trial completion must be monitored until they have normalised or have been sufficiently characterised.

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

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 STATISTICAL DESIGN – MODEL

7.1.1 Objectives

The primary objective of this trial is to investigate the safety and tolerability of BI 1265162 by using descriptive statistics for all endpoints comparing active dose groups to placebo. The primary endpoint is defined in Section 5.2.1. Inferential statistics is not planned (as explained in Section 7.2).

The secondary objective is the exploration of the pharmacokinetics (PK) of BI 1265162 after single dosing. Endpoints as specified in Section 5.5.1 will be analysed by descriptive statistics. Secondary endpoints ($AUC_{t1\text{-}t2}$ and C_{max}) as defined in Section 5.5.1.1 will be subjected to The main analysis is based on the descriptive statistics and the is regarded as further analysis.

7.2 NULL AND ALTERNATIVE HYPOTHESES

Safety and tolerability of the different dose groups of BI 1265162 are to be determined on the basis of the investigated parameters in comparison to placebo. It is not planned to test any statistical hypotheses with regard to these variables in a confirmatory sense. Instead, they will be described in their entirety and evaluated by descriptive statistical methods.

Confidence intervals will be computed and will have to be interpreted in the perspective of the exploratory character of the study, i.e. confidence intervals are considered as interval estimates for effects.

7.3 PLANNED ANALYSES

All individual data will be listed.

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

7.3.1 Primary analyses

Analysis of safety and tolerability is described in Section 7.3.3.

7.3.2 Secondary analyses

The secondary parameters (refer to Section 5.5.1) will be calculated according to the BI Standard Operating Procedure (SOP) ‘Standards and processes for analyses performed within

Clinical Pharmacokinetics/Pharmacodynamics' (001-MCS-36-472). Analyses will be performed for parent drug.

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

Relevant protocol violations may be

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

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

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

The PK parameter analysis set (PKS) includes all subjects in the Treated Set (TS) who provide at least one PK parameter that was not excluded according to the description above.

Descriptive statistics will be calculated for PK endpoints.

7.3.3 Safety analyses

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

Treatments will be compared in a descriptive way. The placebo control group in the safety evaluation will consist of all placebo treated subjects, regardless of the dose group in which they were treated. The active treatment groups will be compared to the placebo group in a descriptive way. Tabulations of frequencies/proportions will be used for the evaluation of categorical (qualitative) data, and tabulations of descriptive statistics will be used to analyse continuous (quantitative) data.

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

Measurements (such as ECG, vital signs, or laboratory parameters) or AEs will be assigned to treatments (see Section 4.1) based on the actual treatment at the planned time of the measurement or on the recorded time of AE onset (concept of treatment emergent AEs). Therefore, measurements planned or AEs recorded prior to first intake of trial medication will be assigned to 'screening', those between first trial medication intake until the trial termination date will be assigned to the treatment period. These assignments including the corresponding time intervals will be defined in detail in the TSAP.

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

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

Laboratory data will be compared to their reference ranges. Values outside the reference range will be flagged in the listings. Additionally, differences from baseline will be evaluated.

For vital signs and the differences from baseline will be evaluated. Additionally, plots over the time will be provided for spirometry data.

A centralised evaluation of all 12-lead ECGs recordings (see Section 5.2.4) will be the basis for the derivation of further ECG parameters based on the ECG variables QT, HR, QTcF, QTcB, PR, QRS, and RR. The baseline value of an ECG variable is defined as the mean of the triple ECG measurements prior to drug administration. The derivation of the quantitative and qualitative ECG endpoints and their analyses will be described in the TSAP.

7.3.5 Pharmacokinetic analyses

The pharmacokinetic parameters listed in Section 5.5.1 for drug BI 1265162 will be calculated according to the BI SOP 'Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics' (001-MCS-36-472).

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

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

7.4 HANDLING OF MISSING DATA

7.4.1 Safety

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

7.4.2 Plasma/urine drug concentration - time profiles

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

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

7.4.3 Pharmacokinetic parameters

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

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

7.5 RANDOMISATION

The subjects of the first cohort per dose level will not be randomised to maintain a treatment sequence of active-placebo-active-active due to safety reasons. In the second cohort subjects will be randomised within each dose group in a 3:1 ratio, which reflects the ratio of subjects receiving active drug to placebo.

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

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

7.6 DETERMINATION OF SAMPLE SIZE

It is planned to include a total of 56 subjects in this trial. The planned sample size is not based on a power calculation. The size of 8 subjects per dose group (6 on active treatment, and 2 on placebo) is commonly used in single-rising dose studies of the present type and is in general considered as sufficient for the exploratory evaluation of single dose safety and pharmacokinetics [R95-0013].

8. INFORMED CONSENT, DATA PROTECTION, TRIAL RECORDS

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

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

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

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

8.1 STUDY APPROVAL, SUBJECT INFORMATION, AND INFORMED CONSENT

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

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

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

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

8.2 DATA QUALITY ASSURANCE

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

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

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

8.3 RECORDS

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

8.3.1 Source documents

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

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

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

8.3.2 Direct access to source data and documents

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

8.3.3 Storage period of records

Trial site:

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

Sponsor:

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

8.4 EXPEDITED REPORTING OF ADVERSE EVENTS

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

8.5 STATEMENT OF CONFIDENTIALITY

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

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

8.6 COMPLETION OF TRIAL

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

9. REFERENCES

9.1 PUBLISHED REFERENCES

P87-3333 Beasley CRW, Rafferty P, Holgate ST. The role of preservatives in Atrovent-induced bronchoconstriction. Thorax. 1987. 42: 230-231.

P88-1291 Rafferty P, Beasley R, Holgate ST. Comparison of the efficacy of preservative free ipratropium bromide and ATROVENT® nebulizer solution. Thorax. 1988. 43: 446-450.

P96-3855 Ramsey B W. Management of Pulmonary Disease in patients with Cystic Fibrosis. NEJM 1996; 335 (3): 179-188. July 18.

P05-08465 Hodder R; Pavia D; Dewberry H; Alexander K; Iacono P; Ponitz H; et al. Low incidence of paradoxical bronchoconstriction in asthma and COPD patients during chronic use of Respimat Soft Mist inhaler. Respir Med. 2005. 99: 1087-1095.

P05-12782 Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, Crapo R, Enright P, Grinten CPM van der, Gustafsson P, Jensen R, Johnson DC, MacIntyre N, McKay R, Navajas D, Pedersen OF, Pellegrino R, Viegi G, Wanger J Standardisation of spirometry. Eur Respir J 26 (2), 319 - 338 (2005).

P11-05794 Poole P, Black PN. Mucolytic agents for chronic bronchitis or chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2010 Feb 17;(2):CD001287.

P13-14084 Mogayzel PJ Jr, Naureckas ET, Robinson KA, Mueller G, Hadjiliadis D, Hoag JB, Lubsch L, Hazle L, Sabadosa K, Marshall B; Pulmonary Clinical Practice Guidelines Committee. Cystic fibrosis pulmonary guidelines. Chronic medications for maintenance of lung health. Am J Respir Crit Care Med. 2013 Apr 1;187(7):680-9.

R95-0013 Broom C. Design of first-administration studies in healthy man. Early Phase Drug Evaluation in Man. O'Grady J, Linet OI (Eds.), Macmillan Press: London, 1990, 206 213.

R01-1277 Davis PB, Drumm M, Konstan MW. Cystic fibrosis. Am J Respir Crit Care Med. 1996;154(5):1229-56.

R06-1037 Guidance for industry: estimating the maximum safe starting dose in initial clinical trials for therapeutics in adult healthy volunteers. U.S.Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER) 2005.

R07-4722 Guidance for industry: E14 clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs. Rockville: U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER); 2005.

R09-4830 Brown BD, Badilini F. HL7 aECG implementation guide (March 21, 2005).

R15-3034 Chronic respiratory diseases: burden of COPD. www.who.int/respiratory/copd/burden/en/ (access date: 11 June 2015) ; World Health Organization (2015).

R15-4955 Clunes MT, Boucher RC. Drug Discov Today Dis Mech. Cystic Fibrosis: The Mechanisms of Pathogenesis of an Inherited Lung Disorder. 2007;4(2):63-72.

R15-4984 Elborn JS, Shale DJ. Lung injury in cystic fibrosis. Thorax 1990; 45:970-973.

R15-5349 Knowles MR, Church NL, Waltner WE, Yankaskas JR, Gilligan P, King M, Edwards LJ, Helms RW, Boucher RC. A pilot study of aerosolized amiloride for the treatment of lung disease in cystic fibrosis. N Engl J Med. 1990 Apr 26;322(17):1189-94.

R15-5485 App EM, King M, Helfesrieder R, Köhler D, Matthys H. Acute and longterm amiloride inhalation in cystic fibrosis lung disease. A rational approach to cystic fibrosis therapy. Am Rev Respir Dis. 1990 Mar;141(3):605-12.

R15-5486 Clarke LL, Grubb BR, Gabriel SE, Smithies O, Koller BH, Boucher RC. Defective epithelial chloride transport in a gene-targeted mouse model of cystic fibrosis. Science. 1992 Aug 21;257(5073):1125-8.

R15-5487 Koehler D, App E, Schmitz-Schumann M, Wuertemberger G, Matthys H. Inhalation of amiloride improves the mucociliary and the cough clearance in patients with cystic fibroses. Eur J Respir Dis Suppl 146, 319 – 326 (1986).

R15-5503 Walters S, Mehta A. Epidemiology of cystic fi brosis. In: Hodson M, Geddes DM, Bush A, eds. Cystic fibrosis, 3rd edn. London: Edward Arnold Ltd, 2007: 21–45.

R15-5505 Pons, G., Marchand, M. C., D'Athis, P., Sauvage, E., Foucard, C., Chaumet-Riffaud, and Lenoir, G. (2000). French multicenter randomized double-blind placebo-controlled trial on nebulized amiloride in cystic fibrosis patients. Pediatr. Pulmonol., 30(1), 25-31.

R15-5507 Mall, M. A., Button, B., Johannesson, B., Zhou, Z., Livraghi, A., Caldwell, R. A, and Boucher, R. C. Airway surface liquid volume regulation determines different airway phenotypes in liddle compared with βENaCoverexpressing mice. J. Biol. Chem., 285(35), 26945-26955 2010.

R15-5546 Genes and human disease: monogenic diseases. who.int/genomics/publicdiseases/en/index2.html#CF (access date: 28 October 2015); Geneva: World Heath Organization (WHO) (2015).

R15-5599 Graham, A., Hasani, A., Alton, E. W. F. W., Martin, G. P., Marriott, C., Hodson, M. E., and Geddes, D. M. (1993). No added benefit from nebulized amiloride in patients with cystic fibrosis. Eur. Respir. J., 6(9), 1243-1248.

R16-0366 E14 Implementation Working Group. ICH E14 guideline: the clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs: questions & answers (R3) (current version dated 10 December 2015). http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E1 4/E14_Q_As_R3__Step4.pdf (access date: 29 January 2015) ; Geneva: International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; 2015.

R17-1997 Rowe S.M., Verkman A.S. Cystic Fibrosis Transmembrane Regulator Correctors and Potentiators. Cold Spring Harb Perspect Med 2013;3:a00976.

9.2 UNPUBLISHED REFERENCES

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

c10884768 Safety, tolerability and pharmacokinetics of single rising inhaled doses of BI 443651 in healthy male volunteers in a partially randomised, single blind, placebo-controlled trial.

c16304878 Investigator`s Brochure BI 1265162 Cystic fibrosis and COPD 05 September 2017.

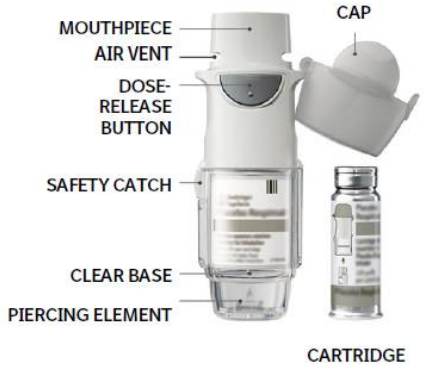
U97-0056 A three-way crossover study in healthy volunteers of lung deposition of fenoterol hydrobromide (100 µg via one puff) delivered from either a BINEB® (ARIANE) nebuliser, or a conventional MDI, or conventional MDI with a spacer. (260.2706) 20 June 1996.

10. APPENDICES

10.1 HANDLING INSTRUCTIONS FOR RESPIMAT INHALER FOR USE IN CLINICAL TRIALS

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.



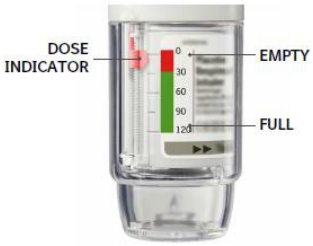
How to store BI 1265162 RESPIMAT

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.

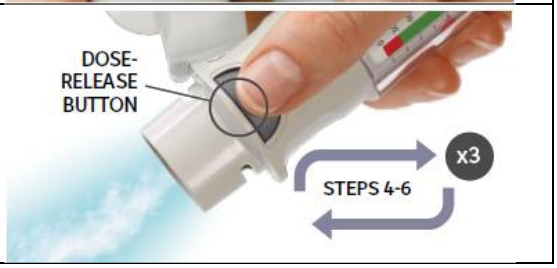
When to get a new BI 1265162 RESPIMAT



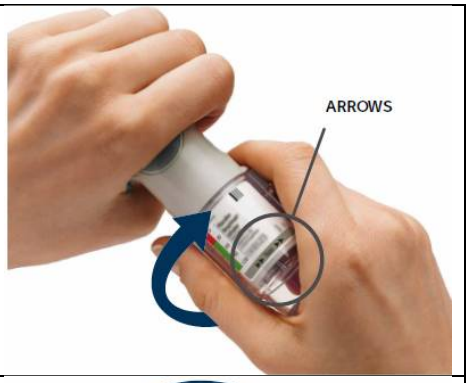
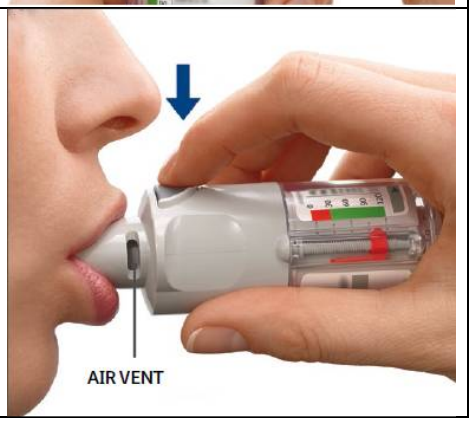
- BI 1265162 RESPIMAT inhaler contains 120 puffs if used as indicated.
- The dose indicator shows approximately how much medication is left.
- When the dose indicator enters the red area of the scale, get a new BI 1265162 RESPIMAT from the investigational site; there are approximately 30 puffs left.
- 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.

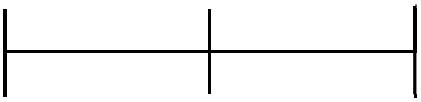
Did you repeat Turn, Open, Press less than three times after inserting the cartridge?
Repeat Turn, Open, Press three times after inserting the cartridge as shown in the steps 4 to 6 under “Prepare for first Use”.

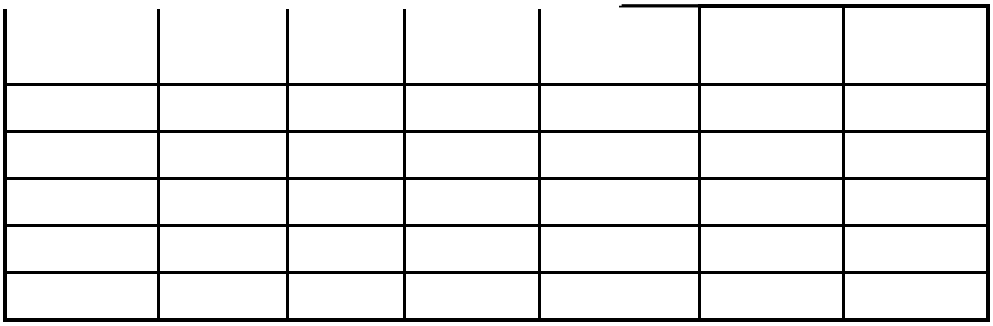
Is the dose indicator on BI 1265162 RESPIMAT pointing to 0? If the dose indicator points to 0, you have used up all your medication and the inhaler is locked.
Once BI 1265162 RESPIMAT is assembled, do not remove the clear base or the cartridge.
Always insert a new cartridge into a **NEW** RESPIMAT.

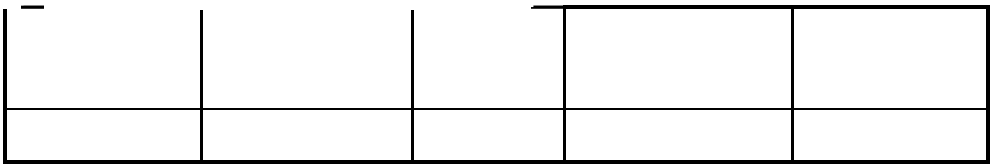
Further information

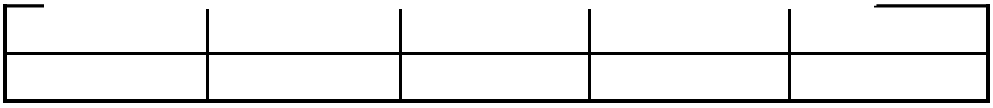
BI 1265162 RESPIMAT inhaler must not be disassembled after inserting the cartridge and replacing the clear base.
Do not touch the piercing element inside the base.

Boehringer Ingelheim Pharma GmbH & Co. KG
D - 55216 Ingelheim, Germany









11. DESCRIPTION OF GLOBAL AMENDMENT(S)

This is the original protocol.

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

Boehringer Ingelheim

APPROVAL / SIGNATURE PAGE

Document Number: c15848245 **Technical Version Number:1.0**

Document Name: clinical-trial-protocol

Title: Safety, tolerability and pharmacokinetics of single rising inhaled doses of BI 1265162 in healthy male volunteers in a partially randomised, single blind, placebo-controlled trial

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Author-Clinical Monitor		19 Sep 2017 14:30 CEST
Approval-Team Member Medicine		19 Sep 2017 14:41 CEST
Author-Trial Statistician		19 Sep 2017 15:42 CEST
Approval-Therapeutic Area		19 Sep 2017 16:17 CEST
Author-Trial Clinical Pharmacokineticist		20 Sep 2017 09:05 CEST
Verification-Paper Signature Completion		20 Sep 2017 13:19 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed

LOCAL SIGNATURE

(Principal Investigator)

Trial Title: **Safety, tolerability and pharmacokinetics of single rising inhaled doses of BI 1265162 in healthy male volunteers in a partially randomised, single blind, placebo-controlled trial**

Trial Number: **1399-0001**

Clinical Trial Protocol Version: **1.0**

I herewith certify that I agree to adhere to the Clinical Trial Protocol and to all documents referenced in the Clinical Trial Protocol.

Principal Investigator (Print full name) Site number

20 Sep 2017
Date (dd Mmm yyyy) Signature

The signature section for the Principal Investigator will not be completed in case the signature will be provided electronically via the Portal Clinergize™. The e-signature statement will appear on the bottom of this page.

LOCAL SIGNATURE

(Local Clinical Monitor)

Trial Title: **Safety, tolerability and pharmacokinetics of single rising inhaled doses of BI 1265162 in healthy male volunteers in a partially randomised, single blind, placebo-controlled trial**

Trial Number: **1399-0001**

Clinical Trial Protocol Version: **1.0**

I herewith certify that I agree to adhere to the Clinical Trial Protocol and to all documents referenced in the Clinical Trial Protocol.

_____
Local Clinical Monitor (Print full name)

19 SEP 2017
Date (dd Mmm yyyy) Signature

Clinical Trial Protocol

	Document Number: c15848245-03
EudraCT No.:	2017-001106-15
BI Trial No.:	1399-0001
BI Investigational Product:	BI 1265162
Title:	Safety, tolerability and pharmacokinetics of single rising inhaled doses of BI 1265162 in healthy male volunteers in a partially randomised, single blind, placebo-controlled trial
Lay Title	This study tests the safety, tolerability and how different doses of BI 1265162 are taken up in the body of healthy men.
Clinical Phase:	I
Trial Clinical Monitor:	Phone: Fax:
Principal Investigator:	Phone: Fax:
Status:	Final Protocol (Revised Protocol (based on global amendment 2))
Version and Date:	Version: 3.0 Date: 19 February 2018
Page 1 of 82	

CLINICAL TRIAL PROTOCOL SYNOPSIS

Name of company: Boehringer Ingelheim		**Tabulated Trial Protocol**	
Name of finished product: Not applicable			
Name of active ingredient: BI 1265162			
Protocol date: 19 September 2017	**Trial number:** 1399-0001		**Revision date:** 19 February 2018

Title of trial:	Safety, tolerability and pharmacokinetics of single rising inhaled doses of BI 1265162 in healthy male volunteers in a partially randomised, single blind, placebo-controlled trial
Principal Investigator:	
Trial site:	
Clinical phase:	I
Objectives:	To investigate safety, tolerability and pharmacokinetics, following single doses of BI 1265162
Methodology:	Single-blind, partially randomised within dose groups, placebo-controlled, parallel-group design
No. of subjects:	
total entered:	56*
each treatment:	8 per dose group (6 on active drug and 2 on placebo) * Additional subjects may be entered to allow testing of additional doses on the basis of experience gained during the trial conduct (e.g. preliminary PK data), provided the planned and approved highest dose will not be exceeded. Thus, the actual number of subjects entered may exceed 56, but will not exceed 72 subjects entered.
Diagnosis:	Not applicable
Main criteria for inclusion:	Healthy male subjects, age of 18 to 50 years, body mass index (BMI) of 18.5 to 29.9 kg/m^2
Test product:	BI 1265162
dose:	
mode of admin.:	Inhalation by RESPIMAT
Comparator product:	Placebo
dose:	Not applicable
mode of admin.:	Inhalation by RESPIMAT
Duration of treatment:	Single dose

Name of company: Boehringer Ingelheim		**Tabulated Trial Protocol**	
Name of finished product: Not applicable			
Name of active ingredient: BI 1265162			
Protocol date: 19 September 2017	**Trial number:** 1399-0001		**Revision date:** 19 February 2018
Criteria for pharmacokinetics:	Secondary endpoints: AUC_{t1-t2} and C_{max}		
Criteria for safety:	Primary endpoint to assess safety and tolerability of BI 1265162 is the number [N (%)] of subjects with drug-related adverse events. Further criteria of interest: AEs including clinically relevant findings from the physical examination, safety laboratory tests, 12-lead electrocardiogram (ECG), continuous ECG monitoring, vital signs (blood pressure [BP], pulse rate [PR]) .		
Statistical methods:	Descriptive statistics will be calculated for all endpoints.		

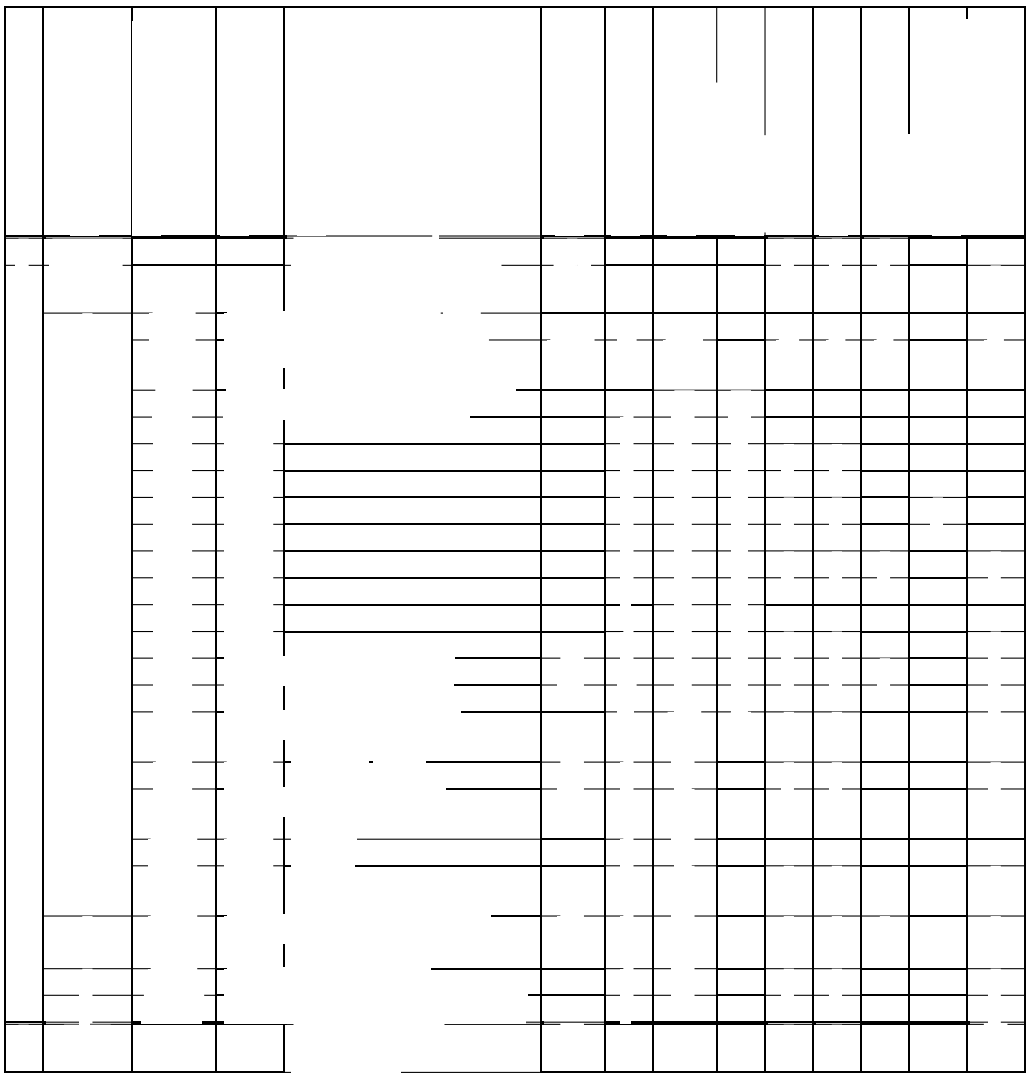


TABLE OF CONTENTS

ABBREVIATIONS

AE	Adverse event
AESI	Adverse events of special interest
AMG	Arzneimittelgesetz (German drug law)
ANCOVA	Analysis of covariance
AUC_{t1-t2}	Area under the concentration-time curve of the analyte in plasma over the time interval t_1 to t_2
BI	Boehringer Ingelheim
b.i.d.	*Bis in die*, twice daily
BLQ	Below limit of quantification
BMI	Body mass index (weight divided by height squared)
BP	Blood pressure
CA	Competent authority
CF	Cystic fibrosis
CI	Confidence interval
C_{max}	Maximum measured concentration of the analyte in plasma
COPD	Chronic obstructive pulmonary disease
CRF	Case report form
CTP	Clinical trial protocol
CTR	Clinical trial report
CV	Arithmetic coefficient of variation
DILI	Drug induced liver injury
ECG	Electrocardiogram
EDTA	Ethylenediaminetetraacetic acid

EOT	End of trial
gCV	Geometric coefficient of variation
gMean	Geometric mean
HR	Heart rate
IB	Investigator's brochure
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ISF	Investigator site file
LC-MS/MS	Liquid chromatography with tandem mass spectrometry
MedDRA	Medical Dictionary for Regulatory Activities
NC	Not calculated
NOA	Not analysed
NOAEL	No observed adverse effect level
NOR	No valid result
NOS	No sample available
NOTEL	No toxic effect level
PK	Pharmacokinetic(s)
PKS	Pharmacokinetic set
PR	Pulse rate
q.d.	*Quaque die*, once daily
QT	Time between start of the Q-wave and the end of the T-wave in an electrocardiogram
QTc	QT interval corrected for heart rate using the method of Fridericia (QTcF) or Bazett (QTcB)
RDC	Remote data capture
REP	Residual effect period
SAE	Serious adverse event
SCR	Screening
SRD	Single-rising dose
SUSAR	Suspected Unexpected Serious Adverse Reaction

TMF	Trial master file
TDMAP	Trial Data Management and Analysis Plan
TSAP	Trial statistical analysis plan
ULN	Upper limit of normal

2.2 TRIAL OBJECTIVES

The primary objective of this trial is to investigate the safety and tolerability of BI 1265162 in healthy male subjects following inhalative administration of single rising doses.

Secondary objective is the exploration of the pharmacokinetics (PK) of BI 1265162 after single dosing.

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

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

This single-rising dose trial is designed as single-blind, partially randomised, and placebo-controlled within parallel dose groups.

Partially randomised means that the subjects will be treated in two equally sized cohorts per dose group, with the first cohort being treated in a fixed sequence and the second cohort being treated in a randomised order.

A total of 56 healthy male subjects is planned to participate in the trial, according to 7 sequential groups comprising 8 subjects per group. However, additional subjects may be entered to allow testing of intermediate doses within the planned and approved dose range on the basis of experience gained during trial conduct (e.g. preliminary PK data), i.e. the actual number of subjects entered may exceed 56. Such changes may be implemented via non-substantial CTP Amendments.

Within each dose group, 6 subjects will receive the active drug and 2 will receive placebo. Only one dose is tested within each dose group

The dose groups to be evaluated are outlined in Table 3.1: 1 below.

On the first study day of each dose level, the first cohort will be treated in the following order: first subject (active) followed at least 1 h later by the second subject (placebo) followed at least 1 h later by the third subject (active) followed at least 10 min later by the fourth subject (active). If BI 1265162 treatment is safe and showed acceptable tolerability in the first cohort, the subjects in the second cohort will be treated not earlier than 2 days later than the first treated volunteer in the first cohort. In the second cohort, a time interval of at least 10 min will be maintained between dosing of individual subjects in a random order. The dose groups will be investigated consecutively in ascending order of doses. A time interval of at least 6 days will be maintained between the administration of the study drug to the first cohort in a dose group and the first cohort in the next dose group. The decision to proceed to the next dose group will be based upon the safety, tolerability data of the preceding dose groups and explorative PK data in some dose groups (see Section 7.3.4).

The next dose will only be given if, in the opinion of the investigator, no safety concerns arose in the preceding dose group (i.e. no dose-limiting events occurred) and if none of the pre-specified trial-specific stopping criteria were met (refer to Section 3.3.4.2).

A documented Safety Review must take place prior to each dose escalation. Furthermore, an unscheduled safety review meeting can be requested anytime for any reasonable cause by the Principal Investigator (or an authorised deputy) or the sponsor of the study, e.g. because of any unforeseen adverse events, etc. Dose escalation will only be permitted if no safety concerns exist in the opinion of the Principal Investigator (or an authorised deputy) and the Trial Clinical Monitor (or an authorised deputy).

The minimum data set for review consists of the following data:

- AEs in the current and preceding dose groups up to at least 48h post dosing (including clinically relevant findings from ancillary safety testing listed below) (Note: AEs may be ongoing at the time of Safety Reviews and AE information may be subject to change prior to Database Lock)
- Results from 12-lead ECG and continuous ECG monitoring in the current and preceding dose groups.
- Vital signs in the current and preceding dose groups
- Clinical laboratory tests in the current and preceding dose groups
- Preliminary PK data as per Section 7.3.4
- Check of criteria for stopping subject treatment as per Section 3.3.4.1

The decision to escalate the dose will be made jointly by the Principal Investigator (or an authorised deputy) and the Trial Clinical Monitor (or an authorised deputy) after in-depth analysis of all available safety data, especially SAEs (if occurred), AEs and out-of-range laboratory results (if considered clinically significant). Safety Reviews can be conducted face-to-face or by video/telephone conference. The Trial Clinical Monitor is responsible for organization and minutes of the reviews. Minutes will be signed off by the Principal Investigator (or an authorised deputy) and filed in the ISF and TMF.

The investigator (after consultation with the sponsor) is allowed to alter the scheduled dose levels (e.g. add low and/or intermediate dose levels) on the basis of experience gained during the study, provided the planned and approved highest dose is not exceeded. In this case, the total number of subjects in this trial might increase. The investigator and/or the sponsor should stop dose escalation in case the safety evaluation leads to concerns that would not allow higher dosing.

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

3.1.1 Administrative structure of the trial

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

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

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

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

Safety laboratory tests will be performed by the local laboratory of the trial site (Medizinisches Versorgungszentrum Dr. Klein, Dr. Schmitt & Partner, Kaiserslautern, Germany).

The analyses of BI 1265162 concentrations in plasma and urine will be performed at the Department of Drug Metabolism and Pharmacokinetics, BI Pharma GmbH & Co. KG, Biberach, Germany.

The digitally recorded 12-lead ECGs will be sent to a specialised contract research organisation ( ) for evaluation.

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

Data management and statistical evaluation will be done by BI or a contract research organisation appointed by BI according to BI SOPs.

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

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

For single -rising dose trials, the design described in Section 3.1 is viewed favourable under the provision not to expose the subjects involved to undue risks since the main study objective is to investigate safety and tolerability of BI 1265162.

With the rising dose design, single-blind conditions regarding the subject's treatment (active or placebo) are maintained within each dose group. However, the current dose level will be known to subjects and investigators. The disadvantage of this trial design is a possible observer bias with regard to the dose-depending effects as well as time effects, but it has the virtue of minimizing subject risk by sequentially studying ascending doses. As time-effects

are expected to be small relative to the differences between the doses in the broad range investigated, unbiased comparisons between treatments can still be expected.

It is standard in trials involving healthy volunteers to include a placebo group as control for the evaluation of safety and tolerability. Each dose group consists of 8 subjects with 6 on active treatment, and 2 on placebo. The placebo control group includes all subjects of all dose groups treated with placebo. 6 subjects per active treatment group are in general considered as sufficient for the exploratory evaluation of pharmacokinetics.

3.3 SELECTION OF TRIAL POPULATION

It is planned that 56 healthy male will enter the study. The actual number of subjects entered may exceed the total of 56 if additional intermediate doses will be tested (see Section 3.1). Subjects will be recruited from the volunteers' pool of the trial site.

Only male subjects will be included into the study because hitherto no data on reproductive toxicology are available.

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

3.3.1 Main diagnosis for study entry

The study will be performed in healthy subjects.

3.3.2 Inclusion criteria

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

1. Healthy male subjects according to the assessment of the investigator, based on a complete medical history including a physical examination, vital signs (BP, PR), 12-lead ECG, and clinical laboratory tests
2. Age of 18 to 50 years (incl.)
3. BMI of 18.5 to 29.9 kg/m^2 (incl.)
4. FEV_1 and FVC of equal or greater than 80% of predicted normal, at screening and prior to randomisation
5. 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) is deviating from normal and judged as clinically relevant by the investigator

2. Repeated measurement of systolic blood pressure outside the range of 90 to 140 mmHg, diastolic blood pressure outside the range of 50 to 90 mmHg, or pulse rate outside the range of 50 to 90 bpm
3. Any laboratory value outside the reference range that the investigator considers to be of clinical relevance
4. Any evidence of a concomitant disease judged as clinically relevant by the investigator
5. Gastrointestinal, hepatic, renal, respiratory, cardiovascular, metabolic, immunological or hormonal disorders
6. Cholecystectomy and/or surgery of the gastrointestinal tract that could interfere with the pharmacokinetics of the trial medication (except appendectomy and simple hernia repair)
7. Diseases of the central nervous system (including but not limited to any kind of seizures or stroke), and other relevant neurological or psychiatric disorders
8. History of relevant orthostatic hypotension, fainting spells, or blackouts
9. Chronic or relevant acute infections
10. History of relevant allergy or hypersensitivity (including allergy to the trial medication or its excipients)
11. Use of drugs within 30 days prior to administration of trial medication if that might reasonably influence the results of the trial (incl. QT/QTc interval prolongation)
12. Participation in another trial where an investigational drug has been administered within 60 days prior to planned administration of trial medication, or current participation in another trial involving administration of investigational
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 30 g per day for males)
16. Drug abuse or positive drug screening
17. Blood donation of more than 100 mL within 30 days prior to administration of trial medication or intended donation during the trial
18. Intention to perform excessive physical activities within one week prior to administration of trial medication or during the trial
19. Inability to comply with dietary regimen of trial site
20. A marked baseline prolongation of QT/QTc interval (such as QTc intervals that are repeatedly greater than 450 ms in males) or any other relevant ECG finding at screening
21. A history of additional risk factors for Torsades de Pointes (such as heart failure, hypokalemia, or family history of Long QT Syndrome)
22. A history of chronic kidney disease (EGFR $\underline{<59}$ mls/min including corrections as per ethnicity)
23. Subject is assessed as unsuitable for inclusion by the investigator, for instance, because considered not able to understand and comply with study requirements, or has a condition that would not allow safe participation in the study
24. The subject has a diagnosis history of pulmonary hyperreactivity

25. Male subjects with WOCBP partner who are unwilling to use male contraception (condom or sexual abstinence) from the first administration of trial medication until 14 days after last administration of trial medication (BI 1265162 or placebo)

For study restrictions, refer to Section 4.2.2.

3.3.4 Removal of subjects from therapy or assessments

3.3.4.1 Removal of individual subjects

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

- The subject withdraws consent for trial treatment or trial participation, without the need to justify the decision
- The subject needs to take concomitant drugs that interfere with the investigational product or other trial medication
- The subject is no longer able to participate for other medical reasons (such as surgery, adverse events (AEs), or diseases)

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

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

If a subject is removed from or withdraws from the trial prior to first administration of trial medication, the data of this subject will not be entered in the case report form (CRF) or trial database and will not be reported in the clinical trial report (CTR). If a subject is removed from or withdraws from the trial after first administration of trial medication, this will be documented and the reason for discontinuation must be recorded in the CRF. In this case, the data will be included in the CRF/trial database and will be reported in the CTR. At the time of discontinuation a complete end of trial examination will be performed if possible and the information will be recorded in the CRFs. If the discontinuation occurs before the end of the REP (see Section 5.2.2.2), the discontinued subject should if possible be questioned for AEs and concomitant therapies at or after the end of the REP in order to ascertain collection of AEs and concomitant therapies throughout the REP, if not contrary to any consent withdrawal of the subject. These discontinuations will be discussed in the CTR.

3.3.4.2 Discontinuation of the trial by the sponsor

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

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

- The expected enrolment goals overall or at a particular trial site are not met
- Violation of GCP, or the CTP, or the contract with BI by a trial site or investigator, disturbing the appropriate conduct of the trial
- The sponsor decides to discontinue the further development of the investigational product.
- Dose escalation will be stopped as soon as at least 2 subjects at one dose level on active drug showed relevant individual QT prolongation, i.e. a QTc increase of greater 60 ms from baseline in connection with absolute QT or QTc greater than 500 ms, which has been confirmed by a repeat ECG recording (e.g. follow-up ECG).

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

3.3.5 Replacement of subjects

In case that more than 2 subjects on active per dose group do not complete the trial, the trial clinical monitor together with the trial pharmacokineticist and the trial statistician are to decide if and how many subjects will be replaced. A replacement subject will be assigned a unique study subject number, and will be assigned to the same treatment as the subject he replaces.

4. TREATMENTS

4.1.2 Method of assigning subjects to treatment groups

Prior to the screening visit, subjects will be contacted in writing and informed about the planned visit dates. The subjects willing to participate will be recruited to dose groups according to their temporal availability. As soon as enough subjects have been allocated to 1 of the 14 dose cohorts (2 cohorts per dose group), the following subjects will be allocated to one of the other dose cohorts. Therefore, the allocation of subjects to dose cohorts is not influenced by trial personnel, but only by the subjects' temporal availability. As the study

includes healthy subjects from a homogenous population, relevant imbalances between the dose groups are not expected.

The randomization list with study subject numbers and allocated treatments will be provided to the trial site and the sponsor (TCM) in advance. The allocation of subjects to study subject numbers will be performed prior to the first administration of trial medication. For this purpose, the subjects will be allocated to a study subject number by the method 'first come first served'. Once a subject number has been assigned, it cannot be reassigned to any other subject.

The randomisation procedure is described in Section 7.5.

4.1.3 Selection of doses in the trial

The doses selected for this trial cover the subtherapeutic as well as the estimated therapeutic range and include a safety margin (see Section 1.2).

4.1.4 Drug assignment and administration of doses for each subject

The treatments to be evaluated are outlined in Table 4.1.4: 1 below. The number of actuations for placebo corresponds to the number of actuations of the respective dose level.

Each newly assembled RESPIMAT Inhaler (has to be done on the day of application) has to be primed by qualified medical/pharmaceutical study personnel at the trial site under the responsibility of the investigator. To avoid contamination, except those devices used for training, priming should NOT take place in the same room where the subject is inhaling trial medication or the trial will be performed or samples will be processed. The inhaler should be primed under e.g. hood/outside by actuating it until an aerosol is visible plus three additional actuations. All priming actuations should be directed to the ground. For detailed priming instructions please refer to the RESPIMAT Inhaler handling instructions in Appendix 10.1.

Both the study drug as well as the placebo treatment (depending on randomisation) will be inhaled with the RESPIMAT in a sitting or standing position under supervision of the investigating physician or an authorised designee. If more than one actuation is needed, planned time 0:00h will always be the first actuation. If more than one actuation will be needed, the duration from first to last actuation will be recorded. 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.

The so-called four-eye principle (two-person rule) should be applied for administration of trial medication and – if applicable – its preparation (e.g. assembling of device), otherwise correct dosage cannot be ensured.

Subjects will be kept under close medical surveillance until 24 h following drug administration. During the first 4 h after 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 except for medical examination), or to sleep. For restrictions with regard to diet see Section 4.2.2.2.

4.1.5 Blinding and procedures for unblinding

4.1.5.1 Blinding

The treatments administered (active or placebo) will be single-blind (blinded to subjects only). However, the current dose level will be known to the subjects.

Within the ECG laboratory, the staff involved with interval measurements and assessments will be blinded with respect to the treatment and also with regard to the recording date and time as well as the time points of the ECGs. The interval measurements for a given subject will be performed in a random and blinded sequence by a single technician. No more than two different blinded readers will evaluate the ECGs of the study.

In addition, the trial pharmacokineticist, trial pharmacometrician and bioanalyst may receive the randomisation codes prior to official unblinding to perform the interim / preliminary PK analysis. He or she will confirm in writing that the codes will be treated confidentially.

In addition, the drug metabolism scientist may receive the randomisation codes prior to official unblinding to perform metabolites in safety testing analysis (MIST). He or she will confirm in writing that the codes will be treated confidentially.

The database of this trial will be handled open-label, because no bias with regard to data cleaning of safety measures is expected.

4.1.5.2 Procedures for emergency unblinding

As this trial will be conducted single-blinded, the treatment information will be known. Therefore, no emergency envelopes will be provided.

4.1.6 Packaging, labelling, and re-supply

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

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

- BI trial number
- Name of product and strengths or identification code
- Pharmaceutical dosage form, quantity of dosage units

- Route and mode of administration
- Term 'For Clinical Trial Use' (domestic language)
- Sponsor name and address
- Storage conditions
- Use-by date
- Subject or medication number
- Batch Number

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

No re-supply is planned.

4.1.7 Storage conditions

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

4.1.8 Drug accountability

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

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

Only authorised personnel as documented in the form 'Trial Staff List' may dispense medication to trial subjects. The trial medication must be administered in the manner specified in the CTP. All unused medication will be disposed locally by the trial site upon written authorisation by the clinical monitor. Receipt, usage and disposal must be documented on the respective forms. Account must be given for any discrepancies.

The investigator must maintain records of the product's delivery to the trial site, the inventory at the site, the use by each subject, and the disposal of unused products.

These records will include dates, quantities, batch / serial numbers, expiry ('use-by') dates, and the unique code numbers assigned to the investigational products and trial subjects. The

investigator will maintain records that document adequately that the subjects were provided the doses specified by the CTP, and that reconcile all investigational products received from the sponsor.

4.2 OTHER TREATMENTS, EMERGENCY PROCEDURES, RESTRICTIONS

4.2.1 Other treatments and emergency procedures

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

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

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

From 1 h before drug intake until lunch, fluid intake is restricted to 240 mL of water served at 2 h and 4 h post-dose (mandatory for all subjects). From lunch onwards, liquid intake is restricted to an additional 3000 mL. Subjects will be asked to drink the additional amount till one hour prior to the stop of urine collection on day 2. The total amount of liquid intake will be documented.
Standardised meals (identical for each dose group) will be served at the time points described in the study Flow Chart. Use of table salt is not allowed during in-house confinement at the trial site.

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

Alcoholic beverages, consumption of seafood and dried fruits are not permitted from 48 hours before the study drug administration and until last blood sampling.

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

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

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

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

4.3 TREATMENT COMPLIANCE

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

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

5. VARIABLES AND THEIR ASSESSMENT

5.1 EFFICACY - CLINICAL PHARMACOLOGY

5.1.1 Endpoints of efficacy

No efficacy endpoints will be evaluated in this trial.

5.1.2 Assessment of efficacy

Not applicable.

5.2 SAFETY

5.2.1 Endpoints of safety

Primary endpoint to assess safety and tolerability of BI 1265162 is the number [N (%)] of subjects with drug-related adverse events.

Further criteria of interest:

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

5.2.2 Assessment of adverse events

5.2.2.1 Definitions of adverse events

Adverse event

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

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

Serious adverse event

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

- results in death,

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

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

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

AEs considered 'Always Serious'

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

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

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

Adverse events of special interest (AESIs)

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

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

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

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

Intensity (severity) of AEs

The intensity (severity) of 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

Causal relationship of AEs

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

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

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

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

- No plausible time to onset of the event relative to the time of drug exposure is evident (e.g. pre-treatment cases, diagnosis of cancer or chronic disease within days / weeks of drug administration; an allergic reaction weeks after discontinuation of the drug concerned)
- Continuation of the event despite the withdrawal of the medication, taking into account the pharmacological properties of the compound (e.g. after 5 half-lives). Of note, this criterion may not be applicable to events whose time course is prolonged despite removing the original trigger.

- Additional arguments amongst those stated before, like alternative explanation (e.g. situations where other drugs or underlying diseases appear to provide a more likely explanation for the observed event than the drug concerned).
- Disappearance of the event even though the trial drug treatment continues or remains unchanged.

5.2.2.2 Adverse event collection and reporting

AE collection

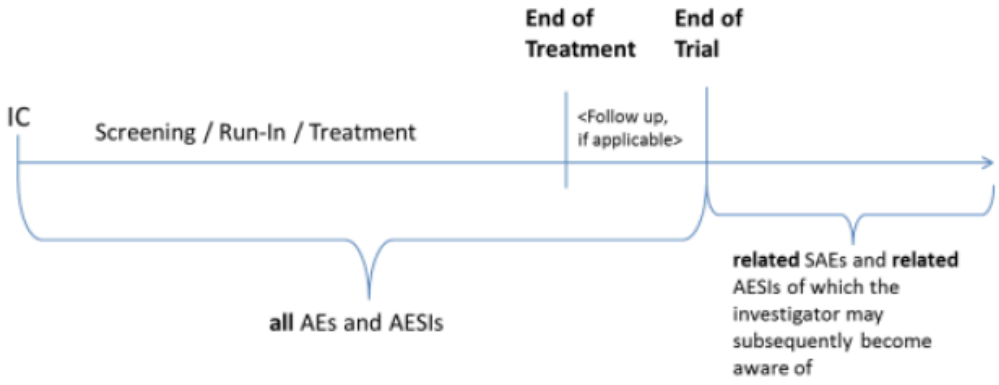
Upon enrolment into a trial, the subject's baseline condition is assessed (for instance, by documentation of medical history/concomitant diagnoses), and relevant changes from baseline are noted subsequently.

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

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

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

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



The REP for BI 1265162, when measurable drug levels or PD effects are still likely to be present after the last administration, is not known for this first-in-human trial. Therefore, all AEs reported until the end of trial examination (last per protocol contact) will be considered on treatment; please see Section 7.3.3.

AE reporting to sponsor and timelines

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

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

Information required

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

The following should also be recorded as an (S)AE in the CRF and 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 CRF only.

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

5.2.3 Assessment of safety laboratory parameters

For the assessment of laboratory parameters, blood and urine samples will be collected by the trial site at the time points indicated in the Flow Chart after the subjects have fasted for at least 8 h (excluding sample at 06:00h post administration).

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

Category	**Test name**	A[1]	B[2]	C[3]
Haematology	Haematocrit	X	X	X
	Haemoglobin	X	X	X
	Red blood cells (RBC)	X	X	X
	White blood cells (WBC)	X	X	X
	Platelets	X	X	X
	Reticulocyte count	X	X	X
Automatic WBC differential (relative and absolute)	Neutrophiles	X	X	X
	Eosinophils	X	X	X
	Basophils	X	X	X
	Monocytes	X	X	X
	Lymphocytes	X	X	X
Manual differential WBC (if automatic differential WBC is abnormal and clinically relevant in the opinion of the investigator)	Polymorphnuclear neutrophils (segs), band neutrophils (stabs), eosinophils, basophils, monocytes, lymphocytes			
Coagulation	Activated partial thromboplastin time (aPTT)	X	X	X
	Prothrombin Time (Quick and INR)	X	X	X
Enzymes	Aspartate aminotransferase (AST/GOT, SGOT)	X	X	X
	Alanine aminotransferase (ALT/GPT, SGPT)	X	X	X
	Alkaline phosphatase	X	X	X
	Gammaglutamyl transferase (GGT)	X	X	X
	Lactate dehydrogenase	X	X	X
	Amylase	X	X	X
	Lipase	X	X	X

Table 5.2.3: 1 Routine laboratory tests (cont'd)

Category	**Test name**	A[1]	B[2]	C[3]
Substrates	Glucose (plasma)	X	-	-
	Creatinine	X	X	X
	eGFR, calculated from serum creatinine using CKD-EPI formula	X	X	X
	Bilirubin, total	X	X	X
	Bilirubin, direct	X	X	X
	Cholesterol, total	X	X	X
	Triglycerides	X	X	X
	C-reactive protein	X	X	X
	Urea	X	X	X
Electrolytes	Calcium	X	X	X
	Sodium	X	X	X
	Potassium	X	X	X
	Chloride	X	X	X
Hormones	Thyroid stimulating hormone (TSH)	X	-	-
	*Aldosterone	-	X	-
0-4h and 0-24h collection Urine**	Urine potassium	-	X	-
	Urine sodium	-	X	-
	Urine chloride	-	X	-
	Urine creatinine	-	X	-
	Potassium-creatinine-quotient	-	X	-
	Sodium-creatinine-quotient	-	X	-
Urinalysis (Stix) [Urin-Sediment will be performed , if urinalysis abnormal]	Urine nitrite	X	X	X
	Urine protein	X	X	X
	Urine glucose	X	X	X
	Urine ketone	X	X	X
	Urobilinogen	X	X	X
	Urine bilirubin	X	X	X
	Urine RBC	X	X	X
	Urine WBC	X	X	X
	Urine pH	X	X	X
Urine sediment (microscopic examination if erythrocytes, leukocytes nitrite or protein are abnormal in urine)	Only positive findings will be reported (for instance, the presence of sediment bacteria, casts in sediment, squamous epithelial cells, erythrocytes, leukocytes)			

[1]A: parameters to be determined at screening examination
[2]B: parameters to be determined during the study (for time points refer to Flow Chart)
[3]C: parameters to be determined during the Follow-up-examination

* Aldosterone (after a 15-minute resting period in supine position) samples may be stored at about -20C in case shipment/analytics on the same day is not possible

** For baseline from blank urine sample (planned time -1:30), urine collected 0-4h and all Urine collected from 0-24h. These will be stored intermittent in a refrigerator. After processing the 12-24h PK urine fraction (cf. Section 5.5.2.3), all collected fractions (0-24h) will be mixed for the 24h urine electrolyte measurement. Mixing should be done by transferring the entire content of all collection containers into a single PE/PP or glass

container, and stirring the mixed fractions for about 1 min (manually or using a stir bar or other stirring device out of PE, PP, Teflon or glass).

The tests listed in Table 5.2.3: 2 are exclusionary laboratory tests which may be repeated as required. The results will not be entered in the CRF/database and will not be reported in the CTR. It is planned to perform these tests during screening only. Drug screening will be performed at screening and 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/p24-antigen (qualitative)

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

The laboratory tests listed in Table 5.2.3: 1 and 5.2.3: 2 will be performed at Medizinisches Versorgungszentrum Dr. Klein, Dr. Schmitt & Partner, Kaiserslautern, Germany with the exception of the urinalysis stix and drug screening tests. These tests will be performed at the trial site using Combur 9 Test (Roche Diagnostics, GmbH, Mannheim, Germany) and AccuSign® DOA 10 test (Diagnostik Nord GmbH, Schwerin, Germany).

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

5.2.4 Electrocardiogram

5.2.4.1 12-lead resting ECG

Recording

Twelve-lead resting ECGs (I, II, III, aVR, aVL, aVF, V1 - V6) will be recorded using a computerised electrocardiograph (CardioSoft EKG System, GE Medical Systems, Freiburg, Germany) at the time points given in the Flow Chart. Electrode placement will be performed according to the method of Wilson, Goldberger and Einthoven modified by Mason and Likar (hips and shoulders instead of ankles and wrists). Precise electrode placement will be marked with an indelible mark on the skin to allow reproducible placement throughout the study.

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 recording will always precede all other study procedures scheduled for the same time (except for blood drawing from an intravenous cannula that is already in place) to avoid compromising ECG quality.

ECGs will be recorded as single ECGs or as triplicate ECGs (i.e. three single ECGs recorded within 180 sec) as indicated in the Flow Chart. Three triple ECGs will be recorded at baseline as indicated in the Flow Chart.

ECGs may be repeated for quality reasons for instance due to alternating current artefacts, muscle movements, or electrode dislocation. For repetition within triplicate ECGs the time window of 180 sec applies as well. The repeat ECGs are assigned to the respective scheduled time point. For the repeats due to quality reasons, only the repeated ECG recordings will be sent to the central ECG lab, whereas the initially recorded ECGs will be discarded.

Additional (unscheduled) ECGs may be collected by the Investigator for safety reasons. These ECGs are assigned to the prior scheduled time point. Unscheduled ECGs will not be included into the statistical analysis of interval lengths.

Data transfer

ECGs will be transferred electronically to the central ECG lab
for evaluation.

In case of repeat ECGs due to quality reasons, only the repeated ECG recordings will be transferred to the central ECG lab, whereas the initially recorded ECGs will be discarded. Unscheduled ECGs (for safety reasons) will be transferred to the central ECG lab but will not be included into the statistical analysis of interval lengths.

Data transfer from the central ECG lab to the sponsor is described in the ECG data transfer agreement (see TMF).

Evaluation

a) Central ECG lab

Central ECG lab evaluation (of visit 2 ECGs only) will be performed for the first of three replicate ECGs per time point given in the Flowchart. For baseline, where 3 triplicate ECGs are recorded, only the first triplicate ECG (i.e. 3 single ECGs) will be evaluated.
RR and QT intervals will be determined semi-automatically, whereas PR, QRS intervals and QRS-axis are measured automatically by a validated GE 12-SL-algorithm or equivalent.

Heart rate (HR) and the QT interval corrected for HR (QTc e.g. QTcF and QTcB) will be determined by the sponsor (see TSAP for details).
All semi-automatic interval measurements in one subject will be performed on the

same lead. The intervals will be measured from four cardiac cycles (beats) in lead II. If lead II shows a flat T wave or is not measurable for any reason, lead V5 will be used, or if that lead is not measurable, then lead I will be used. The lead actually used will be reported in the CTR.
For automatic interval measurements no lead will be provided

For blinding arrangements see Section 4.1.5.1. No more than two blinded readers will evaluate all ECGs of the study. ECGs from a particular subject should be evaluated by a single reader. Evaluation of ECGs will comply with the ICH E14 guidance document and supplements [R07-4722, R16-0366] as well as the FDA requirements for annotated digital ECGs [R09-4830].

b) Trial site

All local ECGs will be evaluated by the investigator or a designee.

For the inclusion or exclusion (see Section 3.3) of a subject and for the assessment of cardiac safety during the study, the QT and QTcB values generated by the computerised ECG system or their manual corrections by the investigators will be used.
In doubtful cases, ECGs may be sent upfront (i.e. prior to the regular data transfer) for cardiologic assessment by the central lab. In this case, these centrally measured results would overrule any other results obtained.

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

5.2.4.2 Continuous ECG monitoring

Cardiac rhythm (including heart rate) will be monitored by means of continuous 3-lead ECG recording for at least 15 min before (for baseline assessment) until 4 h following drug administration using patient monitors (e.g. ApexPro Telemetry System, GE Medical Systems, Freiburg, Germany).

5.2.5 Assessment of other safety parameters

5.2.5.1 Vital signs

Systolic and diastolic blood pressures (BP) as well as pulse rate (PR) or heart rate (heart rate is considered to be equal to pulse rate) will be measured by a blood pressure monitor (e.g. Dash 3000, GE Medical Systems, Freiburg, Germany) at the times indicated in the Flow Chart, after subjects have rested for at least 5 min in a supine position. All recordings should be made using the same type of blood pressure recording instrument on the same arm if possible.

5.2.5.2 Medical examinations

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

5.4 APPROPRIATENESS OF MEASUREMENTS

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

5.5 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

Date and clock time of drug administration and pharmacokinetic sampling will be recorded in the CRFs. Planned sampling times should be adhered to as close as possible. However, these sampling times only represent guidance; thus, deviations which may occur especially shortly after inhalation are not regarded as protocol violations.

PK sampling times and periods may be adapted during the trial based on information obtained during trial conduct (e.g. preliminary PK data) including addition of samples and visits as long as the total blood volume taken per subject does not exceed 500 mL. Such changes would be implemented via non-substantial CTP Amendments.

5.5.1 Pharmacokinetic endpoints

The following pharmacokinetic parameters will be determined if feasible:

5.5.1.1 Secondary endpoints

- AUC_{t1-t2} (area under the concentration-time curve of the analyte in plasma over the time interval t_1 to t_2)

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

5.5.2 Methods of sample collection

5.5.2.1 Plasma sampling for pharmacokinetic analysis

For quantification of BI 1265162 plasma concentrations, 4.9 mL of blood will be taken from an antecubital or forearm vein into an K_3-EDTA (tripotassium ethylenediaminetetraacetic acid)-anticoagulant blood drawing tube at the times indicated in the Flow Chart. Blood will be withdrawn by means of either an indwelling venous catheter or by venipuncture with a metal needle.

The EDTA-anticoagulated blood samples will be centrifuged for about 10 min at about 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 1.0 mL plasma. The process from blood collection until transfer of plasma aliquots into the freezer should be completed within 60 min, with interim storage of blood samples and aliquots in ice water or on ice. For each aliquot the time when the sample was placed in the freezer will be documented. Until transfer on dry ice to the analytical laboratory, the aliquots will be stored upright at about -20°C or below at the trial site. 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 about -20°C or below until analysis.

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

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

5.5.3 Analytical determinations

5.5.3.1 Analytical determination of analyte plasma concentration

BI 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 Drug Metabolism and Pharmacokinetics Germany, Boehringer Ingelheim Pharma GmbH & Co KG, Biberach, Germany. All details of the analytical method will be available prior to the start of sample analysis.

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

5.6 BIOMARKER

Not applicable.

5.7 PHARMACODYNAMICS

Not applicable.

5.8 PHARMACOKINETIC - PHARMACODYNAMIC RELATIONSHIP

Not applicable.

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

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

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

The acceptable deviation from the scheduled time for vital signs, spirometry, ECG and laboratory tests will be ± 30 min for the first 4 h after trial 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 venipuncture are scheduled for the same time, venipuncture should be the last of the measurements (if at the same time point as spirometry, spirometry should be last measurement) due to its inconvenience to the subject and possible influence on physiological parameters.

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

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

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

6.2.1 Screening period

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

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

6.2.2 Treatment period

Each subject will receive one dose of the respective trial medication (BI 1265162 or placebo) at Visit 2.

Trial medication will be administered by each subject under direct supervision of the investigator or [redacted] designee. Details on treatments and procedures of administration are described in Section 4.1.4.

Study participants will be admitted to the trial site in the morning of Day 1 and kept under close medical surveillance for at least 24 h following drug administration. The subjects will then be allowed to leave the trial site after formal assessment and confirmation of their fitness by the investigator or [redacted] designee. On all other study days, the study will be performed in an ambulatory fashion.

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

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

6.2.3 End of trial period

For AE assessment, laboratory tests, recording of ECG and vital signs, and physical examination during the end of trial period, see Sections 5.2.2 to 5.2.5.
Subjects who discontinue treatment before the end of the planned treatment period should undergo the end of trial visit.

All abnormal values (including laboratory parameters) that are judged clinically relevant by the investigator will be monitored using the appropriate tests until a return to a medically acceptable level is achieved. Adverse events persisting after trial completion must be monitored until they have normalised or have been sufficiently characterised.

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

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 STATISTICAL DESIGN – MODEL

7.1.1 Objectives

The primary objective of this trial is to investigate the safety and tolerability of BI 1265162 by using descriptive statistics for all endpoints comparing active dose groups to placebo. The primary endpoint is defined in Section 5.2.1. Inferential statistics is not planned (as explained in Section 7.2).

The secondary objective is the exploration of the pharmacokinetics (PK) of BI 1265162 after single dosing. Endpoints as specified in Section 5.5.1 will be analysed by descriptive statistics. Secondary endpoints ($AUC_{t1\text{-}t2}$ and C_{max}) as defined in Section 5.5.1.1 will be subjected to The main analysis is based on the descriptive statistics and the is regarded as further analysis.

7.2 NULL AND ALTERNATIVE HYPOTHESES

Safety and tolerability of the different dose groups of BI 1265162 are to be determined on the basis of the investigated parameters in comparison to placebo. It is not planned to test any statistical hypotheses with regard to these variables in a confirmatory sense. Instead, they will be described in their entirety and evaluated by descriptive statistical methods.

Confidence intervals will be computed and will have to be interpreted in the perspective of the exploratory character of the study, i.e. confidence intervals are considered as interval estimates for effects.

7.3 PLANNED ANALYSES

All individual data will be listed.

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

7.3.1 Primary analyses

Analysis of safety and tolerability is described in Section 7.3.3.

7.3.2 Secondary analyses

The secondary parameters (refer to Section 5.5.1) will be calculated according to the BI Standard Operating Procedure (SOP) ‘Standards and processes for analyses performed within

Clinical Pharmacokinetics/Pharmacodynamics' (001-MCS-36-472). Analyses will be performed for parent drug.

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

Relevant protocol violations may be

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

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

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

The PK parameter analysis set (PKS) includes all subjects in the Treated Set (TS) who provide at least one PK parameter that was not excluded according to the description above.

Descriptive statistics will be calculated for PK endpoints.

7.3.3 Safety analyses

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

Treatments will be compared in a descriptive way. The placebo control group in the safety evaluation will consist of all placebo treated subjects, regardless of the dose group in which they were treated. The active treatment groups will be compared to the placebo group in a descriptive way. Tabulations of frequencies/proportions will be used for the evaluation of categorical (qualitative) data, and tabulations of descriptive statistics will be used to analyse continuous (quantitative) data.

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

Measurements (such as ECG, vital signs, or laboratory parameters) or AEs will be assigned to treatments (see Section 4.1) based on the actual treatment at the planned time of the measurement or on the recorded time of AE onset (concept of treatment emergent AEs). Therefore, measurements planned or AEs recorded prior to first intake of trial medication will be assigned to 'screening', those between first trial medication intake until the trial termination date will be assigned to the treatment period. These assignments including the corresponding time intervals will be defined in detail in the TSAP.

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

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

Laboratory data will be compared to their reference ranges. Values outside the reference range will be flagged in the listings. Additionally, differences from baseline will be evaluated.

For vital signs and the differences from baseline will be evaluated. Additionally, plots over the time will be provided for spirometry data.

A centralised evaluation of all 12-lead ECGs recordings (see Section 5.2.4) will be the basis for the derivation of further ECG parameters based on the ECG variables QT, HR, QTcF, QTcB, PR, QRS, and RR. The baseline value of an ECG variable is defined as the mean of the triple ECG measurements prior to drug administration. The derivation of the quantitative and qualitative ECG endpoints and their analyses will be described in the TSAP.

7.3.5 Pharmacokinetic analyses

The pharmacokinetic parameters listed in Section 5.5.1 for drug BI 1265162 will be calculated according to the BI SOP 'Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics' (001-MCS-36-472).

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

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

7.4 HANDLING OF MISSING DATA

7.4.1 Safety

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

7.4.2 Plasma/urine drug concentration - time profiles

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

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

7.4.3 Pharmacokinetic parameters

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

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

7.5 RANDOMISATION

The subjects of the first cohort per dose level will not be randomised to maintain a treatment sequence of active-placebo-active-active due to safety reasons. In the second cohort subjects will be randomised within each dose group in a 3:1 ratio, which reflects the ratio of subjects receiving active drug to placebo.

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

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

7.6 DETERMINATION OF SAMPLE SIZE

It is planned to include a total of 56 subjects in this trial. The planned sample size is not based on a power calculation. The size of 8 subjects per dose group (6 on active treatment, and 2 on placebo) is commonly used in single-rising dose studies of the present type and is in general considered as sufficient for the exploratory evaluation of single dose safety and pharmacokinetics [R95-0013].

8. INFORMED CONSENT, DATA PROTECTION, TRIAL RECORDS

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

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

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

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

8.1 STUDY APPROVAL, SUBJECT INFORMATION, AND INFORMED CONSENT

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

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

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

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

8.2 DATA QUALITY ASSURANCE

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

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

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

8.3 RECORDS

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

8.3.1 Source documents

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

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

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

8.3.2 Direct access to source data and documents

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

8.3.3 Storage period of records

Trial site:

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

Sponsor:

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

8.4 EXPEDITED REPORTING OF ADVERSE EVENTS

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

8.5 STATEMENT OF CONFIDENTIALITY

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

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

8.6 COMPLETION OF TRIAL

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

9. REFERENCES

9.1 PUBLISHED REFERENCES

P87-3333 Beasley CRW, Rafferty P, Holgate ST. The role of preservatives in Atrovent-induced bronchoconstriction. Thorax. 1987. 42: 230-231.

P88-1291 Rafferty P, Beasley R, Holgate ST. Comparison of the efficacy of preservative free ipratropium bromide and ATROVENT® nebulizer solution. Thorax. 1988. 43: 446-450.

P96-3855 Ramsey B W. Management of Pulmonary Disease in patients with Cystic Fibrosis. NEJM 1996; 335 (3): 179-188. July 18.

P05-08465 Hodder R; Pavia D; Dewberry H; Alexander K; Iacono P; Ponitz H; et al. Low incidence of paradoxical bronchoconstriction in asthma and COPD patients during chronic use of Respimat Soft Mist inhaler. Respir Med. 2005. 99: 1087-1095.

P05-12782 Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, Crapo R, Enright P, Grinten CPM van der, Gustafsson P, Jensen R, Johnson DC, MacIntyre N, McKay R, Navajas D, Pedersen OF, Pellegrino R, Viegi G, Wanger J Standardisation of spirometry. Eur Respir J 26 (2), 319 - 338 (2005).

P11-05794 Poole P, Black PN. Mucolytic agents for chronic bronchitis or chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2010 Feb 17;(2):CD001287.

P13-14084 Mogayzel PJ Jr, Naureckas ET, Robinson KA, Mueller G, Hadjiliadis D, Hoag JB, Lubsch L, Hazle L, Sabadosa K, Marshall B; Pulmonary Clinical Practice Guidelines Committee. Cystic fibrosis pulmonary guidelines. Chronic medications for maintenance of lung health. Am J Respir Crit Care Med. 2013 Apr 1;187(7):680-9.

R95-0013 Broom C. Design of first-administration studies in healthy man. Early Phase Drug Evaluation in Man. O'Grady J, Linet OI (Eds.), Macmillan Press: London, 1990, 206 213.

R01-1277 Davis PB, Drumm M, Konstan MW. Cystic fibrosis. Am J Respir Crit Care Med. 1996;154(5):1229-56.

R06-1037 Guidance for industry: estimating the maximum safe starting dose in initial clinical trials for therapeutics in adult healthy volunteers. U.S.Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER) 2005.

R07-4722 Guidance for industry: E14 clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs. Rockville: U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER); 2005.

R09-4830 Brown BD, Badilini F. HL7 aECG implementation guide (March 21, 2005).

R15-3034 Chronic respiratory diseases: burden of COPD. www.who.int/respiratory/copd/burden/en/ (access date: 11 June 2015) ; World Health Organization (2015).

R15-4955 Clunes MT, Boucher RC. Drug Discov Today Dis Mech. Cystic Fibrosis: The Mechanisms of Pathogenesis of an Inherited Lung Disorder. 2007;4(2):63-72.

R15-4984 Elborn JS, Shale DJ. Lung injury in cystic fibrosis. Thorax 1990; 45:970-973.

R15-5349 Knowles MR, Church NL, Waltner WE, Yankaskas JR, Gilligan P, King M, Edwards LJ, Helms RW, Boucher RC. A pilot study of aerosolized amiloride for the treatment of lung disease in cystic fibrosis. N Engl J Med. 1990 Apr 26;322(17):1189-94.

R15-5485 App EM, King M, Helfesrieder R, Köhler D, Matthys H. Acute and longterm amiloride inhalation in cystic fibrosis lung disease. A rational approach to cystic fibrosis therapy. Am Rev Respir Dis. 1990 Mar;141(3):605-12.

R15-5486 Clarke LL, Grubb BR, Gabriel SE, Smithies O, Koller BH, Boucher RC. Defective epithelial chloride transport in a gene-targeted mouse model of cystic fibrosis. Science. 1992 Aug 21;257(5073):1125-8.

R15-5487 Koehler D, App E, Schmitz-Schumann M, Wuertemberger G, Matthys H. Inhalation of amiloride improves the mucociliary and the cough clearance in patients with cystic fibroses. Eur J Respir Dis Suppl 146, 319 – 326 (1986).

R15-5503 Walters S, Mehta A. Epidemiology of cystic fi brosis. In: Hodson M, Geddes DM, Bush A, eds. Cystic fibrosis, 3rd edn. London: Edward Arnold Ltd, 2007: 21–45.

R15-5505 Pons, G., Marchand, M. C., D'Athis, P., Sauvage, E., Foucard, C., Chaumet-Riffaud, and Lenoir, G. (2000). French multicenter randomized double-blind placebo-controlled trial on nebulized amiloride in cystic fibrosis patients. Pediatr. Pulmonol., 30(1), 25-31.

R15-5507 Mall, M. A., Button, B., Johannesson, B., Zhou, Z., Livraghi, A., Caldwell, R. A, and Boucher, R. C. Airway surface liquid volume regulation determines different airway phenotypes in liddle compared with βENaCoverexpressing mice. J. Biol. Chem., 285(35), 26945-26955 2010.

R15-5546 Genes and human disease: monogenic diseases. who.int/genomics/publicdiseases/en/index2.html#CF (access date: 28 October 2015); Geneva: World Heath Organization (WHO) (2015).

R15-5599 Graham, A., Hasani, A., Alton, E. W. F. W., Martin, G. P., Marriott, C., Hodson, M. E., and Geddes, D. M. (1993). No added benefit from nebulized amiloride in patients with cystic fibrosis. Eur. Respir. J., 6(9), 1243-1248.

R16-0366 E14 Implementation Working Group. ICH E14 guideline: the clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs: questions & answers (R3) (current version dated 10 December 2015). http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E1 4/E14_Q_As_R3__Step4.pdf (access date: 29 January 2015) ; Geneva: International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; 2015.

R17-1997 Rowe S.M., Verkman A.S. Cystic Fibrosis Transmembrane Regulator Correctors and Potentiators. Cold Spring Harb Perspect Med 2013;3:a00976.

9.2 UNPUBLISHED REFERENCES

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

c10884768 Safety, tolerability and pharmacokinetics of single rising inhaled doses of BI 443651 in healthy male volunteers in a partially randomised, single blind, placebo-controlled trial.

c16304878 Investigator`s Brochure BI 1265162 Cystic fibrosis and COPD 05 September 2017.

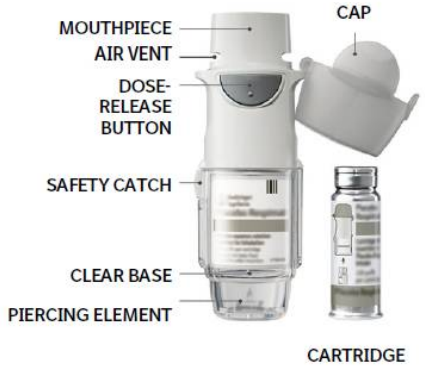
U97-0056 A three-way crossover study in healthy volunteers of lung deposition of fenoterol hydrobromide (100 µg via one puff) delivered from either a BINEB® (ARIANE) nebuliser, or a conventional MDI, or conventional MDI with a spacer. (260.2706) 20 June 1996.

10. APPENDICES

10.1 HANDLING INSTRUCTIONS FOR RESPIMAT INHALER FOR USE IN CLINICAL TRIALS

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.



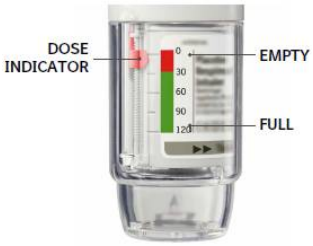
How to store BI 1265162 RESPIMAT

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



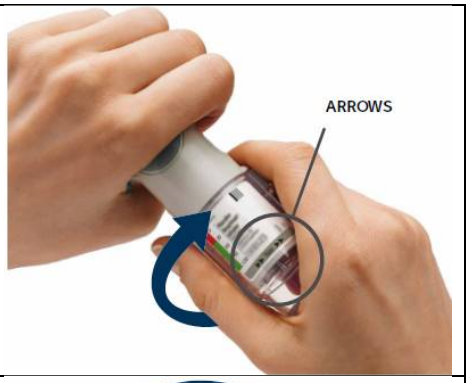
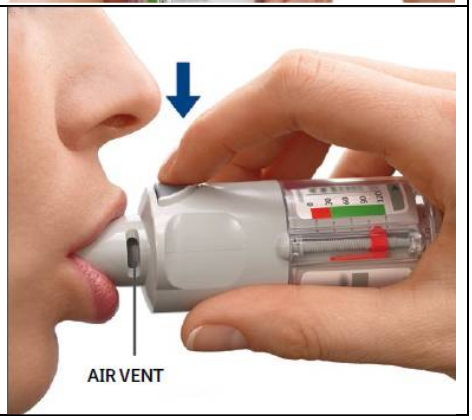
- BI 1265162 RESPIMAT inhaler contains 120 puffs if used as indicated.
- The dose indicator shows approximately how much medication is left.
- When the dose indicator enters the red area of the scale, get a new BI 1265162 RESPIMAT from the investigational site; there are approximately 30 puffs left.
- 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.

Boehringer Ingelheim Pharma GmbH & Co. KG
D - 55216 Ingelheim, Germany

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

Number of global amendment		1
Date of CTP revision		15 November 2017
EudraCT number		2017-001106-15
BI Trial number		1399-0001
BI Investigational Product(s)		BI 1265162
Title of protocol		Safety, tolerability and pharmacokinetics of single rising inhaled doses of BI 1265162 in healthy male volunteers in a partially randomised, single blind, placebo-controlled trial
To be implemented only after approval of the IRB / IEC / Competent Authorities		☐
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		☐
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		☒
Section to be changed		A: Flow-Chart 5.2.3 Assessment of safety laboratory parameters B: 4.1.4 Drug assignment and administration of doses for each subject
Description of change		A: Measurement of urine electrolytes out of the 0-4h PK urine fraction was added B: Wrong entry

Number of global amendment		1
Rationale for change		A: To assess possible early changes in urine electrolytes B: Correction

Number of global amendment		2
Date of CTP revision		19 February 2018
EudraCT number		2017-001106-15
BI Trial number		1399-0001
BI Investigational Product(s)		BI 1265162
Title of protocol		Safety, tolerability and pharmacokinetics of single rising inhaled doses of BI 1265162 in healthy male volunteers in a partially randomised, single blind, placebo-controlled trial
To be implemented only after approval of the IRB / IEC / Competent Authorities		☐
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		☐
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		☒
Section to be changed		Flow Chart
Description of change		Additional PK sampling time point at 72:00h
Rationale for change		Preliminary PK results revealed that for better characterization of BI 1265162 an additional sampling time point (72:00h) is needed in dose group 7.

Boehringer Ingelheim

APPROVAL / SIGNATURE PAGE

Document Number: c15848245 **Technical Version Number:3.0**

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

Title: Safety, tolerability and pharmacokinetics of single rising inhaled doses of BI 1265162 in healthy male volunteers in a partially randomised, single blind, placebo-controlled trial

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Approval-Team Member Medicine		19 Feb 2018 12:36 CET
Author-Trial Clinical Monitor		19 Feb 2018 12:46 CET
Author-Trial Clinical Pharmacokineticist		19 Feb 2018 12:58 CET
Author-Trial Statistician		19 Feb 2018 13:06 CET
Approval-Therapeutic Area		19 Feb 2018 15:21 CET
Verification-Paper Signature Completion		19 Feb 2018 16:57 CET

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed

LOCAL SIGNATURE

(Principal Investigator)

Trial Title: **Safety, tolerability and pharmacokinetics of single rising inhaled doses of BI 1265162 in healthy male volunteers in a partially randomised, single blind, placebo-controlled trial**

Trial Number: **1399-0001**

Clinical Trial Protocol Version: **2.0**

I herewith certify that I agree to adhere to the Clinical Trial Protocol and to all documents referenced in the Clinical Trial Protocol.

Principal Investigator (Print full name) Site number

17 Nov 2017

Date (dd Mmm yyyy) Signature

The signature section for the Principal Investigator will not be completed in case the signature will be provided electronically via the Portal Clinergize™. The e-signature statement will appear on the bottom of this page.

LOCAL SIGNATURE

(Local Clinical Monitor)

Trial Title: **Safety, tolerability and pharmacokinetics of single rising inhaled doses of BI 1265162 in healthy male volunteers in a partially randomised, single blind, placebo-controlled trial**

Trial Number: **1399-0001**

Clinical Trial Protocol Version: **2.0**

I herewith certify that I agree to adhere to the Clinical Trial Protocol and to all documents referenced in the Clinical Trial Protocol.

_____
Local Clinical Monitor (Print full name)

20 Nov 2017
Date (dd Mmm yyyy) Signature

LOCAL SIGNATURE

(Principal Investigator)

Trial Title: **Safety, tolerability and pharmacokinetics of single rising inhaled doses of BI 1265162 in healthy male volunteers in a partially randomised, single blind, placebo-controlled trial**

Trial Number: **1399-0001**

Clinical Trial Protocol Version: **3.0**

I herewith certify that I agree to adhere to the Clinical Trial Protocol and to all documents referenced in the Clinical Trial Protocol.

Principal Investigator (Print full name)

Site number

19 Feb 2018

Date (dd Mmm yyyy) Signature

The signature section for the Principal Investigator will not be completed in case the signature will be provided electronically via the Portal Clinergize™. The e-signature statement will appear on the bottom of this page.

001-MCS-40-106_RD-09 (5.0) / Saved on: 15 Mar 2016

LOCAL SIGNATURE

(Local Clinical Monitor)

Trial Title: **Safety, tolerability and pharmacokinetics of single rising inhaled doses of BI 1265162 in healthy male volunteers in a partially randomised, single blind, placebo-controlled trial**

Trial Number: **1399-0001**

Clinical Trial Protocol Version: **3.0**

I herewith certify that I agree to adhere to the Clinical Trial Protocol and to all documents referenced in the Clinical Trial Protocol.

Local Clinical Monitor (Print full name)

19 Feb 2018

Date (dd Mmm yyyy) Signature

001-MCS-40-106_RD-09 (5.0) / Saved on: 15 Mar 2016