

## CLINICAL TRIAL PROTOCOL

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<b>EudraCT No.:</b>	2015-001789-25	
<b>BI Trial No.:</b>	1320.17	
<b>BI Investigational Product(s):</b>	BI 1026706	
<b>Title:</b>	A randomized, double-blind, placebo-controlled, parallel group, Phase I trial in healthy current smoker subjects to assess pharmacodynamic effects on segmental endotoxin induced inflammatory response and safety of 4 weeks oral administration of BI 1026706	
<b>Brief Title:</b>	Clinical trial to assess pharmacodynamic effects on segmental endotoxin induced inflammatory response of BI 1026706 versus placebo	
<b>Clinical Phase:</b>	Phase I	
<b>Trial Clinical Monitor:</b>	<div style="background-color: black; width: 100%; height: 40px; margin-bottom: 5px;"></div> Phone.: <div style="background-color: black; width: 100%; height: 15px; display: inline-block;"></div> Fax: <div style="background-color: black; width: 100%; height: 15px; display: inline-block;"></div>	
<b>Principal Investigator:</b>	<div style="background-color: black; width: 100%; height: 30px; display: inline-block;"></div> MD. Tel: <div style="background-color: black; width: 100%; height: 15px; display: inline-block;"></div> Fax: <div style="background-color: black; width: 100%; height: 15px; display: inline-block;"></div>	
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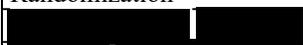
## CLINICAL TRIAL PROTOCOL SYNOPSIS

<b>Name of company:</b>		Boehringer Ingelheim	
<b>Name of finished product:</b>		N/A	
<b>Name of active ingredient:</b>		BI 1026706	
<b>Protocol date:</b> 06 Aug 2015	<b>Trial number:</b> 1320.17		<b>Revision date:</b> 19 Dec 2016
<b>Title of trial:</b>	A randomized, double-blind, placebo-controlled, parallel group, Phase I trial in healthy current smoker subjects to assess pharmacodynamic effects on segmental endotoxin induced inflammatory response and safety of 4 weeks oral administration of BI 1026706		
<b>Principal Investigator:</b>	[REDACTED], MD. [REDACTED] Tel: [REDACTED] Fax: [REDACTED]		
<b>Trial site(s):</b>	single center trial		
<b>Clinical phase:</b>	I		
<b>Objective(s):</b>	The primary and secondary objectives of the current study are the assessments of anti-inflammatory pharmacodynamic effects on segmental endotoxin induced inflammatory response after 4 weeks treatment with BI 1026706. Further objectives are to evaluate the pharmacokinetics and safety of BI 1026706		
<b>Methodology:</b>	Randomized, double-blind, placebo-controlled, parallel group, 4 weeks treatment of 100 mg BI 1026706 or placebo b.i.d. prior to segmental bronchial LPS challenge, single center		
<b>No. of subjects:</b>			
<b>total entered:</b>	50		
<b>each treatment:</b>	25 subjects per arm		
<b>Diagnosis :</b>	Healthy volunteers		
<b>Main criteria for inclusion:</b>	Volunteers of both sex with females being of non-childbearing potential, age $\geq 18$ and $\leq 65$ years, current smokers with at least 1		

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<b>Protocol date:</b> 06 Aug 2015	<b>Trial number:</b> 1320.17		<b>Revision date:</b> 19 Dec 2016
	cigarette per day over the last 12 months and a smoking history of at least 1 pack year, healthy as assessed by the investigator on a screening examination, FEV1 > 80% and FEV1/FVC > 70% predicted, BMI range: $\geq 18.5$ and $\leq 29.9$ kg/m <sup>2</sup> , negative drug screen, positive cotinine test		
<b>Test product:</b>	BI 1026706 film-coated tablet for oral administration (formulation A1)		
<b>dose:</b>	100 mg b.i.d.		
<b>mode of administration:</b>	Oral administration		
<b>Comparator products:</b>	Placebo film-coated tablet for oral administration (formulation A1)		
<b>dose:</b>	Not applicable		
<b>mode of administration:</b>	Oral administration		
<b>Duration of treatment:</b>	28 days		
<b>Endpoints</b>	<p>The primary endpoint will be total cell count of neutrophils in Bronchoalveolar Lavage (BAL) after 24 hours of the segmental endotoxin challenge.</p> <p>As secondary endpoints total and differential cell counts of neutrophils (only differential cell count), eosinophils, monocytes, macrophages and lymphocytes will be determined in BAL, 24 hours following segmental endotoxin challenge</p>		
<b>Safety criteria:</b>	Physical examination, vital signs (blood pressure, pulse rate), 12-lead ECG, body weight, lung function, adverse events and clinical laboratory tests		
<b>Statistical methods:</b>	Treatment differences of primary and secondary endpoints between both treatment groups will be analyzed with an analysis of variance (ANOVA) model. In the primary analysis, the dependent variable is the respective endpoint at 24 hours post endotoxin challenge on the logarithmic scale, while treatment will be used as independent		

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<b>Protocol date:</b> 06 Aug 2015	<b>Trial number:</b> 1320.17		<b>Revision date:</b> 19 Dec 2016
	variable.  Descriptive statistics will be calculated for all endpoints		

**FLOW CHART**

Trial Periods	Screening Period	Randomized Treatment Period					Follow-up Period	End of trial
		2	3	4	5	6		
Visit	1							8 <sup>8</sup>
Day	-28 to -3	1	8	15	22	28 <sup>11</sup>	29	32 to 34
Weeks after randomization			1	2	3	4		
Time window (±days) for visits			±2	±2	±2	±2	none	
Informed consent <sup>1</sup>	X							
Review of in-/exclusion criteria	X	X						
Demographics	X							
Smoking status	X	X		X		X		
Medical history / baseline conditions	X							
Skin prick test	X							
Drug screening <sup>10</sup>	X							
Cotinine test <sup>10</sup>	X					X		
Alcohol screening <sup>10</sup>	X					X	X	
Physical examination	X	X		X		X	X	X
Body weight and height <sup>6</sup>	X	X				X		
Vital signs	X	X	X	X	X	X	X	X
12-lead resting ECG	X	X		X		X	X	X
Pulmonary function test	X	X		X		X	X	X
Pulse oximetry						X	X	
Safety dipstick urine test	X	X <sup>14</sup>		X	X <sup>14</sup>	X <sup>14</sup>		X <sup>14</sup>
Safety laboratory blood tests	X <sup>12, 13</sup>	X		X <sup>12</sup>		X	X	X
Randomization		X						
								
Bronchoscopy with BAL <sup>5</sup>						X	X <sup>7</sup>	
LPS challenge						X		
								
Administration of trial drugs in clinic <sup>9</sup>		X	X	X	X	X		
Dispense trial drug for home administration		X	X	X	X			
Dispense drug diary		X						
Check subject's drug diary			X	X	X	X		
Collection of trial drug used at home			X	X	X	X	X	
Treatment compliance check			X	X	X	X	X	
Assessment of adverse events	X	X	X	X	X	X	X	X
Concomitant therapy	X	X	X	X	X	X	X	X
Trial Completion <sup>8</sup>								X

<sup>1</sup>All subjects must sign an informed consent form consistent with ICH-GCP guidelines prior to participation in the trial. Re-consenting may become necessary when new relevant information becomes available and should be conducted according to the sponsor's instructions



<sup>5</sup>Biopsies will be taken during bronchoscopy. Bronchoscopies and medical checks (including spirometry) prior to discharge of subject will be performed according to the SOP of the investigational trial site (provided in the ISF), which is based on guidelines for investigative bronchoscopies

<sup>6</sup>Height will only be captured at screening

<sup>7</sup>The bronchoscopy at Visit 7 has to be performed 24±1 hours after LPS-challenge. The bronchoscopy will occur following an overnight fast of at least 8 hours.

<sup>8</sup>End of trial visit also needs to be completed if the subject withdraws from or is removed from the trial following randomization

<sup>9</sup>On Day 1 (Visit 2) and Day 28 (Visit 6), the morning administration of trial medication (i.e. the first drug administration of the day) will occur following an overnight fast of at least 8 hours and will be administered with about 240 mL of water. On Days 1 and 28, fasting will continue up to 2 hours following morning administration of trial medication and no liquid intake will be allowed within the 2 hours before and 2 hours after the morning administration of trial medication

<sup>11</sup>The maximum treatment period of 28 days should not exceed the given time window

<sup>13</sup>Safety laboratory to include serum pregnancy testing for female subjects.

<sup>14</sup>Urine dipstick test to include pregnancy testing for female subjects. Testing at Visit 2 is only needed if the time period between Visit 1 and Visit 2 exceeds 7 days.

**FLOW CHART – STUDY DRUG ADMINISTRATION,**

Day	Time windows (days)	Clinic visit Number (applicable for PK only)	Planned Time [h:min]	time (actual day) [h:min]	Event <sup>1</sup> and comment
1		2	-0:10	07:50	Prior to first IMP administration
			<b>0:00</b>	<b>08:00</b>	<b>First drug administration in clinic with about 240 mL of water (following an overnight fast of at least 8 hours)</b>
			0:30	08:30	
			2:30	10:30	
			8:00	16:00	
2 to 7			12:00	20:00	drug administration at home <sup>2</sup>
			0:00	08:00	drug administration at home <sup>2</sup>
			12:00	20:00	drug administration at home <sup>2</sup>
8	±2	3	-0:10	07:50	
			0:00	08:00	drug administration in <b>clinic</b>
			12:00	20:00	drug administration at home <sup>2</sup>
9 to 14			0:00	08:00	drug administration at home <sup>2</sup>
			12:00	20:00	drug administration at home <sup>2</sup>
15	±2	4	-0:10	07:50	
			0:00	08:00	drug administration in <b>clinic</b>
			12:00	20:00	drug administration at home <sup>2</sup>
16 to 21			0:00	08:00	drug administration at home <sup>2</sup>
			12:00	20:00	drug administration at home <sup>2</sup>
22	±2	5	-0:10	07:50	
			0:00	08:00	drug administration in <b>clinic</b>
			12:00	20:00	drug administration at home <sup>2</sup>
23 to 27			0:00	08:00	drug administration at home <sup>2</sup>
			12:00	20:00	drug administration at home <sup>2</sup>
28	-2	6	-0:10	07:50	Prior to IMP administration
			<b>0:00</b>	<b>08:00</b>	<b>drug administration in clinic with about 240 mL of water (following an overnight fast of at least 8 hours)</b>
			1:00	09:00	
			2:30	10:30	
			8:00	16:00	
			<b>12:00</b>	<b>22:00</b>	<b>drug administration at home</b>

<sup>1</sup>Actual time of drug intake will be documented by the subject in a subject drug diary

<sup>2</sup> subjects are asked to take their medication at home between 7-10 a.m. in the morning and between 7-10 p.m. in the evening.

<sup>3</sup>The time between tablet intake in the evening on Day 28 (Visit 6) and the bronchoscopy on Day 29 (Visit 7) should preferable not exceed 14 hours. Subjects are asked to take medication on Day 28 (Visit 6) as late as possible and ideally close to 10 p.m. in the evening

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## ABBREVIATIONS

AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine Aminotransferase
ANOVA	Analysis of Variance
AST	Aspartate Aminotransferase
ATS	American Thoracic Society
[REDACTED]	
BAL	Bronchoalveolar Lavage
BI	Boehringer Ingelheim
b.i.d.	bis in die (twice daily dosing)
BIRDS	Boehringer Ingelheim Regulatory Documents for Submission
BMI	Body Mass Index
BP	Blood Pressure
CA	Competent Authority
CC-RE	Clinical Center Reference Endotoxin
CI	Confidence Interval
CML	Local Clinical Monitor
[REDACTED]	
COPD	Chronic Obstructive Pulmonary Disease
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Contract Research Organization
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
CV	Coefficient of Variation
DDI	Drug-Drug Interaction
DILI	Drug-Induced Liver Injury
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
ERS	European Respiratory Society
EudraCT	European Clinical Trials Database
FEV	Forced Expiratory Volume
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
[REDACTED]	
GLI	Global Lung Function Initiative
[REDACTED]	
IB	Investigator's Brochure
ICS	Inhaled Corticosteroids
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ISF	Investigator Site File

i.v.	Intravenous
HCG	Human Chorionic Gonadotropin
HV	Healthy Volunteer
LABA	Long Acting Beta Agonist
LAMA	Long Acting Muscarinic Agonist
LPS	Lipopolysaccharide
mL	Milliliter
MedDRA	Medical Dictionary for Drug Regulatory Activities
MRD	Multiple Rising Dose

ST	Medical Sub team
OCS	Oral corticosteroids

OPU	Operative Unit
-----	----------------

PD	Pharmacodynamics
PDS	Pharmacodynamics Set

p.o.	per os (oral)
q.d.	quaque die (once a day)
RDC	Remote Data Capture
REP	Residual effect period, after the last dose of medication with measureable drug levels or pharmacodynamic effects still likely to be present
RS	Randomized Set
SABA	Short Acting Beta Agonist
SAE	Serious Adverse Event
SAMA	Short Acting Muscarinic Agonist
s.c.	Subcutaneous
SmPC	Summary of Product Characteristics
SRD	Single Rising Dose
SOP	Standard Operating Procedure
TCM	Trial Clinical Monitor
TDMAP	Trial Data Management and Analysis Plan
TEAE	Treatment Emergent Adverse Events
t.i.d.	ter in die (3 times a day)

TMF	Trial Master File
TMW	Trial Medical Writer
TS	Treated Set
TSAP	Trial Statistical Analysis Plan
WHO	World Health Organization

## 1. INTRODUCTION

COPD is characterized by progressive airflow limitation that is not fully reversible. The airflow limitation is associated with an atypical chronic inflammatory reaction to particulate matter of the airways, in which many cell types play a role, in particular macrophages, neutrophils and CD8 T lymphocytes.

Smoking is responsible for 90% of all cases of COPD, in the developed world, although only about 20% of all cigarette smokers develop relevant airways obstruction. Other risk factors for COPD, such as environmental exposure to dust or fumes and  $\alpha$ 1antitrypsin deficiency, have less impact on the prevalence of COPD [\[P15-01740\]](#).

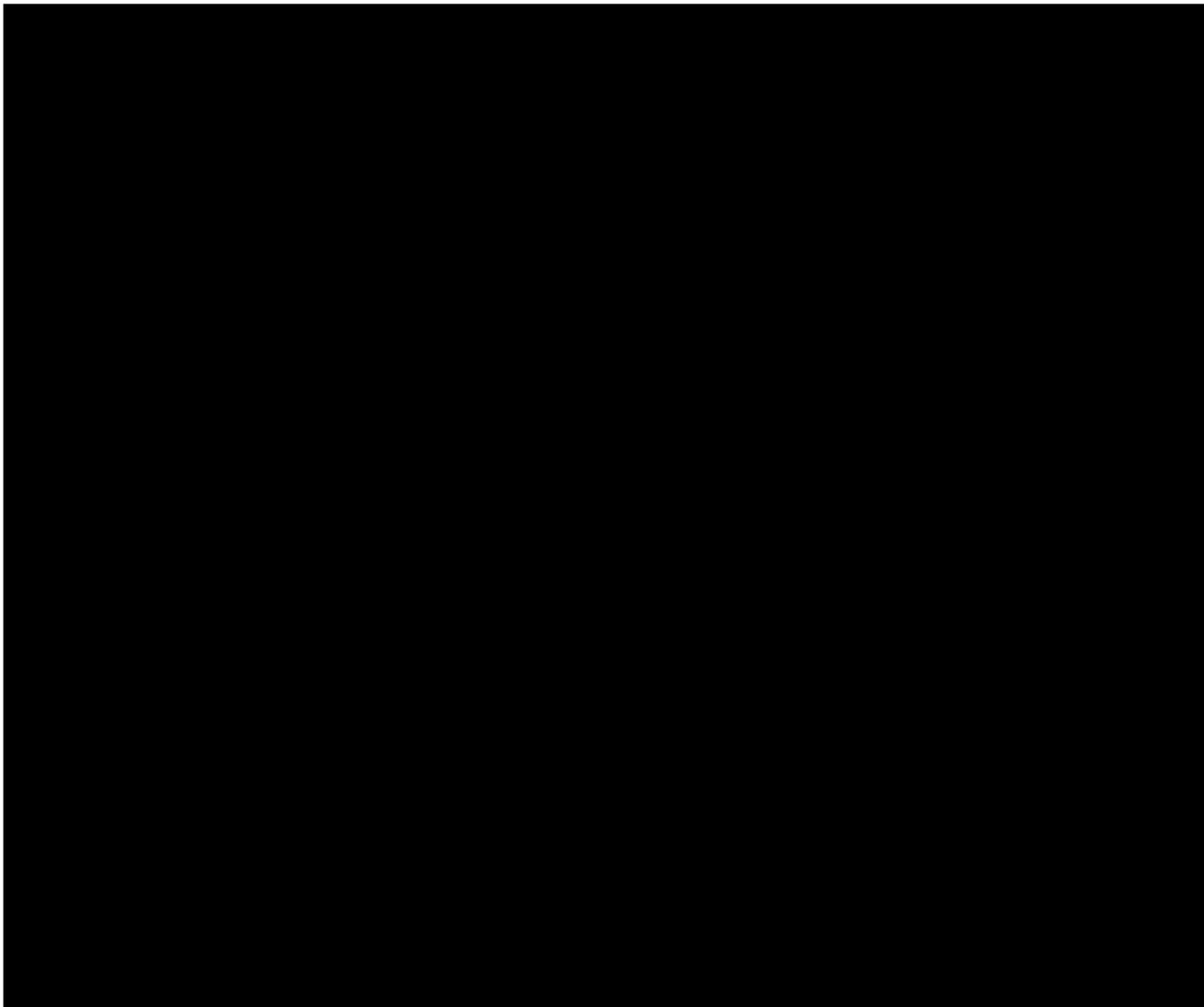
COPD prevalence is still rising due to increased smoking, particularly among women and adolescents. According to the 2015 estimates of the World Health Organization (WHO), 65 million people suffer from moderate to severe COPD. By 2030, COPD will be the third leading cause of death worldwide [\[R15-3034\]](#).

Despite the available treatment options, COPD remains associated with significant morbidity and mortality signifying the need for developing new drugs for the treatment of COPD. Medical intervention should improve the disease-related quality of life by relieving symptoms and reduce COPD exacerbations.

Smoking cessation is the cornerstone of COPD management. Bronchodilator medications, short- and long-acting  $\beta$ 2 agonists (SABA and LABA) as well as short- and long-acting muscarinic antagonists (SAMA and LAMA) and their combinations are the foundation of pharmacologic treatment with LABA and LAMA central to the symptomatic management of COPD [\[P14-01052\]](#).

The principles of anti-inflammatory treatment of COPD have been derived from the treatment of asthma, leading to the use of inhaled corticosteroids (ICS). In contrast to asthma, ICS has little effect on the neutrophilic inflammation characteristic to COPD. ICS is used in combination with LABA or LAMA in patients with more severe COPD and history of exacerbations [\[P14-01052\]](#). Oral corticosteroids (OCS) are mainly used for the acute treatment of exacerbations, usually co-administered with antibiotics.

The only non-steroidal anti-inflammatory medication available on the market is roflumilast, a PDE4 inhibitor (Daxas<sup>®</sup> or Daliresp<sup>®</sup>), indicated for severe COPD with chronic bronchitis and a history of exacerbations. In the EU, roflumilast is indicated as maintenance treatment and in the USA to reduce risk of exacerbation [\[R11-4791\]](#) in COPD. The efficacy of this compound may be limited by dose-limiting side effects such as diarrhea, nausea, and headache [\[R11-4442, P09-11235\]](#).



## 1.2 DRUG PROFILE

For a more detailed description of the drug profile BI 1026706, refer to the current Investigator's Brochure (IB) For LPS as IMP, refer to the IB [REDACTED]. The documents are included in the Investigator Site File (ISF).

## 2. RATIONALE, OBJECTIVES, AND BENEFIT - RISK ASSESSMENT

### 2.1 RATIONALE FOR PERFORMING THE TRIAL

[REDACTED]

This study is primarily conducted as a proof of mechanism trial to investigate the anti-inflammatory properties of BI 1026706 administered for 4 weeks at the dosage of 100 mg b.i.d. followed by segmental endotoxin challenge in smoking healthy subjects being current smokers at time of inclusion. The study may provide an initial indication of whether treatment may have an effect on pharmacodynamics (PD) biomarkers in particular the number of neutrophils in bronchoalveolar lavage (BAL) will be assessed - and could be used as a potential indicator of anti-inflammatory action in the airways. [REDACTED]

Safety and tolerability of BI 1026706 will also be monitored. [REDACTED]

[REDACTED]

### 2.3 BENEFIT - RISK ASSESSMENT

A possible direct individual benefit for the healthy subjects participating in this trial is unlikely during the 28 days of treatment with BI 1026706. However, their participation in the study is of major importance to the clinical development of BI 1026706 for the improvement of symptoms in patients with COPD.

Subjects on BI 1026706 may have an improved, faster resolution of the inflammatory lung condition induced by the LPS challenge. Subjects will have a 50% chance to receive placebo. Beyond close monitoring of safety, clinical laboratories, and clinical evaluations there is no specific benefit for these subjects, apart from encouragement to discontinue smoking. The decision to include a placebo group is essential for the evaluation of PD effects as well as for the assessment of safety and tolerability of BI 1026706 in healthy current smokers.

As per ICH M3 guidance, women not of childbearing potential can be included in this study as repeated dose toxicity studies (including an evaluation of the female reproductive organs) have been conducted with no cause of concern. Close monitoring of pregnancy status during the concerned trial will be implemented to further safeguard this decision.

Overall, the risk to the subjects participating in this study is considered low compared with the potential benefit that a successful clinical development of [REDACTED] could provide to patients with COPD.

The risk for subjects is acceptable based on the data and trial results mentioned in [Section 2.3.2](#) below. The subjects participating in this study will be exposed to:

- the risks of the study procedures
- the known risks related to exposure to the investigational product
- unknown risks that might be related to exposure to the investigational product

### **2.3.1 The risks of the study procedures**

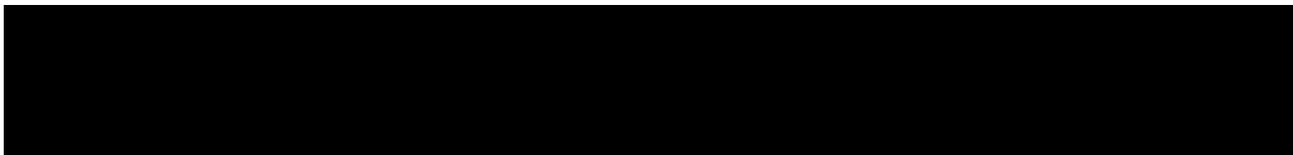
The use of an indwelling cannula for the purpose of blood sampling may be accompanied by mild bruising and also, in rare cases, by transient inflammation of the vein wall. After initial irritation, the presence of an indwelling cannula is usually painless and hardly noticeable. The same applies to vein puncturing for further blood sampling. In rare cases, a nerve might be injured while inserting the cannula. This could be followed by paresthesia, reduced sensibility or pain for a long-term period.

The total amount of blood to be withdrawn during the trial as scheduled will not exceed [REDACTED]. No safety-related risk to the subjects is expected from this blood withdrawal.

Bronchoscopy will be performed twice in each subject as part of the LPS challenge protocol to obtain BAL. Potential risks related to the bronchoscopy procedure are lidocaine intoxication, lidocaine overdose (seizures or heart rhythm problems), vocal cord spasm, lung infections or pneumonia, sore throat, and fever. The instillation of LPS to the lung at the selected dose is in general a well-tolerated procedure with only limited systemic effects. Possible side effects include fever, headache, nausea, bradycardia, and bronchoconstriction.

Bronchial biopsies are a standardized and safe procedure. They may lead to mucosal bleeding which can be treated with topical application of adrenalin.

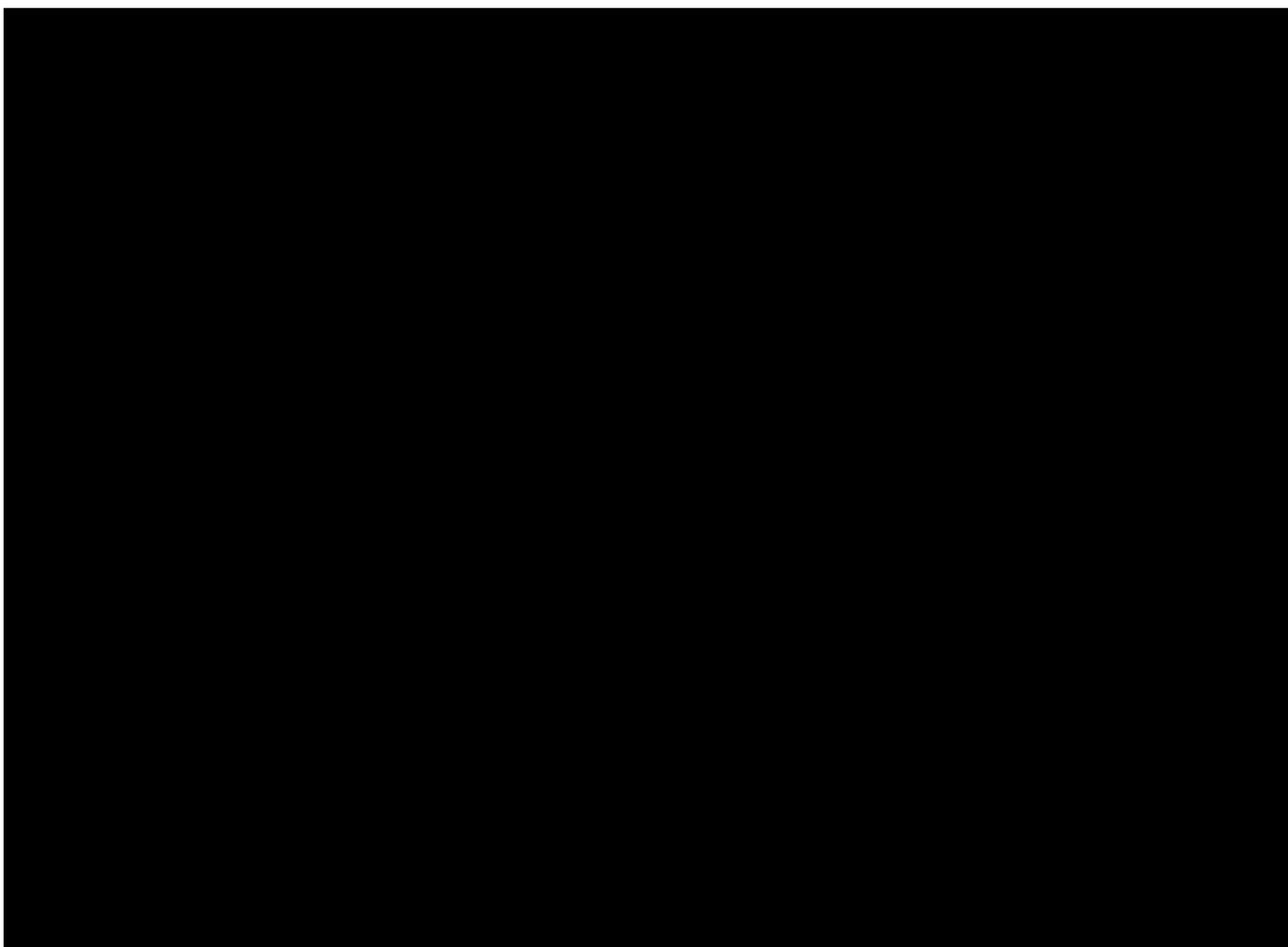
The bronchoscopy and biopsies procedures with LPS instillation in this study will only be performed by physicians with extensive training and experience with this procedure, with the intent to mitigate the above risks.

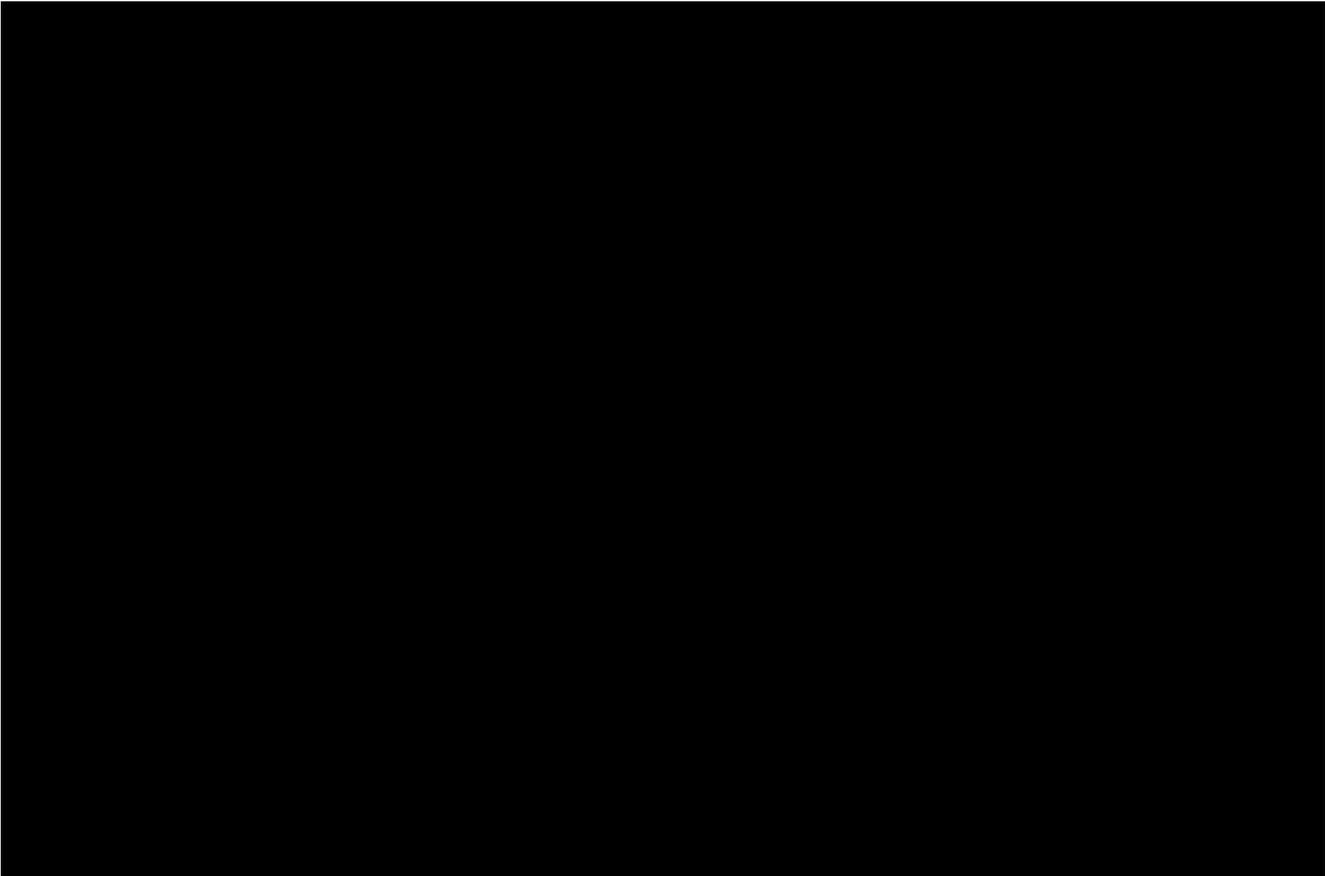


Bronchoscopies, BAL and LPS challenge will not be conducted or will be stopped if a subject experiences any adverse event regarded by the investigator as contraindication to the procedure.

The investigational site is appropriately trained and experienced in the conduct of these procedures in human beings, is aware of expected side effects of the procedures and knowledgeable of the required therapeutic actions.

Other study procedures such as spirometry, electrocardiogram (ECG) recording and blood pressure measurements are standard procedures in general medical care and unlikely to cause any side effects.





### 3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

#### 3.1 OVERALL TRIAL DESIGN AND PLAN

An overview of the trial design is shown in Figure 3.1.1.

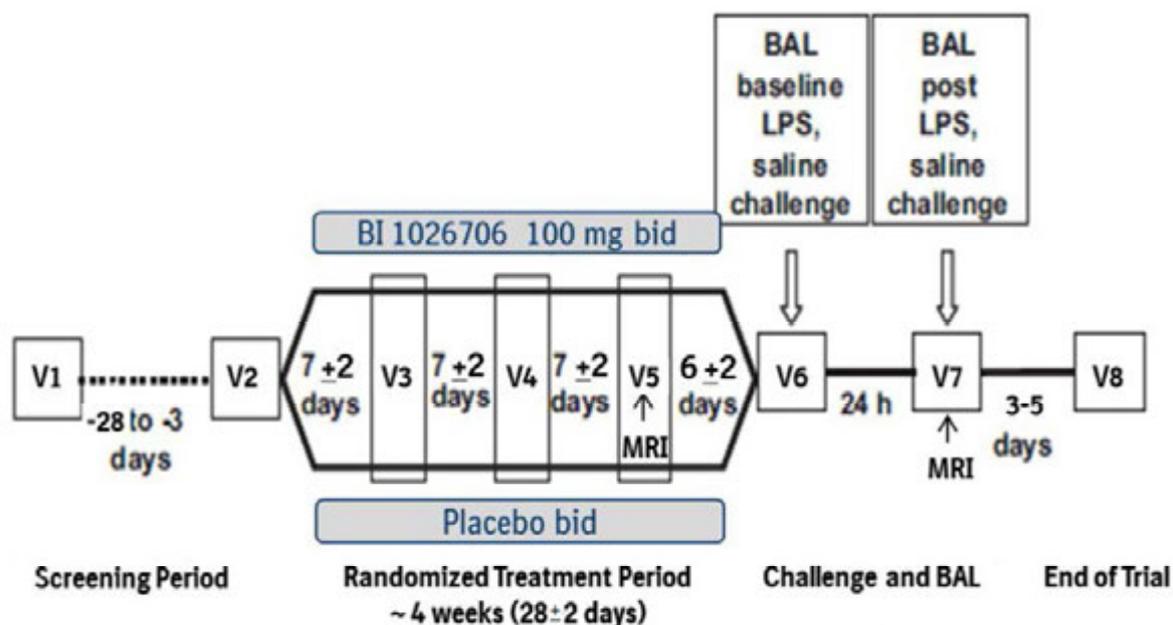


Figure 3.1.1: Study Design

This is a randomized, double-blind, placebo-controlled, parallel-group, single center study to assess the proof of mechanism and safety of BI 1026706 compared to placebo. The respective treatment will be administered orally as tablet twice daily during the 4 week treatment period. The random allocation to active or placebo treatment will have a ratio of 1:1.

A total of 50 subjects will participate in the trial consisting of 2 treatment groups of 25 subjects, each treated for 28 ± 2 days.

This trial consists of 8 Visits. Visit 1 is the screening visit. Between Visits 2-6 subjects will receive either BI 1026706 or placebo for 28 ± 2 days, depending on the treatment group they have been randomized to. In addition, at Visit 6 baseline BAL will be conducted following LPS and saline challenge. At Visit 7 the BAL will be examined for the 24 hours post LPS and saline challenge. Visit 8 is the end-of-trial examination.

The screening period lasts from the signature of informed consent at Visit 1 until randomization (directly followed by first administration of trial medication) on Day 1 (Visit 2).

The screening visit (Visit 1) will take place 3 to 28 days prior to randomization.

The treatment period lasts from the first administration of trial medication on Day 1 (Visit 2) until Day 28 ± 2 days (Visit 6).

The follow-up period lasts from Day 29 (Visit 7) until the End of trial (Day 32 to 34, Visit 8).

Please refer to [Section 8.6](#) for the definition of the end of trial.

Subjects are included in the study once they have signed the informed consent and their participation concludes when they have undergone the last planned visit. The end of trial visit (Visit 8) also needs to be completed if the subject withdraws from or is removed from the trial following randomization ([see Section 3.3.3](#))

All trial relevant documentation will be stored by Boehringer Ingelheim in the Trial Master File (TMF). Trial relevant documentation for the study sites will be filed in the Investigator Site File (ISF).

An overview of all relevant trial activities is provided in the [Flow Chart](#). For details on the administered treatments, refer to [Section 4.1](#). For visit schedule and details of trial procedures at selected visits, refer to [Sections 6.1](#) and [6.2](#), respectively.

### 3.1.1 Administrative structure of the trial

Boehringer Ingelheim 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 standard operating procedures (SOPs), direct the clinical trial team in the preparation, conduct, and reporting of the trial, order the materials as needed for the trial, and ensure appropriate training and information of local clinical monitors (CML), Clinical Research Associates (CRAs), and investigators of participating countries. Data Management and Statistical Evaluation will be done by BI according to BI SOPs.

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

Relevant documentation on the participating (Principal) Investigators and other important participants, including their *curricula vitae*, will be filed in ISF.

The study will be conducted at a clinical research center [REDACTED] specialized on pulmonary diseases, and experienced in the management of healthy volunteers and patients with respiratory diseases. The Principal Investigator is an expert in the respiratory therapy area.

A local laboratory facility will handle all laboratory analyses of the trial. Lung function assessment (spirometry) will be performed with site's own equipment according to international accepted guidelines.

Safety status will be assessed by clinical laboratory tests, vital signs, physical examination, electrocardiogram (ECG), and monitoring of adverse events. As a further safety measure, the pulmonary function will be examined by spirometry according to [Flowchart](#).

Bronchoscopies and medical checks (including spirometry) prior to discharge of subject will be performed according to the Fraunhofer Institute study site standard operating procedure (provided in the ISF), which is based on guidelines for investigative bronchoscopies.

On the last day of treatment (Visit 6), subjects undergo bronchoscopy with BAL and segmental instillation of endotoxin and saline (control), each in different segments of contralateral lungs. Twenty-four hours later (Visit 7), subjects undergo a second bronchoscopy for the collection of BAL fluid from both challenged segments. BAL fluid from both days will be processed and total and differential cell counts will be determined.

During bronchoscopies at Visits 6 and 7 biopsies will be taken and further processed for biomarker analyses. Instructions on the procedures are provided in the ISF.

### **3.2 DISCUSSION OF TRIAL DESIGN, INCLUDING THE CHOICE OF CONTROL GROUP(S)**

A randomized, double-blind, placebo-controlled, parallel-group design is chosen for this trial in order to assess anti-inflammatory PD effects, safety, tolerability [REDACTED] in subjects treated with BI 1026706 compared with placebo.

To avoid extensive trial duration and minimize the risks related with the planned trial procedures, this trial has a parallel group design. All subjects are smoking healthy volunteers who will not have clinically significant diseases and related treatment. Therefore, treating the control group with placebo does not raise ethical concerns and allows to assess the effect of BI 1026706 on inflammation after LPS challenge as well as to reliably evaluate safety and tolerability of BI 1026706.

The reliability of safety and tolerability observations is further ensured by the double-blind design of the trial.

A balanced random allocation with a ratio of 1:1 to receive BI 1026706 or placebo is chosen to create treatment groups comparable with respect to known as well as unknown risk factors and to maximize the power of analyzing any effects.

The sample size of 50 entered (randomized) subjects should result in a sufficient precision to estimate relevant differences between treatments in this exploratory trial.

The treatment period of 4 weeks for BI 1026706 or placebo to be administered orally as tablets twice daily to subjects is deemed adequate to evaluate safety, tolerability, [REDACTED], pharmacodynamics, and effect on inflammation after LPS challenge.

### 3.3 SELECTION OF TRIAL POPULATION

A log of all subjects enrolled into the trial (i.e. who have signed 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 trial entry

Healthy smoking volunteers with FEV<sub>1</sub> of >80% and FEV<sub>1</sub>/FVC of >70% of the predicted normal value at screening visit are eligible for inclusion if they fulfil all the inclusion criteria ([Section 3.3.2](#)) and none of the exclusion criteria ([Section 3.3.3](#)).

Please refer to [Section 8.3.1](#) (source documents) for the documentation requirements pertaining to the in- and exclusion criteria.

#### 3.3.2 Inclusion criteria

- 1) Signed informed consent consistent with ICH-GCP guidelines and local legislation prior to participation in the trial.
- 2) Healthy volunteers of both sex between 18 and 65 years (inclusive) of age, on the day of subject's signature of informed consent.
- 3) Healthy subjects as assessed by the investigator, based on a screening examination including medical history, physical examination, vital signs (Blood pressure, pulse rate, body temperature 12-lead ECG, lung function and clinical laboratory results.
- 4) FEV<sub>1</sub> of >80% and FEV<sub>1</sub>/FVC of >70% of the predicted normal value at screening visit will be calculated according to the Global Lung Function Initiative (GLI) Equations as described in [\[R15-0845\]](#).
- 5) Current smokers with a smoking history of at least 1 pack year (see [Appendix 10.1](#) for calculation) and with at least 1 cigarette per day in the previous year confirmed by a positive cotinine test.
- 6) BMI range:  $\geq 18.5$  and  $\leq 29.9 \text{ kg/m}^2$  at screening visit (Visit 1)
- 7) Hemoglobin levels within normal ranges or assessed as clinically non-significant deviation by the investigator at screening visit (Visit 1).
- 8) Subjects must show a negative urine drug screening.
- 9) Negative breath alcohol test.
- 10) Negative skin prick test or positive skin prick test; without clinical equivalent of an allergy, performed within the 12 months prior to study start or at Visit 1. . Subjects with a positive skin prick test are considered to be sensitized and are allowed to participate if there is no expected exposure during the planned trial participation period of the subject as assessed and documented by investigator. Positive skin prick

test should be documented as baseline condition (e.g. 'allergen skin test positive'). The specific allergen and the off-season character should be entered as additional information in the eCRF.

- 11) GFR must be  $\geq 30$  mL/min at Visit 1.
- 12) Females NOT of childbearing potential are defined as: Women who are postmenopausal (12 months with no menses without an alternative medical cause; in questionable cases a blood sample with simultaneous levels of FSH above 40 U/L and estradiol below 30 ng/L is confirmatory) or who are permanently sterilized (defined as hysterectomy, bilateral oophorectomy or bilateral salpingectomy).

### 3.3.3 Exclusion criteria

- 1) History of any relevant lung disease (i.e. COPD, asthma, chronic bronchitis, pulmonary fibrosis, pulmonary alveolar proteinosis (PAP), pneumocystis infection, active tuberculosis, silicosis or any other lung surfactant overproduction syndromes).
- 2) Lower respiratory tract infection not resolved 4 weeks prior to Screening.
- 3) Subjects with clinically relevant abnormal hematology, blood chemistry, or urinalysis at the screening visit (Visit 1).
- 4) Any finding of the medical examination (including blood pressure, pulse rate, body temperature and ECG) deviating from normal and of clinical relevance.
- 5) Subjects with a history of any clinically significant cardiovascular, metabolic, renal (including renal stones), hepatic, gastrointestinal, hematological, dermatological, venereal, neurological, psychiatric or other major disorders.
- 6) Subjects with a malignancy for which the subject has undergone resection, radiation therapy or chemotherapy within the last five years. Subjects with treated basal cell carcinoma or fully cured squamous cell carcinoma are allowed to participate.
- 7) Subjects with previous surgery of the gastro-intestinal tract likely to affect drug absorption.
- 8) History of relevant orthostatic hypotension, fainting spells or blackouts.
- 9) Subjects with clinically relevant infection or known ongoing clinically relevant inflammatory process.
- 10) History of relevant allergy/hypersensitivity including allergy to drug or its excipients or medications in line with bronchoscopy (bronchodilators, sedatives and local anesthetics).
- 11) Subjects with a marked baseline prolongation of QT/QTcB interval (such as repeated demonstration of a QTcB interval  $>450$  ms), or any other relevant ECG finding at screening visit (Visit 1) according to the investigator.
- 12) Subjects with a history of additional risk factors for Torsades de Pointes (such as heart failure, hypokalemia, or family history of Long QT Syndrome).
- 13) Subjects with previous surgeries that may have left ferromagnetic material in the body, ferromagnetic implants or pacemakers.
- 14) Any HIV infection (1+2) or active, infectious hepatitis B or C at screening visit (Visit 1)
- 15) Neutrophil blood count indicative of immunosuppression according to the investigator at screening visit (Visit 1).

- 16) Participation in another study with any investigational product within 2 months prior to screening or if screening occurs within 6 half-lives of intake of another investigational drug (whichever is greater).
- 17) Subjects who are being treated with non-permitted concomitant medication (please refer to [Section 4.2.2.1](#) “Restrictions regarding concomitant treatment”).
- 18) Subjects with a history of and/or active significant alcohol or drug abuse as assessed by the investigator.
- 19) Subjects who donated more than 100 mL blood in the 4 weeks prior to screening or subjects who have the intention to donate blood between screening and 4 weeks after the end of trial visit.
- 20) Male subjects who do not agree to minimize the risk of female partners becoming pregnant from the first dosing day until 3 months after the trial medication treatment has finished. For details, please see [Appendix 10.2](#).
- 21) Subjects who are committed to an institution by way of official or juridical order will not be enrolled in the trial.
- 22) Receipt of live (attenuated) vaccine within the 4 weeks prior to screening or during the trial.
- 23) Excessive physical activities within 1 week prior to first administration of study medication or during the trial.
- 24) Subjects who are unable to comply with the dietary regimen.
- 25) Subjects who have been previously randomized in this study.
- 26) Subject is assessed as unsuitable for inclusion by the investigator; for instance, because he is not considered able to understand and comply with study requirements or has a condition that would not allow safe participation in the study
- 27) For female subjects:
  - Positive pregnancy test at screening Visit 1, pregnancy or plans to become pregnant within 30 days after study completion
  - Lactation

### 3.3.4 Removal of subjects from therapy or assessments

#### 3.3.4.1 Removal of individual subjects

An individual subject is to be withdrawn from trial treatment if:

- The subject withdraws consent for study treatment or study participation, without the need to justify the decision.
- The subject needs to take concomitant drugs that interfere with the trial medication (see [Section 4.2.2](#))
- The subject can no longer be treated with trial medication for any medical reason (e.g. surgery, adverse events, other diseases or pregnancy) or experiences a respiratory tract infection during the treatment period which might interfere with safe conduct of bronchoscopies or its analyses.
- Decision by Boehringer Ingelheim to discontinue a specific subject (for instance, in case of the occurrence of an SAE that would be incompatible with trial continuation).
- Administrative reasons (protocol violations, persistent non-compliance).

A subject can be removed from the trial after discussion between sponsor and investigator if eligibility criteria are being violated or if the subject fails to comply with the protocol (e.g. non-adherence to dietary rules, non-attendance at study assessments).

For subjects who discontinue participation in the trial, with the subject's agreement, the subject will undergo the procedures for the end of trial visit as outlined in the [flow chart](#) and [Section 6.2.3](#).

Data of subjects who discontinue trial participation prior to randomization will be entered in the trial database and will be listed. Data of subjects who discontinue or withdraw after randomization must be documented. For all subjects the reason for withdrawal (e.g. adverse events) must be recorded in the eCRF. These data will be included in the trial database and reported.

#### 3.3.4.2 Discontinuation of the trial by the sponsor

Boehringer Ingelheim reserves the right to discontinue the trial at any time for 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 1 drug-related serious adverse event is reported that is considered to be unacceptable.
- The expected enrolment goals are not met.
- The trial site or investigator violates GCP or the CTP, disturbing the appropriate conduct of the trial.
- The sponsor decides to discontinue the further development of the investigational product.

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

#### 3.3.5 Replacement of subjects

In case more than 6 subjects do not or are not expected to complete the trial (e.g. due to drop-out rate in the ongoing trial), the trial clinical monitor [REDACTED] and the trial statistician are to decide if and how many subjects will be replaced to ensure a sufficient number of evaluable subjects (as defined in 7.7). A replacement subject will be assigned a unique study subject number, and will be assigned to the same treatment as the subject to be replaced.

## 4. TREATMENTS

### 4.1 TREATMENTS TO BE ADMINISTERED

The study medication will be supplied by Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach, Germany.

#### Treatment administration period:

Treatments (BI 1026706 or placebo) will be administered twice daily starting after randomization at Day 1 in the clinic (Visit 2) and lasts until Day 28. The last study drug administration will be performed in the evening of Day 28 at home.

#### LPS challenge:

The subjects will also be administered LPS as part of the LPS challenge which will be prepared by the reconstitution of E. coli type O113, Clinical Center Reference Endotoxin (CC-RE).

The dose that will be administered to the individual subject is 40 EU (endotoxin units) endotoxin / kilogram body weight (kg b.w). According to the drug fact sheet, this is equal to 4ng endotoxin / kg b.w.

#### 4.1.1 Identity of BI investigational product(s) and comparator product(s)

Table 4.1.1: 1 Test product 1:

Substance:	BI 1026706
Pharmaceutical formulation:	Film-coated tablets (formulation A1)
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG, Birkendorfer Str. 65, 88397 Biberach, Germany
Unit strength:	100 mg
Posology	Twice daily
Route of administration:	Oral

Table 4.1.1: 2 Test product 2 (placebo):

Substance:	Placebo to match BI 1026706
Pharmaceutical formulation:	Film-coated tablets (formulation A1)
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG, Birkendorfer Str. 65, 88397 Biberach, Germany
Unit strength:	Placebo to match 100 mg
Posology	Twice daily
Route of administration:	Oral

#### 4.1.2 Method of assigning subjects to treatment groups

At Visit 2 subjects are randomized to treatment group BI 1026706 or placebo in a 1:1 ratio. After assessment of all in- and exclusion criteria, each eligible subject will be assigned the lowest available medication number at the time of randomization in a blinded manner. Note that the medication number is different from the subject number (the latter is assigned at trial entry). Site personnel will enter the medication number in the eCRF.

#### 4.1.3 Selection of doses in the trial

Based on animal pharmacology data and pharmacokinetic characteristics determined in humans, a dose of 100 mg b.i.d. of BI1026706 has been selected for the present trial and is

expected to meet the anticipated therapeutic exposure (please refer to [IB](#)). [REDACTED]

#### 4.1.4 Drug assignment and administration of doses for each subject

At Visit 2 (Day 1) eligible subjects will be randomized to one of 2 double-blinded treatment arms (100 mg BI 1026706, Placebo in a 1:1 ratio).

BI 1026706 or placebo will be administered orally twice a day (in the morning and evening), beginning on Day 1 (Visit 2) until Day 28.

BI 1026706 or placebo will be administered according to the time given in [Flowchart](#).

Each medication bottle contains 20 tablets of BI 1026706 or Placebo.

At Visit 2 the trial-medication-bottles used for the first administration of trial medication will be dispensed to the subject for home administration. At Visits 3, 4, and 5 new trial-medication bottles will be dispensed for home administration. For details please refer to [Section 4.1.4.3](#) "Trial medication administration at home".

At Visits 3, 4, 5, 6 and 7 the investigator or qualified site staff will take back the remaining medication from the subject. For details please refer to [Section 4.1.4.4](#) "Returning of trial medication after home administration".

Site personnel will enter all medication numbers dispensed to each subject in the Medication Record page of the eCRF.

Any repacking, transferring of tablets from one bottle to another is strictly prohibited. Tablets may only be removed from a bottle directly before the dose administration.

#### 4.1.4.3 Trial medication administration at home

At home, trial medication (BI 1026706 or placebo) will be self-administered by the subject as an oral dose (tablets) with water. Regarding restriction diet and life style please refer to [Section 4.2.2.2](#) “Restrictions on diet and life style”.

The subject will complete a subject-diary confirming whether the trial medication at home has been taken correctly by documenting date and time of each intake.

Dispensing trial medication for home administration prior to release from investigational site: At the end of the on-site study visits preceding home administration, the subject will be provided with sufficient trial medication for self-administration at home until the next clinic visit.

The correct use of trial medication will be explained in detail to the subject by the investigator or qualified site staff at every visit preceding administration of trial medication at home. The subject will be instructed to bring all trial medication bottles (regardless of whether empty or not) back to the investigational site.

#### 4.1.4.4 Returning of trial medication after home administration:

During on-site study Visits 3, 4, 5 and 6, the returned trial medication has to be collected and checked for correctness together with the subject’s diary. Any discrepancy has to be documented by the investigator.

#### 4.1.4.5 Time of administration of any trial medication:

The morning dose will be administered between 07:00 a.m. and 10:00 a.m.  
The evening dose will be administered between 07:00 p.m. and 10:00 p.m.

#### 4.1.4.6 Skipping of trial medication:

In the event that the a.m. trial medication is not administered before 12:00 noon, this a.m. trial medication will be skipped and the next p.m. trial medication will be administered as scheduled. In the event that the p.m. trial medication is not administered before 12:00 midnight, this p.m. trial medication will be skipped and the next a.m. trial medication will be administered as scheduled. This information is included in the written subject information.

#### 4.1.4.7 Missed administration of trial medication:

If a subject missed one or more doses of trial medication, he should take the following doses according to the CTP. This information is included in the written subject information.

### 4.1.5 Blinding and procedures for unblinding

#### 4.1.5.1 Blinding

Subjects, investigators and anyone else involved in trial conduct or analysis or with any other interest in this double-blind trial will remain blinded with regard to the randomized treatment assignments until after database lock. [REDACTED]

The randomization code will be kept secret by Clinical Trial Support until database lock.

#### 4.1.5.2 Unblinding and breaking the code

An emergency code break (envelope) will be available to the Investigator / Pharmacist / investigational drug storage manager. This code break may only be opened in an emergency situation when the identity of the trial drug must be known to the Investigator in order to provide appropriate medical treatment or otherwise assure safety of trial participants. If the code break for a subject is opened, the Sponsor must be informed immediately. The reason for opening the code break must be documented on the envelope and/or appropriate CRF page along with the date and the initials of the person who broke the code. At the end of the trial all emergency envelopes have to be sent back to the sponsor.

#### **4.1.6 Packaging, labelling, and re-supply**

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

No re-supply is planned.

#### **4.1.7 Storage conditions**

Drug supplies will be kept in their original packaging and in a secure limited access storage area according to the recommended storage conditions on the medication label. A temperature log must be maintained for documentation.

If the storage conditions are found to be outside the specified range, the local clinical monitor (as provided in the list of contacts) must be contacted immediately.

## 4.2 CONCOMITANT THERAPY, RESTRICTIONS, AND RESCUE TREATMENT

### 4.2.1 Rescue medication, emergency procedures, and additional treatment(s)

No concomitant therapy will be allowed. An exemption is the use of a bronchodilator as well as lidocaine for the conduct of bronchoscopies.

However, in case of adverse events requiring treatment, symptomatic therapy, according to the judgment of the investigator will be permitted. In case of adverse events, the subjects will be treated as necessary and kept under constant supervision at the investigational site or transferred to hospital until such time that all the results of the evaluations have returned to a medical acceptable level.

A concomitant therapy can be authorized by the investigator, as long as this is not in conflict with the criteria for eligibility (please refer to [Section 3.3.3](#)) and with restrictions regarding concomitant treatments (see [Section 4.2.2.1](#)). In case of doubt, a case-by-case decision will be made after consultation with the sponsor.

All concomitant medications and/or rescue therapies will be recorded on the source documents and recorded in the eCRF.

### 4.2.2 Restrictions

#### 4.2.2.1 Restrictions regarding concomitant treatment

Please see [Section 4.2.1](#).

#### 4.2.2.2 Restrictions on diet and life style

##### Diet and lifestyle restrictions before and after administration of trial medication:

Alcohol, coffee, tea, cola energy drinks and chocolate are not permitted 24 hours preceding the administration of study medication (V2) and until the end of [REDACTED] bronchoscopy at Visit 7.

Citrus fruits, in particular grapefruits and Seville oranges (sour or bitter oranges), and their juices as well as products containing St. John's Wort (*Hypericum perforatum*) are not permitted 5 days prior to the first trial drug administration (Day 1, Visit 2) [REDACTED]

While admitted to the trial site the subjects are restricted from consuming any foods or drinks other than those provided by the site staff. Standard clinic meals will be served when subjects are at the clinic.

Excessive physical activity should be avoided starting 1 week prior to the first trial drug administration and during the course of the study (competitive sport etc.).

On Day 1 (Visit 2) and Day 28 (Visit 6), the morning administration of trial medication will occur following an overnight fast of at least 8 hours. In addition, on these two days, before administration of the morning trial medication (BI 1026706 or placebo), no liquid intake is allowed 2 hours before and 2 hours after administration of trial medication. On all other days there are no restrictions before and after administration concerning food and liquid intake. On Day 29 (Visit 7), the second bronchoscopy will occur following an overnight fast of at least 8 hours.

As a general rule, scheduled procedures (after randomization) should neither be postponed nor skipped due to violation against these restrictions.

### **4.3 TREATMENT COMPLIANCE**

Subjects are requested to bring all remaining trial medication including empty package material with them when attending visits.

## 5. VARIABLES AND THEIR ASSESSMENT

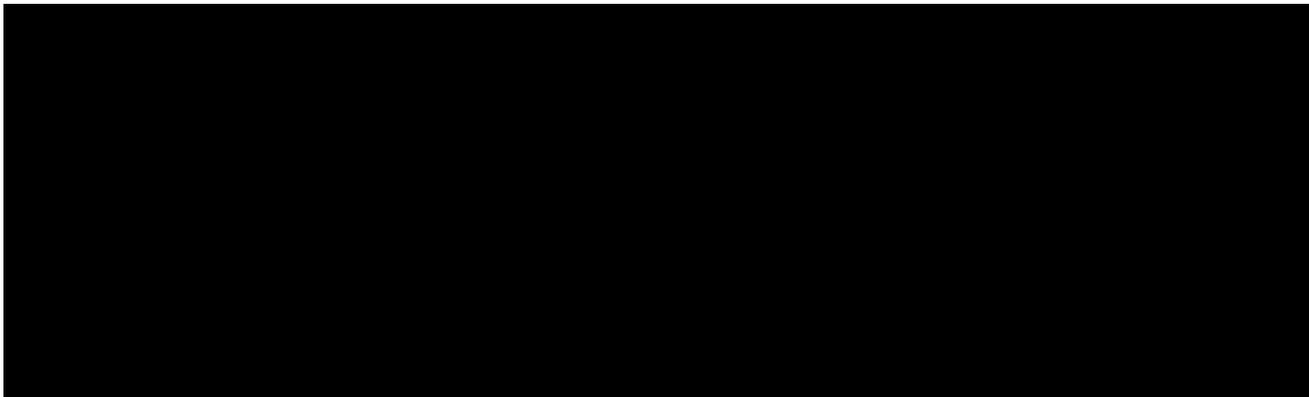
### 5.1 TRIAL ENDPOINTS

#### 5.1.1 Primary Endpoint(s)

Total cell count of neutrophils in Bronchoalveolar Lavage (BAL) after 24 hours of the segmental endotoxin challenge.

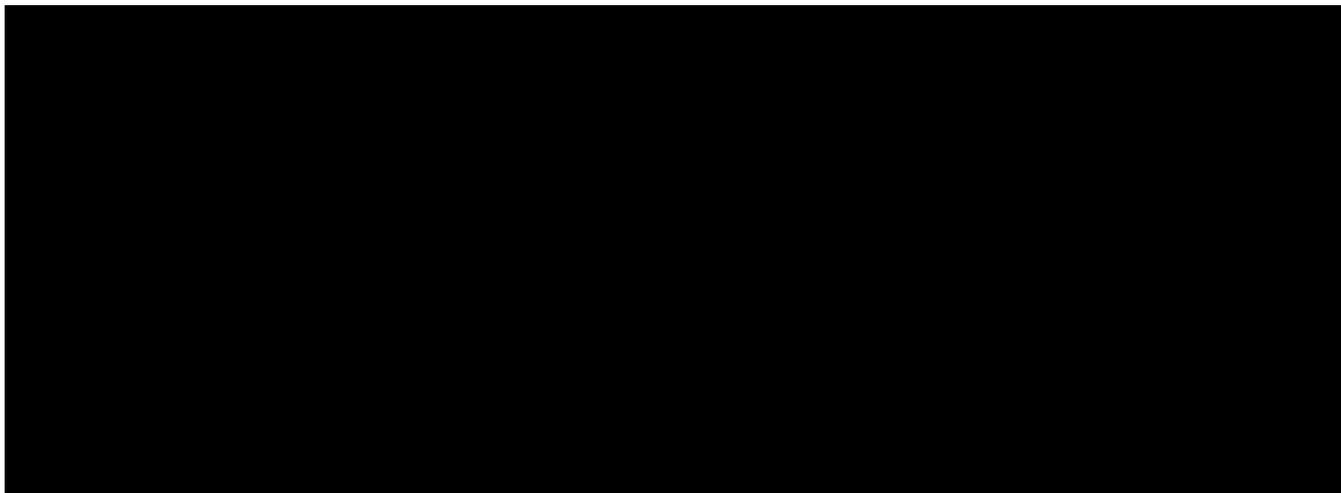
#### 5.1.2 Secondary Endpoint(s)

Total and differential cell count of neutrophils (only differential cell count), eosinophils, monocytes, macrophages and lymphocytes in BAL after 24 hours of the segmental endotoxin challenge.



#### Further endpoints related to safety assessment:

- Number (%) of subjects with treatment emergent adverse events (TEAE).
- Number (%) of subjects with drug related AEs



## 5.2 ASSESSMENT OF EFFICACY

Please refer to [Section 5.1](#) “Trial Endpoints”

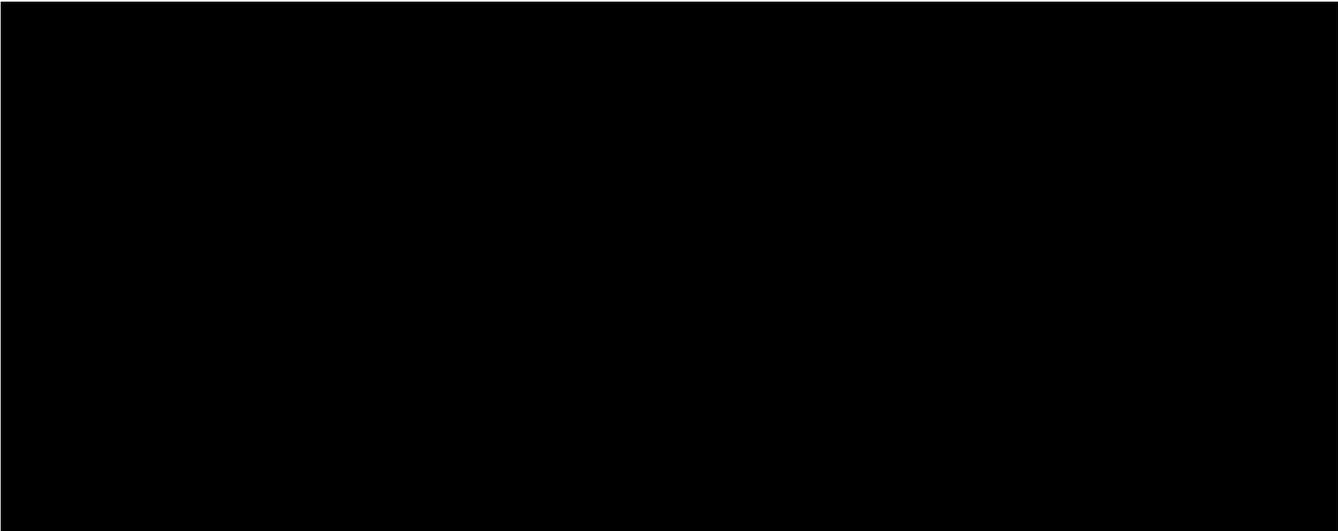
## 5.3 ASSESSMENT OF SAFETY

### 5.3.1 Physical examination

A physical examination will be carried out according to the [Flow Chart](#) and will be performed as complete physical examination. In addition further physical examination should be performed if clarification of AEs is necessary.



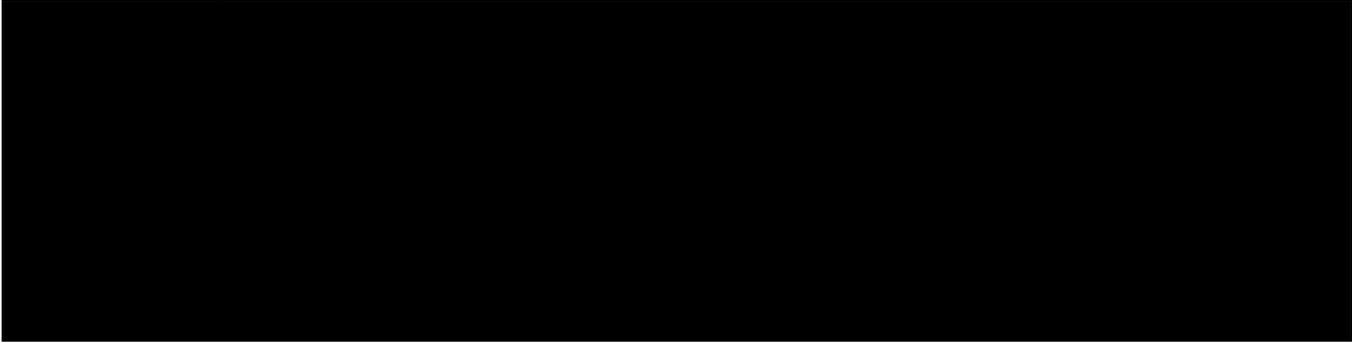
After randomization, new clinically significant findings or worsening of screening conditions that are, in the opinion of the investigator, clinically significant or meet other AE criteria defined in [Section 5.3.7](#) will be reported as adverse events.

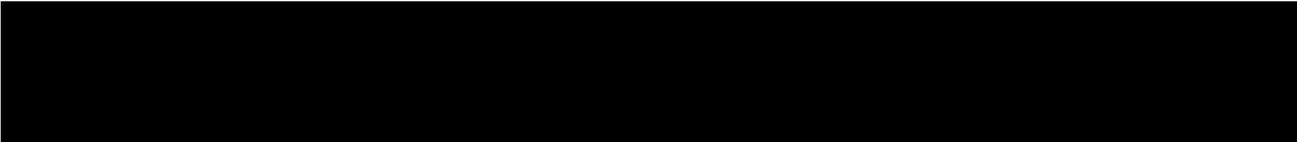


### 5.3.3 Safety laboratory parameters

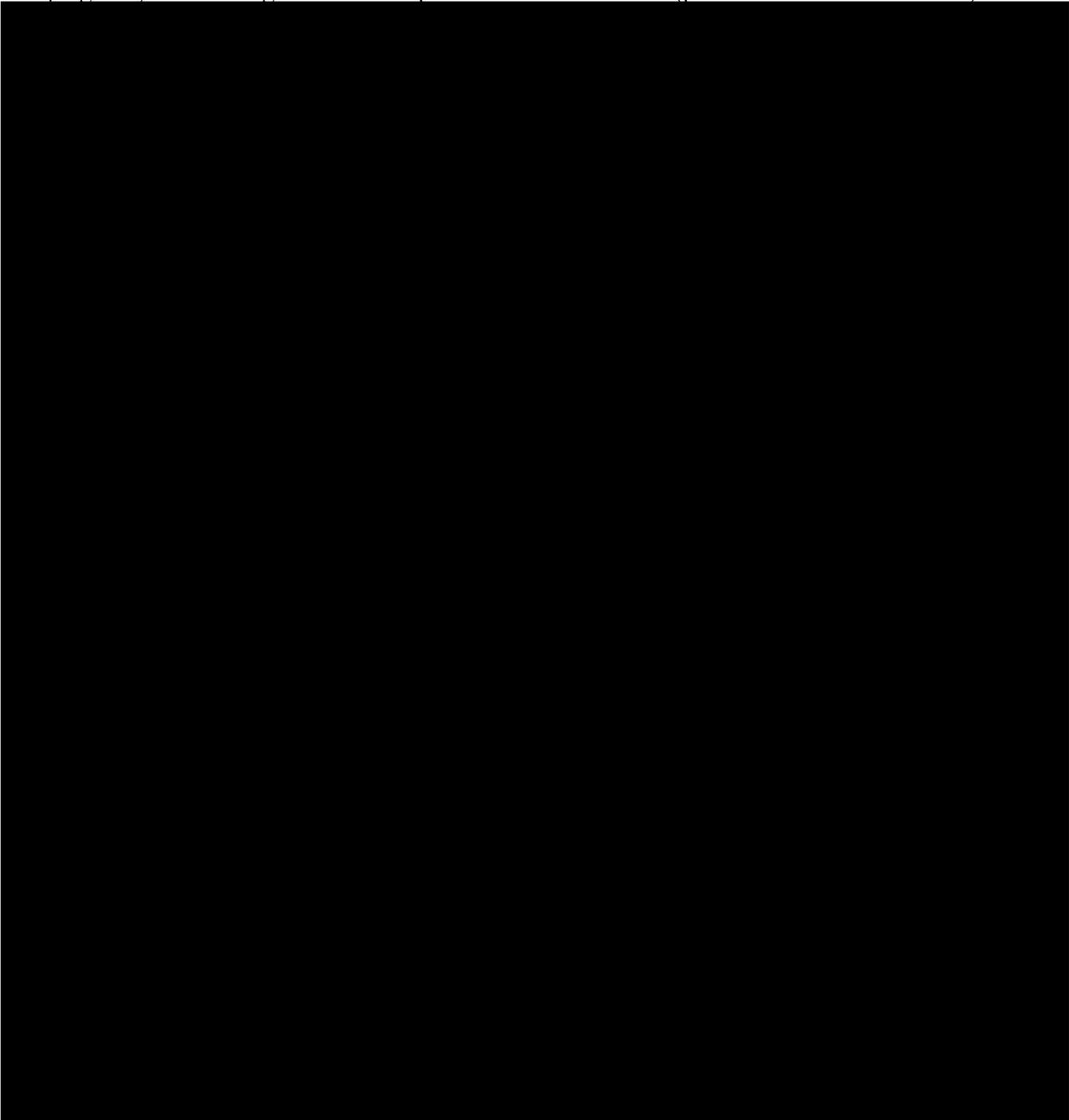
#### 5.3.3.1 Safety laboratory parameters obtained from blood

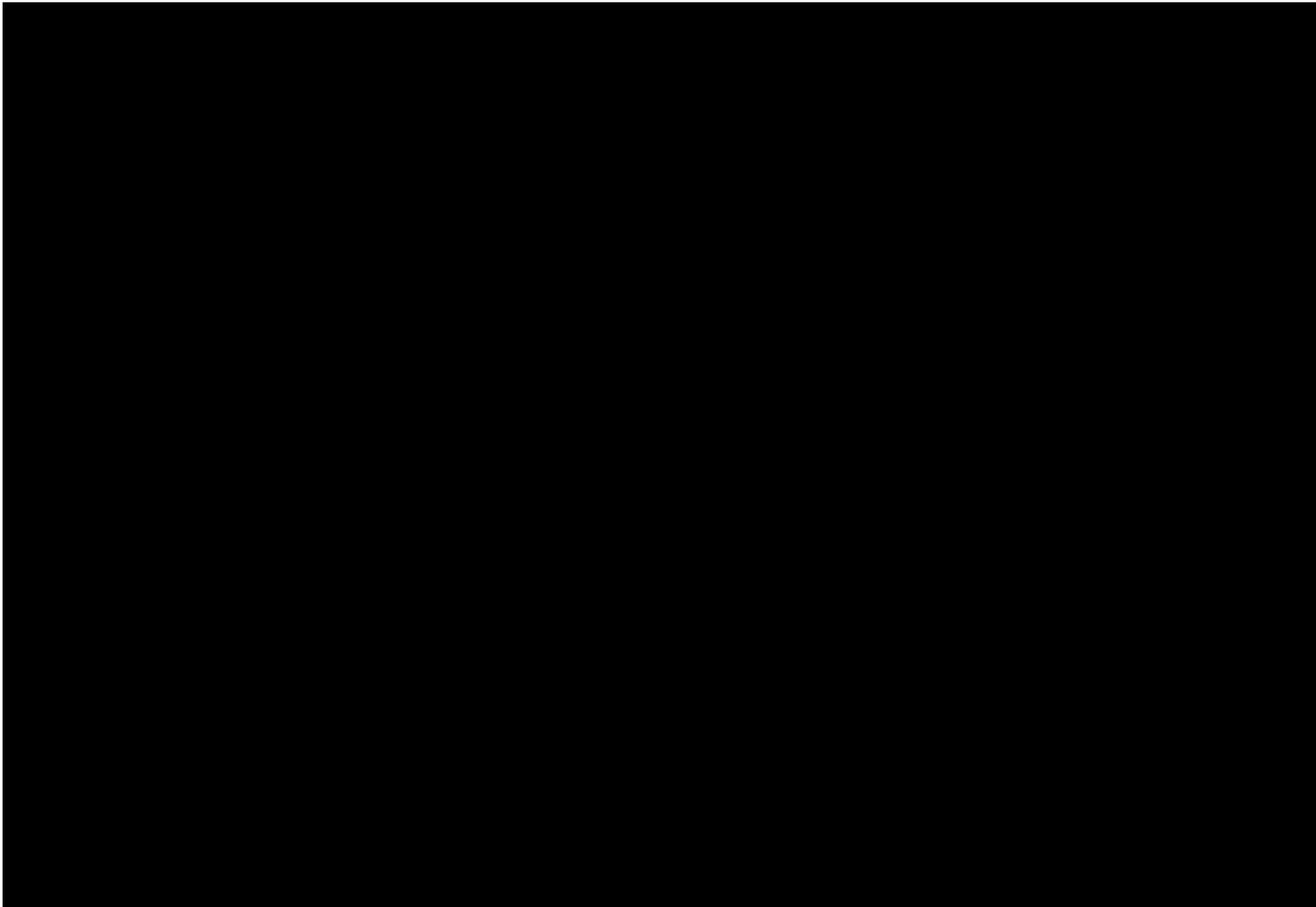
For the assessment of laboratory parameters, blood samples will be collected by the trial site at the time points indicated in the [Flow Chart](#).





The local laboratory will send reports to the investigator. It is the responsibility of the investigator to evaluate the laboratory reports. Clinically relevant abnormal findings as judged by the Investigator will be reported as adverse events (please refer to [Section 5.3.6](#)).





#### 5.3.3.2 Safety laboratory parameters obtained from urine

For the assessment of laboratory parameters, urine samples will be collected by the trial site at the time points indicated in the [Flow Chart](#).

[Redacted]

[Redacted] by the investigator will be reported as adverse events (please refer to [Section 5.3.6](#)).

[Redacted]

#### 5.3.4 Electrocardiogram

12-lead ECGs (I, II, III, aVR, aVL, aVF, V1 - V6) will be recorded using the ECG machine of the investigator site. For time points refer to the Flow Chart.

[Redacted]

The ECG records will be checked for pathological results by the investigator or a designee. Clinically relevant abnormal findings as judged by the Investigator will be reported as adverse events (please refer to [Section 5.3.6](#)).

For the inclusion or exclusion of a subject and for the assessment of cardiac safety during the study, the QT and QTcB values generated by the ECG machines or their manual corrections by the investigators will be used.

Any ECG abnormalities will be carefully monitored and, if necessary, the subject will be removed from the trial and medically treated. Baseline measurements will be defined as the measurements taken prior to the first administration of trial medication.

### 5.3.5 Other safety parameters

#### 5.3.5.1 Pulmonary Function Testing

Spirometry measurements will be performed on the device of the investigational sites. The spirometer and its use must meet American Thoracic Society (ATS) / European Respiratory Society (ERS) criteria [\[P05-12782\]](#) (this includes daily calibration, daily calibration checks and weekly linearity checks before performance of the measurements). In addition peak flow must be reached earlier than 120 ms after the extrapolated start of the maneuver in order to fulfil the acceptable criteria for a forced spirometry maneuver.

### 5.3.6 Assessment of adverse events

#### 5.3.6.1 Definitions of AEs

##### **Adverse event**

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

An AE can therefore be any unfavorable 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:

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

Life-threatening in this context refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if more severe.

Every new occurrence of cancer must be reported as a serious event regardless of the duration between discontinuation of the drug and the occurrence of the cancer.

##### **AEs considered “Always Serious”**

In accordance with the European Medicines Agency initiative on Important Medical Events, Boehringer Ingelheim has set up a list of 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 given above.

The latest list of “Always Serious AEs” can be found in the Remote Data Capture (RDC) system. These events should always be reported as SAEs as described in [Section 5.3.7](#).

##### **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. AESI

need to be reported to the Sponsor's Pharmacovigilance Department within the same timeframe that applies to SAE, see [Section 5.3.7](#).

The following are considered as AESIs:

#### Hepatic injury

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

- an elevation of AST and/or ALT  $\geq 3$  fold upper limit normal (ULN) combined with an elevation of total bilirubin  $\geq 2$  fold ULN measured in the same blood draw sample, and/or
- marked peak aminotransferase (ALT and/or AST) elevations  $\geq 10$  fold ULN

These lab findings constitute a hepatic injury alert and the subjects showing these lab abnormalities need to be followed according to the "DILI checklist" provided via the RDC system.

In case clinical symptoms of hepatic injury (for example, icterus, unexplained encephalopathy, unexplained coagulopathy, right upper quadrant abdominal pain) without available lab results (ALT, AST, total bilirubin), the investigator should make sure these parameters are analyzed, if necessary in an unscheduled blood test. Should the results meet the criteria of hepatic injury, the procedures described in the DILI checklist should be followed.

#### Intensity of AEs

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

- Mild: Awareness of sign(s) or symptom(s) that is/are easily tolerated  
Moderate: Enough 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 between an AE and trial medication, 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.

Yes: There is a reasonable causal relationship between the investigational product administered and the AE.

No: There is no reasonable causal relationship between the investigational product administered and the AE.

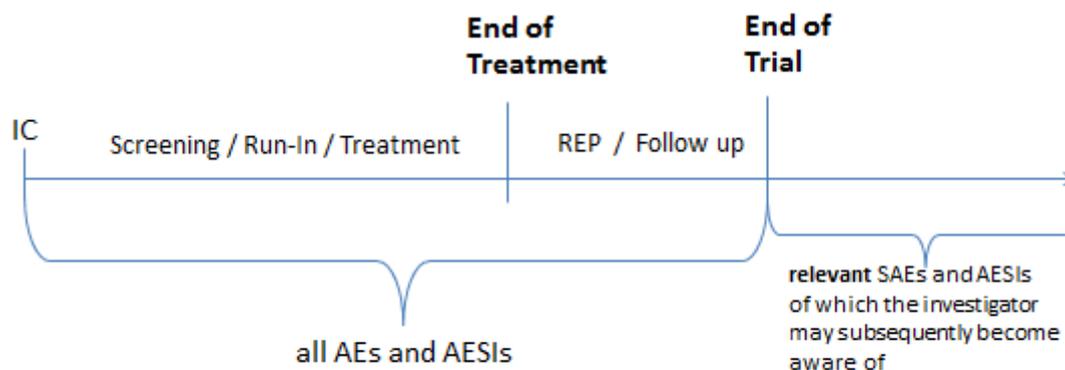
The reason for the decision on causal relationship for unlisted AEs could be provided in the (e)CRF as deemed necessary by the investigator.

### **5.3.7 Adverse event collection and reporting**

#### **AE Collection**

The following must be collected and documented on the appropriate eCRF by the Investigator:

- From signing the informed consent onwards through the Residual Effect Period (REP), until individual subject's end of trial:
  - All AEs (serious and non-serious), and all AESIs.
- After the individual subject's end of trial:
  - The investigator does not need to actively monitor the subject for AEs but should only report relevant SAEs and relevant AESIs of which the investigator may become aware of.



All AEs which considered as on

treatment please see [Section 7.3.4](#). Events which occurred after the REP will be considered as post treatment events.

### AE reporting to sponsor and timelines

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

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

### Information required

For each AE, the Investigator should provide the information requested on the appropriate eCRF pages and the BI SAE form, e.g. onset, end date, intensity, treatment required, outcome, seriousness, and action taken with the investigational drug(s). The Investigator should determine the causal relationship to the trial medication and any possible interactions between the investigational drug and a Non-Investigational Medicinal Product (NIMP)/Auxiliary Medicinal Product (AMP) as comment.

The following should also be recorded as an (S)AE in the eCRF and 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 trial inclusion they will be considered as baseline conditions.

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

#### **Screening failures:**

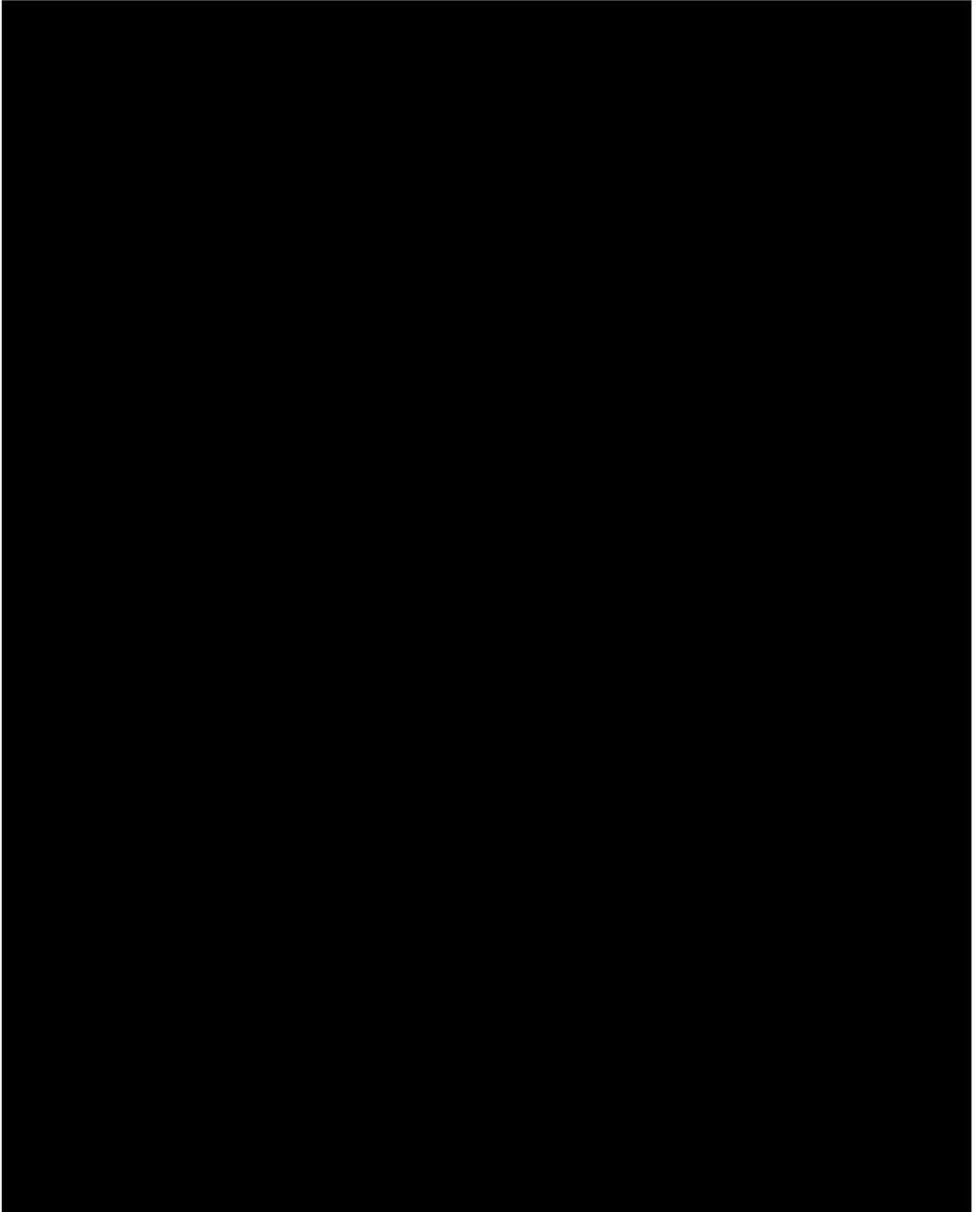
SAEs occurring in patients after having discontinued in the trial due to screening failures, i.e. after the screening period and who did not receive any trial medication, are to be reported if the investigator considered the SAE related to the screening procedure. SAEs which occurred during the screening period are to be reported according to standard procedures.

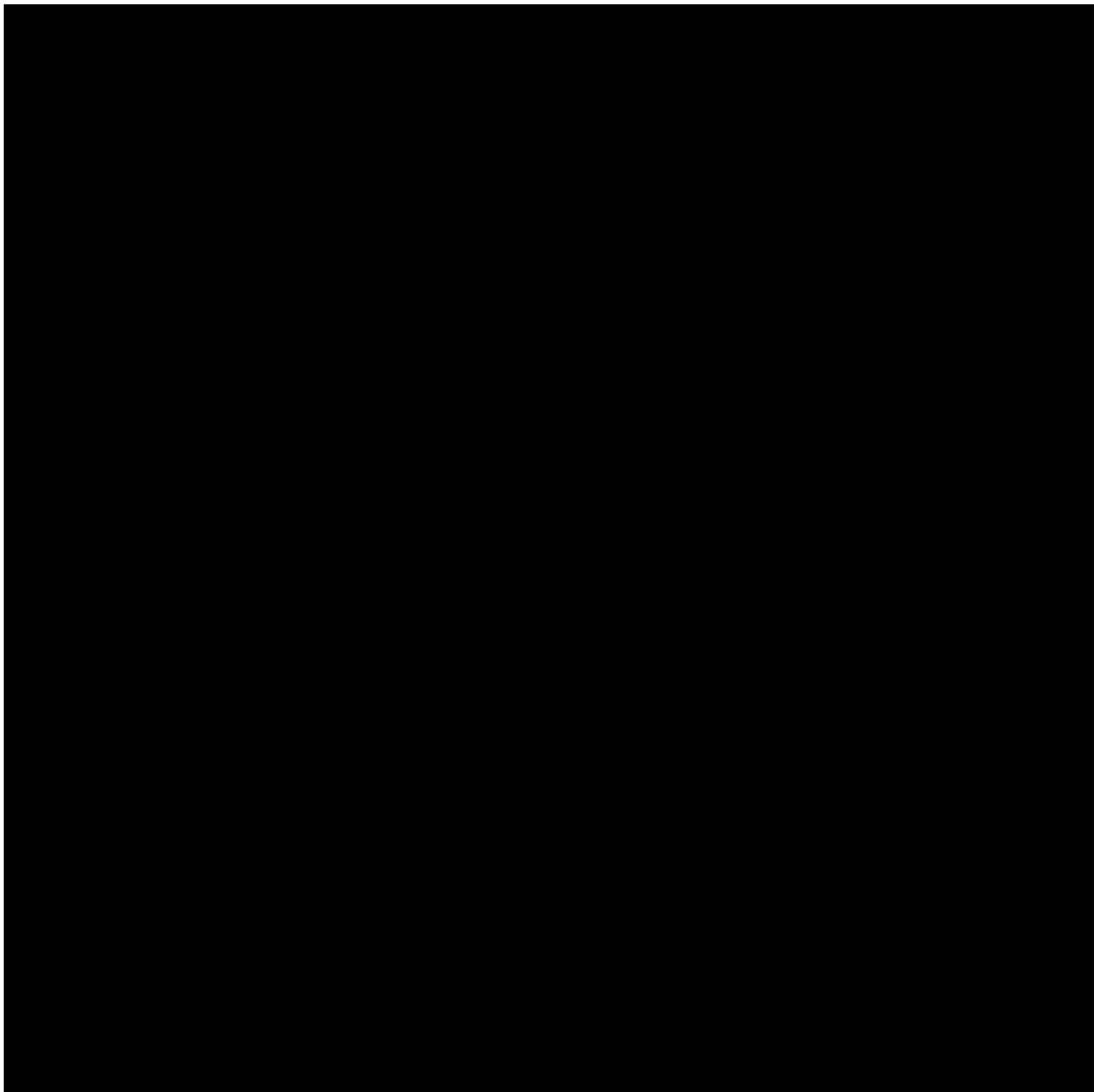
#### **Pregnancy:**

In rare cases pregnancy may occur in a clinical trial. Once a subject has been enrolled into this clinical trial and has taken trial medication, the Investigator must report immediately (within 24 hours) a potential drug exposure during pregnancy (DEDP) to the sponsor's unique entry point (country-specific contact details will be provided in the ISF). The Pregnancy Monitoring Form for Clinical Trials (Part A) should be used. The outcome of the pregnancy associated with the drug exposure during pregnancy must be followed up and reported to the sponsor's unique entry point on the Pregnancy Monitoring Form for Clinical Trials (Part B). The ISF will contain the Pregnancy Monitoring Form for Clinical Trials (Part A and B). As pregnancy itself is not to be reported as an AE, in the absence of an accompanying SAE and/or AESI, only the Pregnancy Monitoring Form for Clinical Trials and not the SAE form is to be completed. If there is an SAE and/or AESI associated with the pregnancy an SAE form must be completed in addition.

#### **Exemptions to SAE Reporting**

Not applicable.

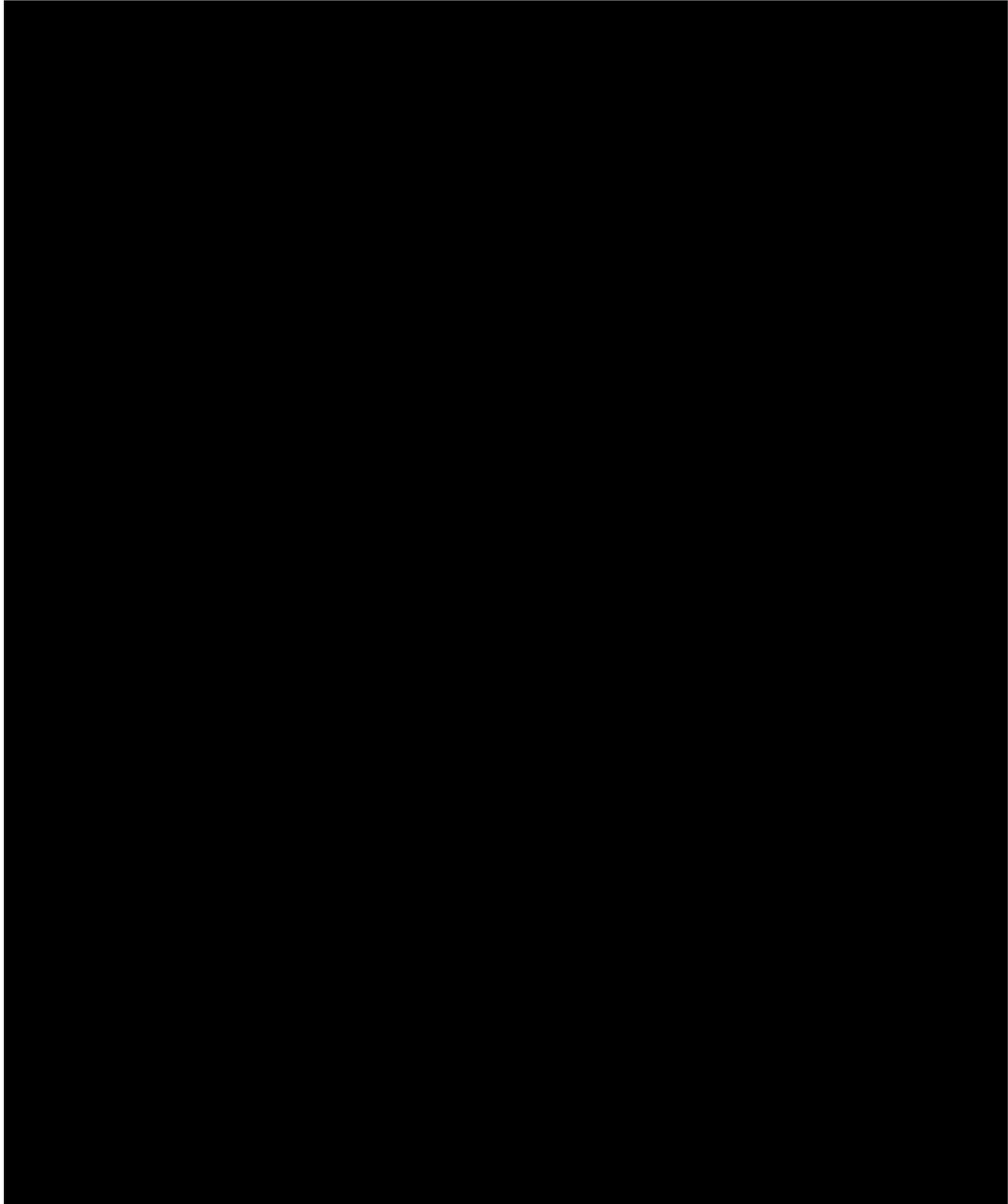




BAL sample will be taken at time points indicated in the Flow Chart. Instruction describing the BAL procedure is provided in the ISF.

The provided BAL samples will be processed in order to the procedure for BAL and processing provided in the ISF. BAL samples need to be processed directly (within 2 hours maximum) after the sample has been taken.

Cellular fraction will be used for total and differential cell count ([see section 5.1](#)). If sufficient material is available, transcriptome analysis may be performed.



## 5.7 APPROPRIATENESS OF MEASUREMENTS

Measurements performed during this trial are standard measurements and will be performed  to monitor safety aspects in an appropriate way.

The PK parameters and measurements outlined in [Section 7.3.5](#) are generally used as measurements to assess drug exposure.

The scheduled measurements are appropriate to see drug induced changes in vital signs, lung function, standard laboratory values and ECG.

These primary and secondary endpoints are standard and accepted for evaluation of pharmacodynamic parameters of an oral drug, and they are widely used in this kind of studies.

Therefore, the appropriateness of all measurements applied in this trial is given.

## 6. INVESTIGATIONAL PLAN

### 6.1 VISIT SCHEDULE

#### 6.1.1 Adherence to the protocol visits and procedures

Subjects should make all efforts to complete the study which includes the follow-up period and end of trial visit. Investigators should encourage treatment compliance and adherence to the protocol procedures. All subjects are to adhere to the visit schedule as specified in the [Flow Chart](#). All deviations from the planned visit schedule should be documented.

Regarding randomization please refer to [Section 7.6](#).

Regarding removal of subjects please refer to [Section 3.3.4](#).

#### 6.1.2 Visit scheduling

All observations and procedures as mentioned in the [Flow Chart](#) for an individual visit should be performed on the same day. Clinical and safety laboratory evaluation of Visit 1 can be repeated maximum twice within the screening period for clinical and/or technical reasons (e.g. the blood sample is clotted) based on investigator's judgment. If more than 2 repeated evaluations are necessary the subject will be discontinued from the study and will be marked as screening failure.

At clinic visits, the administration is under the supervision of the investigator or qualified site staff.

All subjects are to adhere to the visit schedule as specified in the [Flow Chart](#). Some flexibility is allowed in scheduling the visits according to visit time windows as specified in the Flow Charts ( $\pm 2$  days during the treatment period for Visits 3, 4, 5 and 6). Visit 7 must be performed on the day following Visit 6.

If any visit has to be rescheduled, subsequent visits should follow the original visit date schedule (calculated from Visit 2). The total treatment period of  $28 \pm 2$  days must not be exceeded, i.e. Visit 6 must be performed between Day 26 and 30 following randomization (Visit 2).

### 6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

#### 6.2.1 Screening period

##### Informed Consent prior to trial participation:

All subjects must sign and date an Informed Consent consistent with ICH-GCP guidelines prior to trial participation. Please refer to [Section 8.1](#) for details.

##### Re-screening

Subjects who do not fulfil the eligibility criteria (i.e. subjects who do not fulfil all of the inclusion criteria or fulfil at least one of the exclusion criteria) are to be entered as screening

failure. Subjects are allowed to be re-screened twice based on investigator's judgment. Re-screening requires a new informed consent and unique study subject number

Details on particular observations and procedures at Visit 1 (screening visit):

Visit 1 will take place 3 to 28 days prior to randomization.

Observations and procedures will be performed as mentioned in [Flow Chart](#).

- Review of in-/exclusion criteria
- Demographics will be recorded
- Smoking status / calculation of pack-years
- Relevant medical history and baseline conditions
- Alcohol and drug screening
- Cotinine and skin prick test
- Complete physical examination will be conducted
- Body weight and height
- Vital signs measurement
- ECG recording
- Pulmonary function test
- Safety dipstick urine test
- Safety blood sampling and processing. [REDACTED]. For female subjects, pregnancy will be tested in serum.

- AE assessment
- Concomitant therapy documentation and recording, diet and lifestyle restrictions

### 6.2.2 Treatment period(s)

Details on particular observations and procedures at Visits 2, 3, 4, 5, and 6:

Observations and procedures will be performed as mentioned in the Flow Chart.

- Review of in-/exclusion criteria at Visit 2
- Smoking status to be checked at Visit 2, 4, and 6
- Alcohol screening and cotinine test at Visit 6
- Complete physical examination will be conducted at Visit 2, 4, and 6
- Body weight at Visit 2 and 6
- Vital signs measurement
- ECG recording at Visit 2, 4, and 6
- Pulmonary function test at Visit 2, 4, and 6
- Safety dipstick urine test at Visit 2, 4, and 6
- For female subjects, urine pregnancy testing will be conducted at Visit 2 (only if the time period between Visit 1 and Visit 2 exceeds 7 days), Visit 5 and Visit 6 prior to [REDACTED] bronchoscopy, respectively.

- Safety blood sampling and processing at Visit 2, 4, and 6. [REDACTED]
- Randomization will be conducted at Visit 2 after all safety measurements are completed (see [Section 4.1.2](#))

- Regarding administration of trial medication, dispense trial drug for home administration, collection of trial drug used at home, and use of diary please see [Sections 4.1.4](#) and [6.2.4](#))
- Treatment compliance check will be performed at Visit 3, 4, 5, and 6
- Subjects drug diary will be dispensed at Visit 2 and checked at Visits 3, 4, 5, and 6
- AE assessment
- Concomitant therapy documentation and recording, diet and lifestyle restrictions
- Bronchoscopy with LPS challenge and retrieval of BAL and biopsies will be performed at Visit 6. Pulse oximetry will be done during bronchoscopy. In case of female subjects, a negative urine pregnancy testing is required at Visit 6.

As this is a trial in healthy volunteers, no special care after the end of trial is needed.

### 6.2.3 Follow-up Period and End of Trial

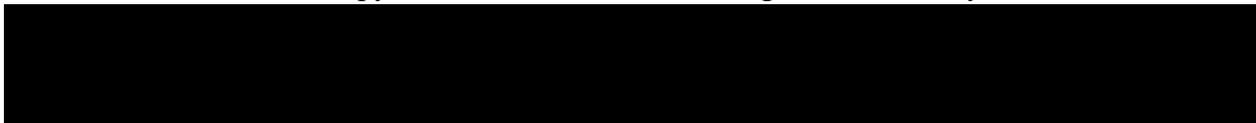
#### Details on particular observations and procedures at Visit 7 and 8

Observations and procedures will be performed as mentioned in the [Flow Chart](#). Timing of Visit 7 in relation to Visit 6 is described in section [6.2.4](#).

- Complete physical examination will be conducted
- Alcohol screening at Visit 7
- Vital signs measurement
- ECG recording
- Safety dipstick urine test at Visit 8 including a pregnancy testing for female subjects
- Safety blood sampling and processing

- Treatment compliance check will be performed at Visit 7
- Subjects drug diary will be checked at Visits 7
- AE assessment

- Concomitant therapy documentation and recording, diet and lifestyle restrictions



- 
- Bronchoscopy with retrieval of BAL and biopsies will be performed at Visit 7, 24 hours ( $\pm 1$  h) after LPS challenge at Visit 6. In case of female subjects, a negative urine pregnancy testing is required at Visit 6. Pulse oximetry will be done during bronchoscopy. Trial is completed at Visit 8.

Subjects who took the trial medication and discontinue prematurely should undergo the EOT examination (Visit 8) as soon as possible after the last dose of trial drug.

#### 6.2.4 Timing for selected observations and procedures

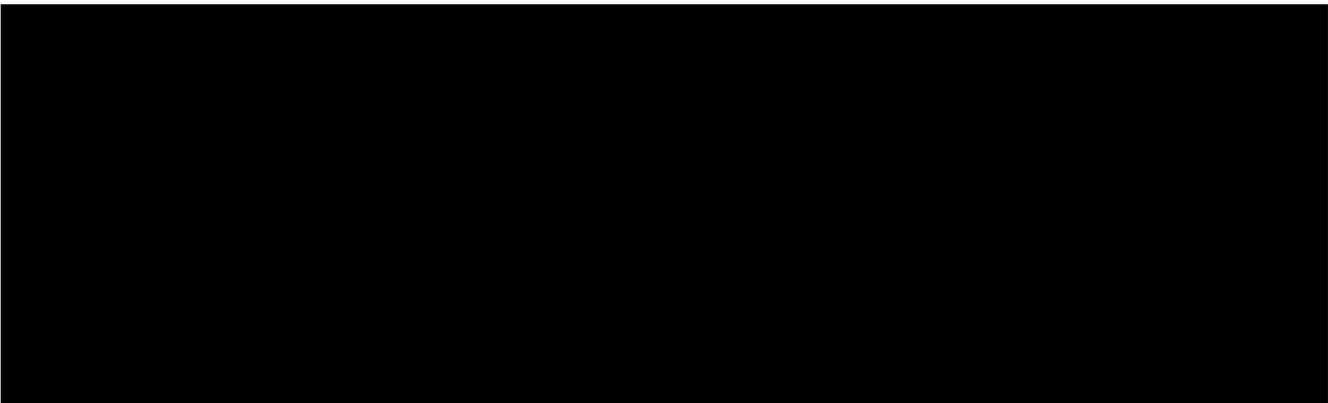
On Day 1 (Visit 2), study participants will be admitted to the trial site and kept under close medical surveillance following drug administration. The subjects will then be allowed to leave the trial site after formal assessment and confirmation of their fitness.

On all other study days during treatment period, the study will be performed in an ambulatory fashion.



On Day 28 (Visit 6), subjects will stay at the investigational site for approximately 9 hours for PK sampling and bronchoscopy with LPS challenge and BAL as well as biopsy sampling. Prior to bronchoscopy, all relevant procedures according to [Flow Chart](#) will be performed.

On Day 29 (Visit 7), 24 hours after Visit 6, the second bronchoscopy with sampling of BAL and biopsies will be performed. Prior to bronchoscopy, all relevant procedures according to [Flow Chart](#)  will be performed. Subjects have to stay at the investigational site for approximately 8 hours and kept under close medical surveillance.



The time between tablet intake in the evening on Day 28 (Visit 6) and the bronchoscopy on Day 29 (Visit 7) should preferable not exceed 14 hours. Subjects are asked to take medication on Day 28 (Visit 6) as late as possible and ideally close to 10 p.m. The second bronchoscopy should be performed in the morning of Day 29 (Visit 7).

## 7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

### 7.1 STATISTICAL DESIGN - MODEL

#### 7.1.1 Objectives

The trial objectives are stated in [Section 2.2](#).

#### 7.1.2 Endpoints

The primary endpoint is the total neutrophil count in BAL 24 hours following endotoxin challenge, see [Section 5.1.1](#).

Secondary endpoints regarding BAL in the segment with endotoxin challenge are stated in [Section 5.1.2](#).

#### 7.1.3 Model

The statistical model used for the primary analysis of primary and secondary endpoints will be an analysis of variance (ANOVA) model on the logarithmic scale. This model will include the effect 'treatment' and is described by the following equation:

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

- $y_{jk}$  logarithm of response (primary or secondary endpoint) measured on subject  $i$  receiving treatment  $k$ ,  $i = 1, \dots, 50$ ,  $k = 1, 2$ ,
- $\mu$  the overall mean,
- $\tau_k$  the  $k$ th treatment effect,
- $e_{ik}$  the random error associated with subject  $i$  receiving treatment  $k$ .

where  $e_{ik} \sim N(0, \sigma_B^2)$  i.i.d.

## 7.2 NULL AND ALTERNATIVE HYPOTHESES

This trial will be conducted to detect statistically significant differences between BI 1026706 and placebo in BAL neutrophil counts 24 hours following endotoxin challenge at the end of treatment.

The null and alternative hypotheses are

$H_0$ : geometric mean ratio of neutrophil counts at the end of the treatment is 1.

$H_a$ : geometric mean ratio of neutrophil counts at the end of the treatment is not equal to 1.

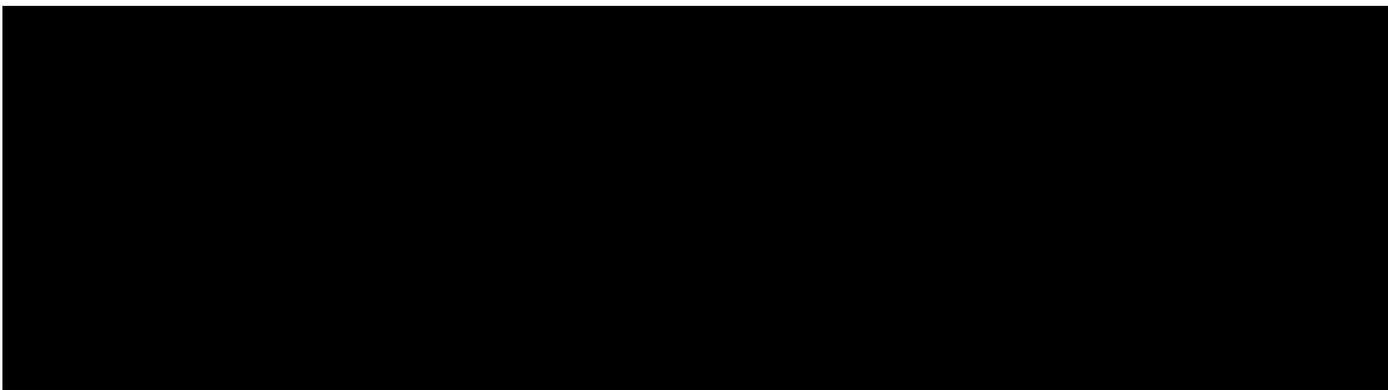
Safety and tolerability of BI 1026706 is to be determined on the basis of the safety assessments in comparison to placebo. It is not planned to test any statistical hypotheses with regard to these variables in a confirmatory sense. Instead, they will be described in their entirety and evaluated by descriptive statistical methods.

### 7.3 PLANNED ANALYSES

Measurements regarding BAL of a subject will be included in the analysis, if they are not flagged for exclusion, e.g. due to PD non-evaluability or a protocol violation relevant to the evaluation of these PD endpoints, which will be decided no later than in the Blinded Report Planning Meeting.

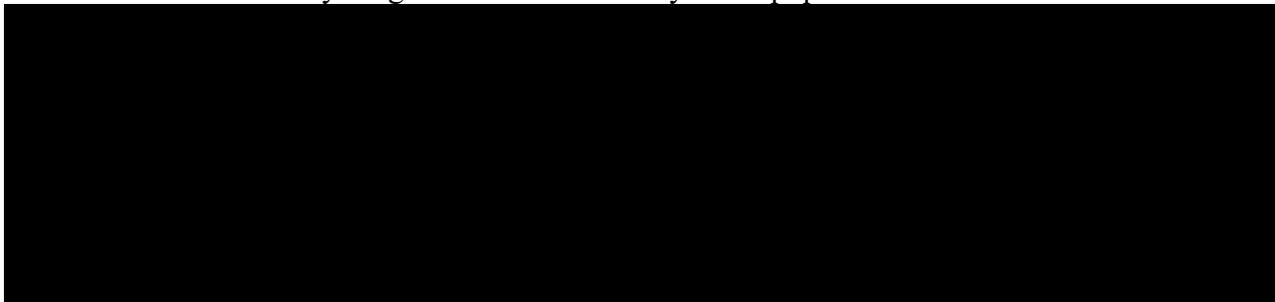
A PD endpoint regarding BAL may be considered as non-evaluable, if for example

- the amount of BAL was not sufficient,
- the LPS administration was not conducted as planned.



Detailed list of protocol violations will be provided in the TSAP.  
The statistical analysis will be based on the following analysis sets.

- Randomized set (RS):  
This subject set includes all randomized subjects, whether treated or not.
- Treated set (TS):  
The treated set includes all subjects who were randomized and treated with at least one dose of study drug. This is the full analysis set population in the sense of ICH-E9.

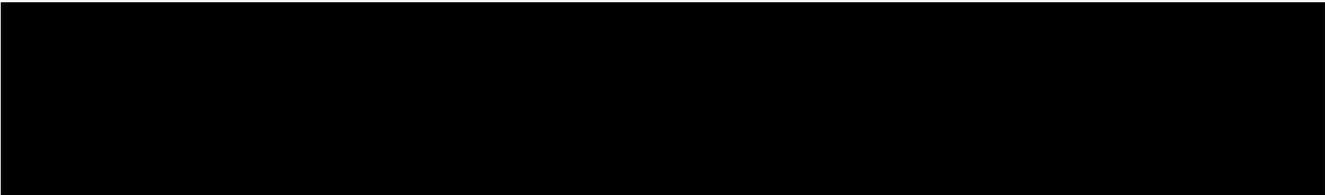


- Pharmacodynamic set (PDS):  
The pharmacodynamic set includes all treated subjects that have evaluable cell counts for the cell types defined in the primary or secondary endpoints following 24 hours of LPS administration.

### 7.3.1 Primary endpoint analyses

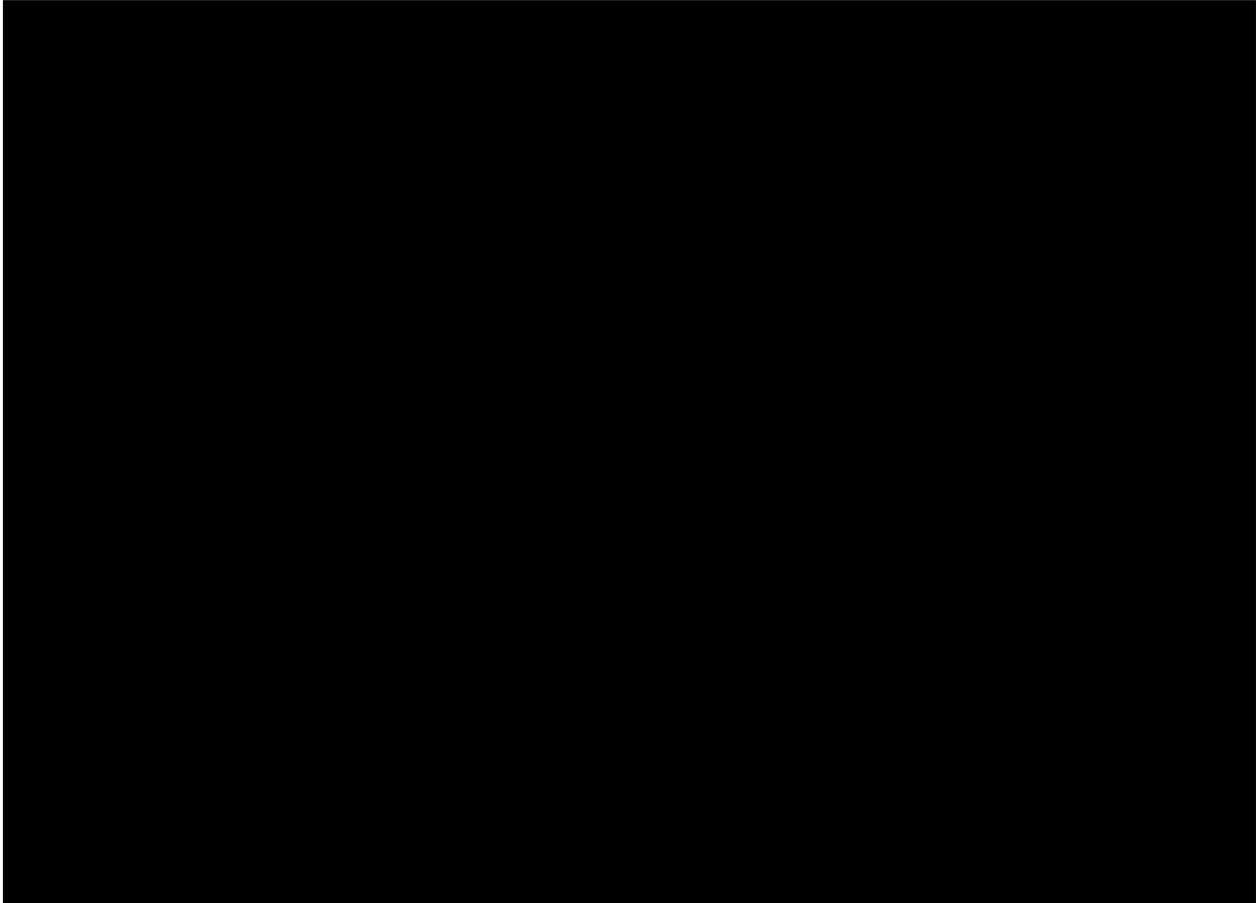
The primary objective of this study will be assessed using the primary endpoint, see [Section 7.1.2](#). The primary endpoint will be logarithmically transformed, and analyzed using the ANOVA as described in [Section 7.1.3](#). The least square means (LS means) of treatment difference and its 90% confidence interval (CI) on the log scale will be obtained from this model and will be exponentiated to obtain the geometric mean ratio and 90% CI in total neutrophil count between BI 1026706 and placebo on the original scale 24 hours post endotoxin challenge.

The primary analysis will be based on the PDS.



### 7.3.2 Secondary endpoint analyses

Secondary endpoints regarding BAL, see [Section 5.1.2](#), will be statistically assessed using the same methods as described for the primary analysis of the primary endpoint. The analysis will be based on the PDS.



#### 7.3.4 Safety analyses

Safety will be assessed for the further endpoints listed in [Section 5.1.3](#) as well as the further safety assessments described in [Section 5.3](#). All treated subjects (that is, all subjects who received at least one dose of study drug), will be included in the safety evaluation. Safety analyses will be descriptive in nature and will be based on BI guideline ‘Analysis and presentation of adverse event data from clinical trials’ (001-MCG-156).

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

Tabulations of frequencies/proportions will be used for the evaluation of categorical (qualitative) data, and tabulations of descriptive statistics will be used to analyze continuous (quantitative) data.

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

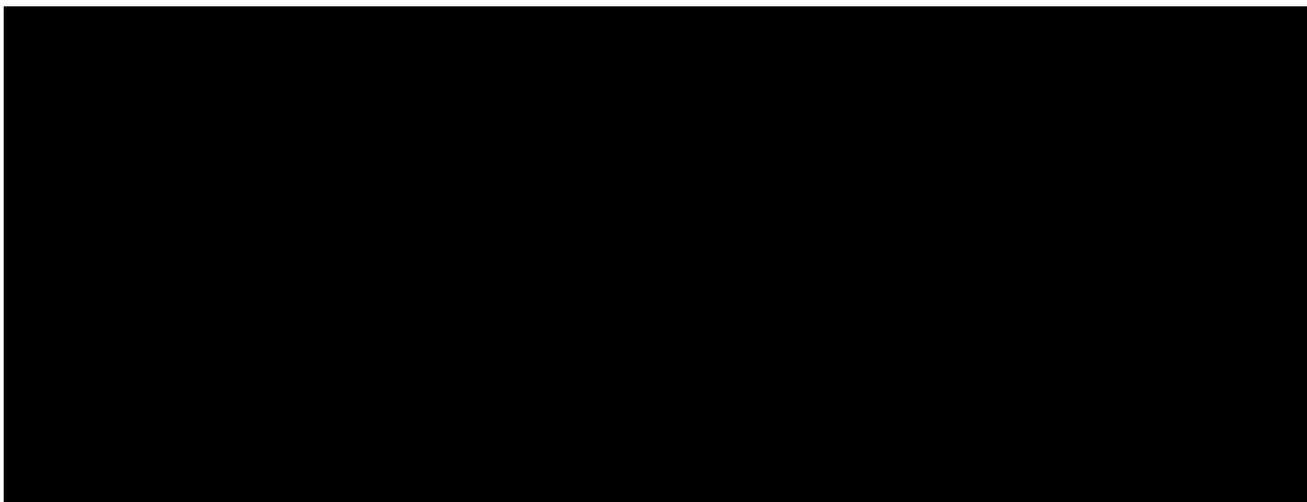
Therefore, measurements planned or AEs recorded prior to first intake of trial medication will be assigned to 'screening', those between first trial medication intake until the end of the REP will be assigned to ‘on-treatment’, and those between end of REP and end-of-trial examination will be assigned to ‘post-treatment’ and those after the end of trial examination will be assigned to ‘post-study’. These assignments including the corresponding time intervals will be defined in detail in the TSAP.

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

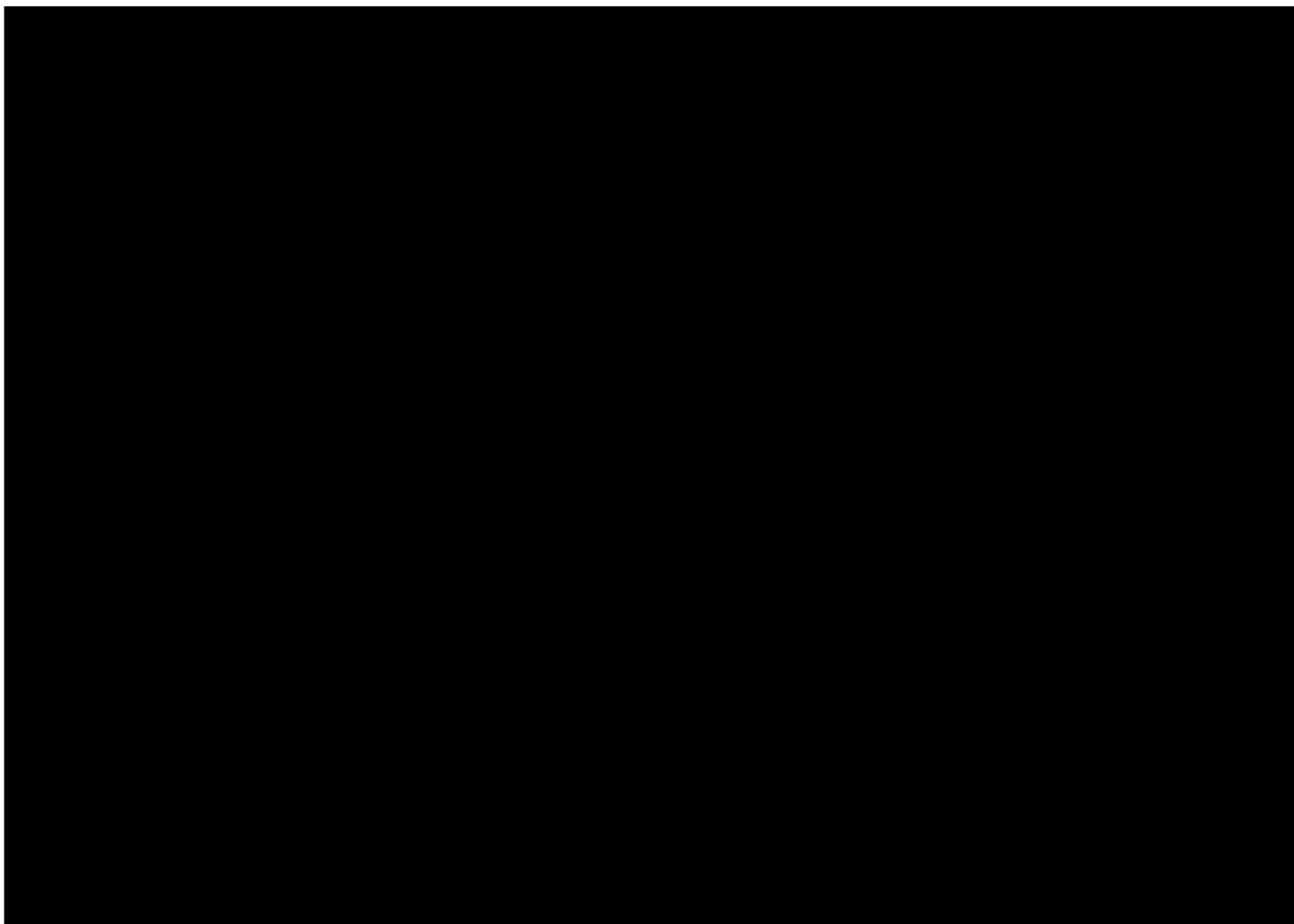
Adverse events will be coded using the MedDRA. Frequency, intensity and causal relationship of AEs will be tabulated by treatment, primary system organ class and preferred term. SAEs and other significant AEs (according to ICH E3), and AESIs will be listed separately (see [Section 5.3.7](#)).

Statistical analysis and reporting of adverse events will concentrate on treatment-emergent and drug-related adverse events. To this end, all adverse events occurring between start of treatment and end of the residual effect period will be considered ‘treatment-emergent’. Adverse events that start before first drug intake and deteriorate under treatment will also be considered as ‘treatment-emergent’.

Frequency, severity, and causal relationship of adverse events will be tabulated by system organ class and preferred term after coding according to the current version of the Medical Dictionary for Drug Regulatory Activities (MedDRA).



Relevant ECG findings will be reported as AEs.



#### **7.4 INTERIM ANALYSES**

No interim analysis is planned.

## 7.5 HANDLING OF MISSING DATA

Missing safety and pharmacodynamic data will not be imputed.

## 7.6 RANDOMIZATION

Subjects will be randomized in blocks to double-blind treatment in a 1:1 ratio, receiving either placebo or 100 mg BI 10276706 b.i.d. The block size will be documented in the CTR.

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

## 7.7 DETERMINATION OF SAMPLE SIZE

This is the first clinical trial conducted in healthy smoking subjects with 28-day exposure, and the sample size of 25 subjects per treatment group is considered sufficient to achieve the aims of this exploratory trial.

Hohlfeld et al. [\[R13-0305\]](#) investigated the effect of Roflumilast compared to placebo on the cell count of different cell types in BAL. Based on their results it is assumed that the mean neutrophil count 24 hours post endotoxin challenge in the placebo group is  $1256 \cdot 10^3/\text{ml}$  with a standard deviation (SD) of  $870 \cdot 10^3/\text{ml}$ . The mean number of neutrophils in the Roflumilast treatment group was  $836 \cdot 10^3/\text{ml}$  with SD of  $314 \cdot 10^3/\text{ml}$  and thus it was only 67% of that for the placebo group 24 hours post endotoxin challenge. This corresponds to a fold-change of 1.50 (placebo vs. roflumilast).

The sample size calculation is based on the following assumptions:

- The primary endpoint is log-normally distributed
- 1-sided significance level  $\alpha = 5\%$
- BI 1026706 will have a similar effect like Roflumilast. Hence a fold-change of 1.50 or in case of number of neutrophils is only 60% under BI 1026706 compared to placebo a fold-change of 1.67.
- The expected coefficient of variation (CV) is similar to the observed CVs in Hohlfeld et al.
- Based on Hohlfeld et al. the expected rate of neutrophil counts being unavailable due to reasons such as dropout, unqualified samples, discontinuation of procedure etc., is 10% to 20%.

[Table 7.7:1](#) below shows the expected power under the assumptions stated above and for various coefficient of variations (CV), evaluable subjects and fold-changes.

Table 7.7: 1 Expected power to detect differences in the treatments based on the primary endpoint for various coefficients of variation, evaluable subjects per group and expected fold-changes.

CV	N per group	Fold-change	
		1.50	1.67
0.38	20	96 %	99 %
	22	97 %	99 %
0.53	20	81 %	93 %
	22	84 %	95 %
0.69	20	64 %	81 %
	22	68 %	84 %

From the Table above, a sample size of 22 evaluable subjects per group will have at least 84% power to detect a significant difference in case the total cell count of neutrophils under BI 1026706 is at most 67% (corresponds to a 1.5 fold-change) of the respective number for placebo on original scale and the CV is not greater than 53%. To account for the potential 10% subjects without evaluable neutrophil counts, a total sample size of  $2 * 25 = 50$  subjects will be entered in the study.

The calculation was performed using the MTT0cv routine from the commercial software nQuery Advisor<sup>®</sup> Version 7.0 (Statistical Solutions Ltd., Cork, Ireland).

## **8. INFORMED CONSENT, DATA PROTECTION, TRIAL RECORDS**

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

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

The Investigator will inform the Sponsor immediately of any urgent safety measures taken to protect the trial 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 the Investigator contract. As a rule, no trial results should be published prior to finalization of the Clinical Trial Report.

The certificate of insurance cover is made available to the Investigator and the subjects, and is stored in the ISF (Investigator Site File).

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

The Investigator must give a full explanation to trial subjects including the items listed below in association with the use of the subject information form, which is prepared avoiding the use of technical terms and expressions. The subject is given sufficient time to consider participation in the trial. The Investigator obtains written consent of the subject's own free will with the informed consent form after confirming that the subject understands the contents. The Investigator must sign (or place a seal on) and date the informed consent form. If a trial collaborator has given a supplementary explanation, the trial collaborator also signs (or places a seal on) and dates the informed consent.

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

## **8.2 DATA QUALITY ASSURANCE**

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

## **8.3 RECORDS**

Case Report Forms (CRF) / eCRF for individual subjects will be provided by the Sponsor. See [Section 4.1.5.2](#) for rules about emergency code breaks. 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. Data reported on the CRF 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; current medical records must also be available. For eCRFs all data must be derived from source documents.

### **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. CRF/eCRF and all source documents, including progress notes 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 (CRA) / on site monitor and auditor may review all CRF/eCRF, 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 documents and essential documents for a period defined by the GCP regulation and trial site's contract with the sponsor.

#### Sponsor:

The Sponsor must retain the essential documents according to the Sponsor's SOPs. When it is no longer necessary for the trial site to retain the source documents and essential documents, the Sponsor must notify the head of trial site.

## **8.4 LISTEDNESS AND EXPEDITED REPORTING OF ADVERSE EVENTS**

### **8.4.1 Listedness**

To fulfil the regulatory requirements for expedited safety reporting, the Sponsor evaluates whether a particular adverse event is "listed", i.e. is a known side effect of the drug or not. Therefore, a unique reference document for the evaluation of listedness needs to be provided. For BI 1026706, this is the current version of the Investigator's Brochure provided in the ISF. For LPS, the reference document for assessing international listedness is the current version of the IB provided in the ISF. The reference document for the contrast medium as auxiliary medicinal product is the UK SmPC of DOTAREM provided in the ISF.

No AEs are classified as listed for matching placebo or invasive procedures.

### **8.4.2 Expedited reporting to health authorities and IEC/IRB**

Expedited reporting of serious adverse events, e.g. suspected unexpected serious adverse reactions (SUSAR) to health authorities and IEC/IRB, will be done according to local 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 given 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.

## **8.6 END OF TRIAL**

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.

The IEC / competent authority in Germany needs to be notified about the end of the trial or early termination of the trial.

## **8.7 PROTOCOL VIOLATIONS**

The investigator should document any deviation from the protocol regardless of their reasons. Only when the protocol was not followed in order to avoid an immediate hazard to trial subjects or for other medically compelling reason, the principal investigator should prepare and submit the records explaining the reasons thereof to the sponsor, and retain a copy of the records.

**8.8            COMPENSATION AVAILABLE TO THE SUBJECT IN THE EVENT OF  
                 TRIAL RELATED INJURY**

In the event of health injury associated with this trial, the Sponsor is responsible for compensation based on the contract signed by the trial site.

## 9. REFERENCES

### 9.1 PUBLISHED REFERENCES

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- R10-1412 Daxas 500 micrograms film-coated tablets (Nycomed) (summary of product characteristics).  
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- R15-3034 Chronic respiratory diseases: burden of COPD.  
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## 9.2 UNPUBLISHED REFERENCES

- c03035551 Investigator's Brochure. BI 1026706

## 10. APPENDICES

### 10.1 CALCULATION OF NUMBER OF PACK YEARS

$$\text{Pack years} = \frac{\text{Number of cigarettes per day}}{20} \times \text{years of smoking}$$

### 10.2 CONTRACEPTION

Male subjects will only be included in this trial when they agree to minimize the risk of female partners becoming pregnant from the first dosing day until 3 months after the trial medication treatment has finished (see [Section 3.3.3](#)).

Hence, male subjects who have sexual intercourse with women of childbearing potential (i.e. fertile, following menarche until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy) will be instructed and must agree to use at least one of the acceptable forms of effective contraception listed below.

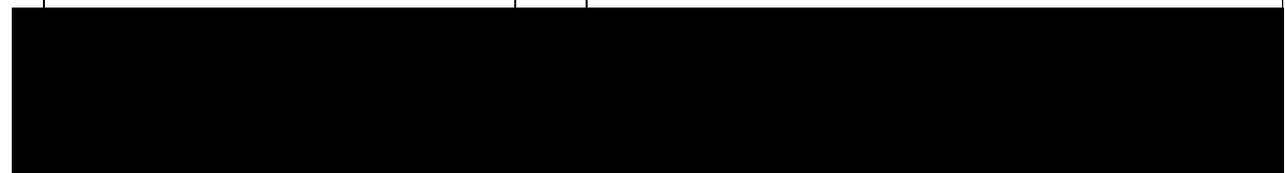
Acceptable forms of effective contraception include:

- Established use of oral, injected or implanted hormonal methods of contraception or tubal ligation by the female partner of the male subject
- Placement of an intrauterine device (IUD) or intrauterine system (IUS) by the female partner of the male subject
- Use of barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository
- Sterilization of the male subject (with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate)

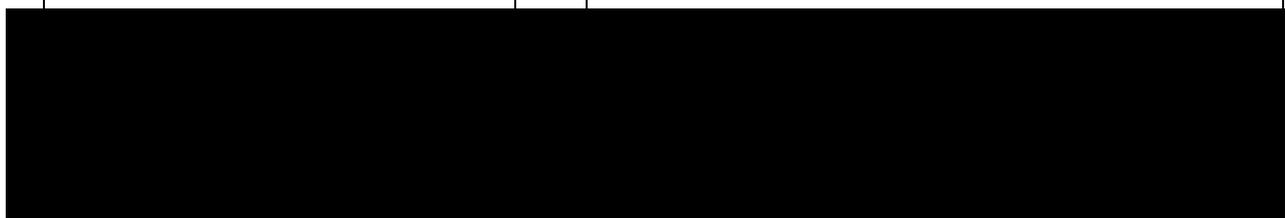




<b>Section to be changed</b>		Title page

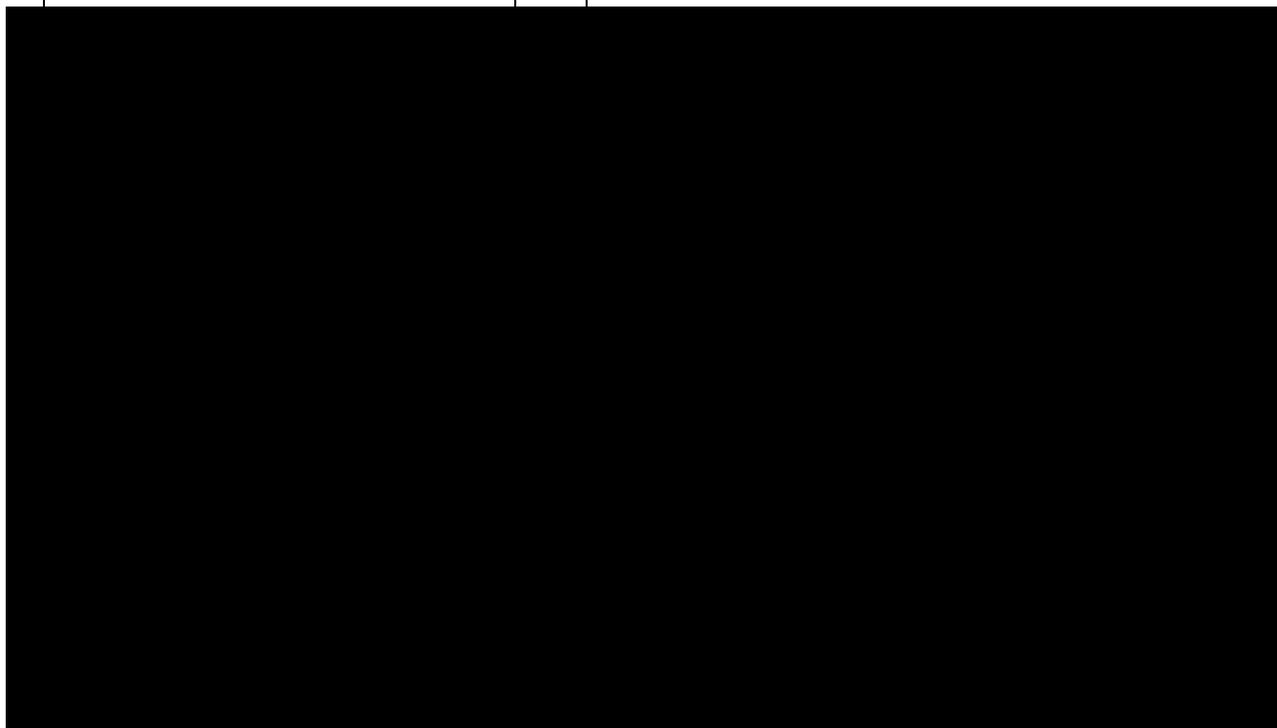


<b>Section to be changed</b>		Flowchart –footnote 5, 3.1.1
<b>Description of change</b>		Medical checks (including spirometry) will be performed prior to discharge of subject according to the SOP of the investigational trial site
<b>Rationale for change</b>		To reflect the SOP of the investigational trial site



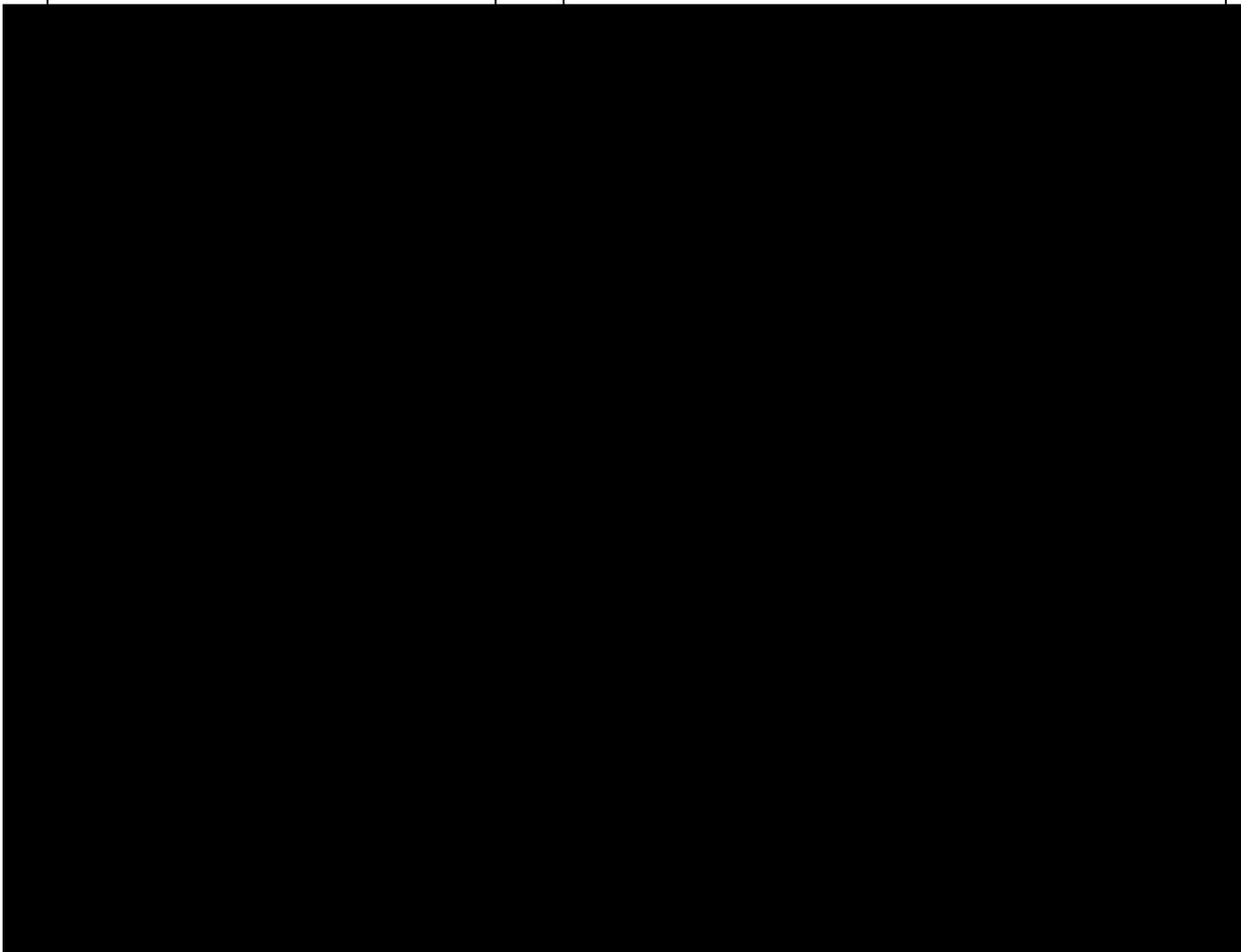
<b>Section to be changed</b>		3.3.5
<b>Description of change</b>		Female subjects will not be used for replacement
<b>Rationale for change</b>		Only male subjects are allowed in the trial
<b>Section to be changed</b>		4.1, 8.4.1
<b>Description of change</b>		Deletion of batch specific information and addition of IMPD as document for assessment of listedness
<b>Rationale for change</b>		To allow use of LPS as IMP as approved
<b>Section to be changed</b>		4.2.2.2, 5.3.2
<b>Description of change</b>		To clarify that standard clinic meals (and not standardized meals) and a certified blood pressure instrument without need for the identical instrument being used are sufficient
<b>Rationale for change</b>		To specify operative requirements at the trial site
<b>Section to be changed</b>		5.3.3.1
<b>Description of change</b>		The date and blood collection times must be recorded in the eCRF or transferred electronically to the sponsor (if possible).

<b>Rationale for change</b>		To allow electronic transfer if possible
<b>Section to be changed</b>		5.3.6.1
<b>Description of change</b>		Need to provide the reason for decision on causal relationship for unlisted AE was clarified
<b>Rationale for change</b>		Investigator could comment in the CRF AE-page as needed, but is not compulsory



<b>Number of global amendment</b>		2
<b>Date of CTP revision</b>		14-JUL-2016
<b>EudraCT number</b>		2015-001789-25
<b>BI Trial number</b>		1320.17
<b>BI Investigational Product(s)</b>		BI 1026706
<b>Title of protocol</b>		A randomized, double-blind, placebo-controlled, parallel group, Phase I trial in healthy male current smoker subjects to assess pharmacodynamic effects on segmental endotoxin induced inflammatory response and safety of 4 weeks oral administration of BI 1026706
<b>To be implemented only after approval of the IRB / IEC / Competent Authorities</b>		YES
<b>To be implemented immediately in order to eliminate hazard –</b>		NO

<b>IRB / IEC / Competent Authority to be notified of change with request for approval</b>		
<b>Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only</b>		NO

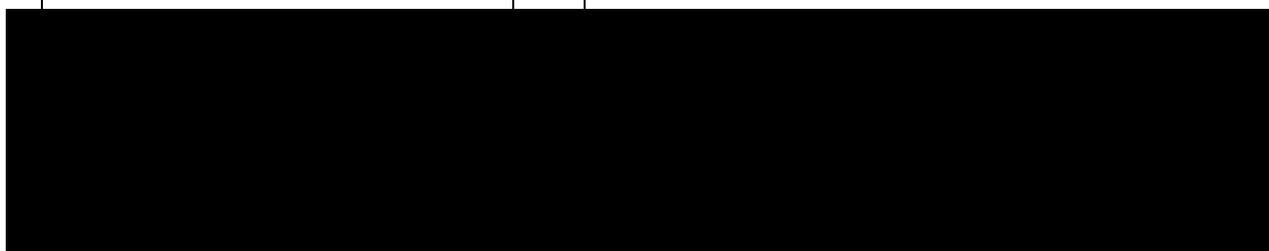


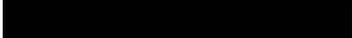
<b>Section to be changed</b>		2.1
<b>Description of change</b>		The study population was specified as healthy male subjects being current smokers at Visit 1. The LPS-endotoxin challenge was added to the rationale.
<b>Rationale for change</b>		To describe precisely rationale and population
<b>Section to be changed</b>		2.3.2



<b>Section to be changed</b>		3.3.2 (Inclusion Criterion number 10)
<b>Description of change</b>		Positive responses to skin prick tests are allowed if the subject is without clinical equivalent of allergies and if an exposure during trial participation is not expected
<b>Rationale for change</b>		To allow inclusion of non-allergic, sensitized subjects without expected exposure during the trial
<b>Section to be changed</b>		3.3.2, 3.3.3
<b>Description of change</b>		Inclusion criteria number 6 and 7, exclusion criterion number 14 and 15 will be assessed based on data collected at Visit 1
<b>Rationale for change</b>		To harmonize time points of assessments of these eligibility criteria
<b>Section to be changed</b>		3.3.3
<b>Description of change</b>		Clarification of the exclusion criterion 23
<b>Rationale for change</b>		To clarify exclusion criterion 23
<b>Section to be changed</b>		3.3.3 (Exclusion Criterion number 25); 6.2.1
<b>Description of change</b>		Re-screening will be allowed twice based on investigator's judgment.
<b>Rationale for change</b>		To allow re-screening of subjects
<b>Section to be changed</b>		3.3.4.1
<b>Description of change</b>		To add withdrawals if the subject experiences a respiratory tract infection during the treatment period which might interfere with safe conduct of bronchoscopies or its analyses.
<b>Rationale for change</b>		To specify handling of premature discontinuations in case of respiratory tract infections during the treatment period which might interfere with safe conduct of bronchoscopies or its analyses.
<b>Section to be changed</b>		4.1
<b>Description of change</b>		Clarification of the reconstitution process in the protocol that serves as example for the nominal dose of 10,000 endotoxin units. This process will be adapted to the actual endotoxin content given in the Certificate of Analysis to ensure an appropriate application dose of LPS.
<b>Rationale for change</b>		To update the reconstitution of LPS.

<b>Section to be changed</b>		4.2.2.2
<b>Description of change</b>		Restrictions on diet and life style were harmonized with site's procedures and harmonized with the revised informed consent form.
<b>Rationale for change</b>		To add alcohol restrictions during the trial
<b>Section to be changed</b>		5.3.3
<b>Description of change</b>		The header of the table 5.3.3.1:1 was aligned with the chapter, i.e. local laboratory to include safety laboratory parameters only
<b>Rationale for change</b>		To ensure consistency within the protocol
<b>Section to be changed</b>		5.3.7
<b>Description of change</b>		Possible interactions between IMP and AMP should be part of AE-reporting
<b>Rationale for change</b>		To receive information on possible interactions
<b>Section to be changed</b>		6.1.2
<b>Description of change</b>		Repeat-testing of clinical and safety laboratory parameters will be allowed maximum twice based on investigator's judgement
<b>Rationale for change</b>		To allow re-testing of clinical and safety parameters



<b>Description of change</b>		The reference document for assessing listedness for LPS will be the Investigator's Brochure
<b>Rationale for change</b>		To harmonize the reference documents
<b>Number of global amendment</b>		3
<b>Date of CTP revision</b>		02 Nov 2016
<b>EudraCT number</b>		2015-001789-25
<b>BI Trial number</b>		1320.17
<b>BI Investigational Product(s)</b>		BI 1026706
<b>Title of protocol</b>		A randomized, double-   in healthy male current smoker subjects to assess pharmacodynamic effects on segmental endotoxin induced inflammatory response and safety of 4 weeks oral administration

		of BI 1026706
<b>To be implemented only after approval of the IRB / IEC / Competent Authorities</b>		YES
<b>To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval</b>		NO
<b>Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only</b>		NO
<b>Section to be changed</b>		Title, Synopsis, Benefit-Risk-Assessment (2.3), Drug-related Risks (2.3.2), Inclusion and Exclusion Criteria (3.3.2; 3.3.3)
<b>Description of change</b>		Women NOT of childbearing potential are added to the study population. Pregnant, lactating and/or females of childbearing potential are still excluded.
<b>Rationale for change</b>		Trial procedures do not include an increased risk to females as compared to male healthy volunteers. Inclusion of females not of childbearing potential is in line with ICH M3.
<b>Section to be changed</b>		Flow Chart, Safety Laboratory Parameters (5.3.3), Details of Trial Procedures at Selected Visits (6.2)
<b>Description of change</b>		Serum pregnancy testing will be added at Visit 1. Urine pregnancy testing will be implemented at Visit 2 (only if time period between Visit 1 and Visit 2 exceeds 7 days), Visits 5, 6 and 8.
<b>Rationale for change</b>		Addition of pregnancy testing for females not of childbearing potential to safeguard their inclusion.
<b>Section to be changed</b>		Removal of Subjects from Therapy or Assessments (3.3.4), Adverse Event Collection and Reporting (5.3.7)
<b>Description of change</b>		Instructions to the investigator are added in case of pregnancy in females not of childbearing potential.
<b>Rationale for change</b>		Addition of instructions regarding removal of pregnant subjects and its reporting within the trial are added to safeguard the inclusion of women not of childbearing potential.

<b>Section to be changed</b>		Inclusion Criteria (3.3.2), Exclusion Criteria (3.3.3)
<b>Description of change</b>		Several in- and exclusion criteria were revised to allow investigator's medical judgement.
<b>Rationale for change</b>		Strict eligibility criteria are revised to allow more medical judgement by the investigator
<b>Section to be changed</b>		Synopsis, Inclusion Criteria (3.3.2)
<b>Description of change</b>		Upper age limit was moved from 50 to 65 years
<b>Rationale for change</b>		Higher age group has an equal risk for the trial.
<b>Section to be changed</b>		Flowchart, Overall Trial design and Plan (3.1)
<b>Description of change</b>		The time window for Visit 6 was revised to allow plus/minus 2 days
<b>Rationale for change</b>		To give more flexibility regarding Visit 6
<b>Section to be changed</b>		Appendix 10.2 - Contraception
<b>Description of change</b>		Instructions for male study subjects regarding female partners and their definition of childbearing potential and effective contraception were updated, e.g. tubal ligation is considered as effective contraception only
<b>Rationale for change</b>		To follow the "Recommendations related to contraception and pregnancy testing in clinical trials" of the Clinical Trial Facilitation Group
<b>Number of global amendment</b>		4
<b>Date of CTP revision</b>		19 Dec 2016
<b>EudraCT number</b>		2015-001789-25
<b>BI Trial number</b>		1320.17
<b>Title of protocol</b>		A randomized, double-blind, placebo-controlled, parallel group, Phase I trial in healthy male current smoker subjects to assess pharmacodynamic effects on segmental endotoxin induced inflammatory response and safety of 4 weeks oral administration of BI 1026706
<b>To be implemented only after approval of the IRB / IEC / Competent Authorities</b>		NO
<b>To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval</b>		NO
<b>Can be implemented without IRB / IEC / Competent</b>		YES

<b>Authority approval as changes involve logistical or administrative aspects only</b>		
<b>Section to be changed</b>		3.3.5, 4.1.4.1
<b>Description of change</b>		Replacement strategy and handling of medication dispense to replacement subjects is specified to allow adaptation to actual drop-out rate
<b>Rationale for change</b>		The drop-out rate in the trial after approximately 50% of subjects recruited into the trial is close to the cut-off point for replacement. To allow a seamless recruitment in the trial, replacement of subjects will need to start already prior to reaching the cut-off of maximum numbers of drop-outs. Spare reserve medication at the site will be used for this purpose which will require implementation of a trial-independent site-staff member with restricted access to randomization codes. This dedicated function will instruct the site's trial staff in a blinded manner which medication is to be dispensed to the replacement subjects.

**APPROVAL / SIGNATURE PAGE**
**Document Number: c03143538**
**Technical Version Number:5.0**
**Document Name: clinical-trial-protocol**

**Title:** A randomized, double-blind, placebo-controlled, parallel group, Phase I trial in healthy current smoker subjects to assess pharmacodynamic effects on segmental endotoxin induced inflammatory response and safety of 4 weeks oral administration of BI 1026706.

**Signatures (obtained electronically)**

Meaning of Signature	Signed by	Date Signed
Approval-Team Member Medicine	██████████	19 Dec 2016 15:17 CET
Approval-Trial Clinical Monitor	██████████████████	19 Dec 2016 16:39 CET
Author-Trial Clinical Pharmacokineticist	██████████	19 Dec 2016 16:51 CET
Author-Trial Statistician	██████████████████	20 Dec 2016 10:47 CET
Approval-Therapeutic Area	██████████ ████████████████████	21 Dec 2016 09:54 CET
Verification-Paper Signature Completion	██████████████████	21 Dec 2016 10:08 CET

**(Continued) Signatures (obtained electronically)**

<b>Meaning of Signature</b>	<b>Signed by</b>	<b>Date Signed</b>
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