CLINICAL TRIAL PROTOCOL

	Document Number:	c11830963-01
EudraCT No.: **EU Trial No:**	2016-001506-42	
BI Trial No.:	1363.7	
BI Investigational Product(s):	BI 443651	
Title:	A two part phase I, multiple-dose, single- and double-blind randomised, double-dummy, placebo-controlled, four-way crossover study to assess safety and tolerability of BI 443651 via Respimat® versus placebo via Respimat® in subjects with mild asthma following methacholine challenge.	
Lay Title:	BI 443651 Methacholine challenge	
Clinical Phase:	Phase I	
Trial Clinical Monitor:	Tel: Fax:	
Coordinating Investigator:	Tel: Fax:	
Status:	Final Protocol	
Version and Date:	**Version: 1.0**	**Date: 23 February 2017**

CLINICAL TRIAL PROTOCOL SYNOPSIS

Name of company:		**Boehringer Ingelheim**	
Name of finished product:		Not applicable	
Name of active ingredient:		BI 443651	
Protocol date: **23 February 2017**	**Trial number:** 1363.7		**Revision date:**

Title of trial:	A two part phase I, multiple-dose, single- and double blind randomised, double-dummy, placebo-controlled, four-way crossover study to assess safety and tolerability of BI 443651 via Respimat® versus placebo via Respimat® in subjects with mild asthma following methacholine challenge.
Coordinating Investigator:	
Trial site(s):	At least 1
Clinical phase:	I
Objective(s):	The primary objective of the study is to investigate safety and tolerability of three consecutive administrations, 12 hours apart, at three different dose-levels (100, 400 and 1200 µg) of BI 443651 administered via oral inhalation in male and female mild asthmatic subjects after a methacholine challenge.
Methodology:	Part 1(pilot study): Multiple dose, single blind, double dummy, randomised, 4-way crossover with dose ordered sequences; Part 2 (main part); Multiple dose, double blind, double-dummy, randomised, 4-way crossover.
No. of subjects:	At least 36

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total entered:	At least 36
each treatment:	Part 1: Minimum 4 completed subjects Part 2: Minimum 32 completed subjects
Diagnosis :	Mild asthma
Main criteria for inclusion:	Male and female subjects, age ≥18 and ≤ 60 years, on SABA prn ± low dose inhaled corticosteroid only, $FEV_1 \geq 70\%$ predicted, PD20 ≤ 1 mg, BMI range: ≥18.5 and ≤ 32.0 kg/m^2
Test product:	BI 443651
dose:	100 µg, 400 µg or 1200 µg BI 443651, three consecutives administration 12h apart.
mode of administration:	Oral inhalation via the Respimat®
Comparator products:	Placebo
dose:	N/A
mode of administration:	Oral inhalation via the Respimat®
Duration of treatment:	4 test periods, each separated by a wash-out of at least 14 days
Endpoints	Primary endpoint: Absolute change from baseline in maximum FEV_1 reduction following methacholine (MCh) challenge.

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	Secondary endpoints: Relative change from baseline in FEV_1 $AUC_{0\text{-}tz}$ following MCh challenge; Time to recovery of FEV_1 to within 95% of post-diluent value.
Safety criteria:	Related AEs (including clinically relevant findings from the physical examination), vital signs (BP, PR), 12-lead ECG, safety laboratory tests (blood, urine).
Statistical methods:	Descriptive statistics will be calculated for all endpoints. The primary endpoint absolute change from baseline in maximum FEV_1 reduction following MCh challenge and the secondary endpoint relative change from baseline in FEV_1 $AUC_{0\text{-}tz}$ following MCh challenge will be analysed using mixed effects models on the original and logarithmic scale, respectively. The secondary endpoint time to recovery of FEV_1 to within 95% of post-diluent value will be analysed using Kaplan-Meier plots and a cox proportional hazards model.

FLOW CHART

1. Visit structure

The trial consists of a screening period (Visit 1), pilot and main study periods (Visit 2 to 5) and end of study period (Visit 6). The pilot and main study each consist of four separate treatment periods, each separated by at least 14 days wash-out. For administrative reasons, each of these four treatment periods within the pilot and main studies is referred to as a 'Visit' and each 'Visit' will consist of up to 3 days of procedures (see table below). The procedures conducted at each of the treatment period 'Visits' (Visit 2 to 5) are the same and are briefly summarized in the following chart. The 'summary of study procedures' flow chart provided below provides a more detailed overview.

	'Visit'	'Days'	Summary of Procedures
Screening Period	1	-14 to -3	Screening procedures; incremental methacholine (MCh) challenge
Part 1 (Pilot Study)			
Treatment Period 1	2	-2 to +2	**Day -1 (-2*) –** Ambulatory Visit – Baseline bolus MCh challenge **Day 1** – Admission to trial site, baseline safety assessments including measurement of electrolytes, **randomisation to treatment;** dose administration (a.m); dose administration (p.m), spirometry **Day 2** - Dose administration (a.m), bolus MCh challenge, measurement of electrolytes.
Treatment Period 2	3	-2 to +2	**Day -1 (-2*)** – Ambulatory Visit – Baseline bolus MCh challenge **Day 1** – Admission to trial site, baseline safety assessments including measurement of electrolytes,; dose administration (a.m); dose administration (p.m), spirometry **Day 2** - Dose administration (a.m), bolus MCh challenge, measurement of electrolytes.

FLOW CHART – CONT-D

Treatment Period 3	4	-2 to +2	**Day -1 (-2*)** – Ambulatory Visit – Baseline bolus MCh challenge Day 1 – Admission to trial site, baseline safety assessments including measurement of electrolytes,; dose administration (a.m); dose administration (p.m), spirometry Day 2 - Dose administration (a.m), bolus MCh challenge, measurement of electrolytes.
Treatment Period 4	5	-2 to +2	**Day -1 (-2*)** – Ambulatory Visit – Baseline bolus MCh challenge **Day 1** – Admission to trial site, baseline safety assessments including measurement of electrolytes,; dose administration (a.m); dose administration (p.m), spirometry **Day 2** - Dose administration (a.m), bolus MCh challenge, measurement of electrolytes.
Part 2 (Main study)			
Treatment Period 1	2	-2 to +2	As Part 1 – Treatment Period 1
Treatment Period 2	3	-2 to +2	As Part 1 – Treatment Period 2
Treatment Period 3	4	-2 to +2	As Part 1 – Treatment Period 3
Treatment Period 4	5	-2 to +2	As Part 1 – Treatment Period 4
For both parts			
End of Treatment	6		Spirometry, laboratory tests, physical examination, vital signs, ECG

*Assessments may be conducted over a period of 2 days to allow for flexibility in subject scheduling.

2 Summary of study procedures

Period	Visit	Day	Planned time (relative to drug administration) [h:min]	Approximate clock time of actual day [h:min][26]	Event and comment[16]	Spirometry[3,25]		Medical examination		12-lead ECG	Vital signs (BP, PR)	Safety lab[19,20,21,22]
Screen[1]	1	-14 to -3[6]			Screening procedures[2], Incremental MCh challenge to determine PD20[7]	X		X		X	X	X
Period 1-4 -Four identical periods with a washout of at least 14 days and no more than 28 days[8]	2/3/4/5	-2 to -1[6]	-48:00[5]		**Ambulatory Visit**			X[11]			X	
				Morning	**Baseline bolus Mch challenge**[9,]	X[23]						
		1[6]		06:00	**Admission to trial site**[12] **Device instruction**[10] Allocation to treatment[13]	X				X	X	X
			-0:30[4]	07:30								
			0:00	08.00	Drug administration[10, 14]							
			0:10	08:10		X						
			0:20	08:20		X						
			0:30	08:30		X						
			0:45	08:45		X						
			1:00	09.00		X				X	X	
			1:30	09:30		X						

2. Summary of study procedures – cont-d

Period	Visit	Day	Planned time (relative to drug administration) [h:min]	Approximate clock time of actual day [h:min][26]	Event and comment[16]	Spirometry[3,25]		Medical examination		12-lead ECG	Vital signs (BP, PR)	Safety lab[19,20,21,22]
			2:00	10.00	breakfast	X						
			2:30	10.30		X						
			3:00	11.00		X						
			4:00	12.00	lunch	X						
			6:00	14.00		X						
			8:00	16:00	snack (voluntary)							
			10:00	18:00	dinner							
			11:30	19.30		X				X	X	
			12:00	20.00	Drug administration[14]							
			12:10	20.10		X						
			12:30	20.30		X						
			13:00	21.00	snack (voluntary)	X					X	
			14:00	22.00		X						
		2[6]	23:00	07:00		X				X	X	
			23:30	07:30								
			24:00	**08:00**	Drug administration[14] 250mL water intake							
			24:10	08:10								

2. Summary of study procedures – cont-d

Period	Visit	Day	Planned time (relative to drug administration) [h:min]	Approximate clock time of actual day [h:min][26]	Event and comment[16]	Spirometry[3,25]		Medical examination		12-lead ECG	Vital signs (BP, PR)	Safety lab[19,20,21,22]
			24:45	08:45						X	X	
			25:00	09:00	**Bolus MCh challenge**[9]	X[18]						
			25:30	09:30								
			26:00	10:00	250mL water intake, thereafter breakfast							
			27:00	11:00								
			28:00	12:00	250mL water intake, thereafter lunch							
			32:00	16:00	snack (voluntary)							
			33:00	17:00	Discharge from trial site					X	X	X[21]
End of Treatment	6	+14[6, 27, 15]			End of trial (EOT) examination[15]	X		X		X	X	X

Guidance Notes

1	All subjects must sign an informed consent consistent with ICH-GCP guidelines prior to participation in the trial, which includes medication washout and restrictions.
2	Screening within 14 days before drug administration including review of inclusion and exclusion criteria, relevant medical history, demographics, concomitant medication, physical examination and review of vital signs/ECG/laboratory, Flexibility in scheduling and repeating screening or baseline procedures according to investigator judgement is permitted. Patient's consent can be obtained prior to the screening period.
3	Spirometry is performed at the screening visit (Visit 1) and Treatment period 1 – Day 1 to determine eligibility for participation in the study. Treatment Periods 2 to 4 – Day 1, eligibility to dose based on the predose FEV % of predicted will be assessed by clinical judgment of the investigator. Prior to methacholine challenge the subject's FEV_1 should be within the range (≥ 70% of predicted normal*) on Day -2 to Day -1 and at Day 2 at Visits 2-5 (Treatment Periods 1 to 4) *Clinical judgement may be applied in borderline cases.
4	
5	Timepoint included for technical (database set-up) reasons only
6	AEs and changes in concomitant therapies will be monitored and recorded throughout the trial
7	Incremental MCh challenge during Visit 1 will use an escalation protocol to determine the PD20 in a given volunteer.
8	In exceptional circumstances, the washout between the two treatment periods can be extended up to a maximum of 8 weeks
9	Bolus MCh challenge performed at Day -2 to Day -1 and Day 2 of each treatment period (Visits 2-5) will follow a single dose equal to the sum of all doses given during the escalation (incremental) protocol at Visit 1 (i.e: the cumulative dose) . The start of the MCh challenge will be scheduled on the time point, and will be considered as the time of the first inhalation of methacholine solution.
10	Subjects will be instructed in the use of the Respimat® at Visit 1. Inhalation technique (using trial medication) will be observed at subsequent clinic visits and instruction in correct use will be reinforced as needed.

Guidance Notes Cont-d

11	A targeted medical examination (heart, lungs) should be performed at the start of each treatment period (Visit 2 -5).
12	The time is approximate; the respective procedures are to be performed and completed **within 2 hours** prior to drug administration.
13	Allocation to treatment **only** at Visit 2 (i.e: Treatment Period 1- Day 1)
14	Drug inhalation will take place under supervision at the trial site at each of the treatment periods (Visits 2 – 5)
15	The follow up visit should be scheduled at least 14 and no more than 28 days after completion of the final treatment period
16	At timepoints where several tasks or procedures are planned pre-dose, the following sequence should be followed insuring that take priority with regards to timing: 1. Blood for safety assessments 2. ECG 3 Vital signs 4. PFTs NB: A snack is allowed (if completed) 1 hour prior to the morning dose. At timepoints where several tasks or procedures are planned post dose, the following sequence should be followed ensuring that take priority with regards to timing: 1. ECGs 2. Vital signs 3. Blood for safety assessments 5. PFTs (on the time-point - Day 1) 6. Meals NB : On Day 2 in the event that there is a timepoint clash with and post methacholine spirometry the post methacholine spirometry is to be prioritised on the timepoint and the to be taken as close as possible to the planned time (using permitted windows).

Guidance Notes Cont-d

18	Spirometry to be performed pre-MCh challenge, post-diluent and post methacholine dose. Post-methacholine spirometry (FEV_1 only) timepoints will be relative to the last exhalation of methacholine solution and will be scheduled as single measurements at 30 seconds and 90 seconds, followed by duplicate measurements (FEV1 and FVC) at 5,10, 20, 30,45 minutes, 1.0, 1.25, 1.5, 1.75, 2.0, 2.25, 2.5, 2.75, 3.0, 3.5, 4.0, 4.5, 5.0, 6.0, 7.0 and 8.0 hours
19	Central laboratory: Central laboratory testing (full laboratory screen) will be performed at the screening visit (Visit 1) and on completion of the study (EOT visit / Visit 6). Details of the tests required are provided in Section 5.3.3.
20	For female subjects: Blood HCG will be performed at screening to confirm eligibility (central laboratory)
21	Electrolytes will be measured prior to start of trial procedures and prior to discharge from the clinic on conclusion of trial procedures at each of the treatment periods (Visits 2 to 5). Initial assessment will be performed by local laboratory. In addition to local testing, a sample for electrolytes will also be sent to the central laboratory.
22	If any significant laboratory test abnormalities are detected, specifically liver function tests, the subject should return to the clinic for repeat testing
23	Spirometry to be performed pre-MCh challenge, post-diluent and post-methacholine dose. Post-methacholine spirometry (FEV_1) timepoints will be relative to the last exhalation of final methacholine solution and will be scheduled as single measurements at 30 seconds and 90 seconds, followed by duplicate measurements (FEV1 and FVC) at 5, 10, 20, 30, 45 minutes, 1.0, 1.25, 1.5, 1.75, 2.0, 2.25, 2.5, 2.75 and 3.0 hours
24	Must be completed within 30 minutes prior to drug administration
25	FEV_1 and FVC in triplicate, unless otherwise specified
26	The cumulative times specified in the planned time column are for orientation only. Depending on the actual a.m dosing time at the given day, the procedures and observations related to that a.m dosing (such as pre a.m dose and post a.m dose measurements of the same day) have to be adapted respectively.
27	The end of treatment (EOT) visit should be scheduled no earlier than 14 days after the last dose of study medication. In the event of early discontinuation, an additional earlier visit may be scheduled at investigator discretion.

TABLE OF CONTENTS

ABBREVIATIONS

AE	Adverse Event
AESI	Adverse Event of Special Interest
AHR	Airway hyper-responsiveness
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
CF	Cystic Fibrosis
CfB	Change from baseline
CFTR	Cystic Fibrosis Transmembrane Conductance Regulator
CI	Confidence Interval
CML	Local Clinical Monitor
COPD	Chronic Obstructive Pulmonary Disease
CRA	Clinical Research Associate
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
DILI	Drug Induced Liver Injury
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EudraCT	European Clinical Trials Database
EOT	End of Trial
FAS	Full Analysis Set
FC	Flow Chart
FIM	First-into-Man
GCP	Good Clinical Practice
GLI	Global Lung Function Initiative
GMP	Good Manufacturing Practice
HCG	Human chorionic gonadotrophin
HERG	Human Ether-A-Go-Go Related Gene
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IPVs	Important protocol violations
IRB	Institutional Review Board
ISF	Investigator Site File
i.v.	intravenous

LABA	Long-acting β-adrenergic agonist
LAMA	Long-acting anti-muscarinic
LoEE	List of Essential Element
LSDD	Last Subject Drug Discontinuation
MCh	Methacholine
MedDRA	Medical Dictionary for Drug Regulatory Activities
MEU	Medicines Evaluation Unit
OPU	Operative Unit
PD	Pharmacodynamics
PD_{20}	Provocative dose causing a 20% decline in FEV1
PK	Pharmacokinetics
p.o.	per os (oral)
q.d.	quaque die (once a day)
RBC	Red Blood Count
REP	Residual effect period, after the last dose of medication with measureable drug levels or 17harmacodynamics effects still likely to be present
SABA	Short-acting β-adrenergic agonist
SAE	Serious Adverse Event
s.c.	Subcutaneous
SPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
SUSARS	Suspected Unexpected Serious Adverse Reactions
TCM	Trial Clinical Monitor
TDMAP	Trial Data Management and Analysis Plan
t.i.d.	ter in die (3 times a day)
TMF	Trial Master File
TSAP	Trial Statistical Analysis Plan
TSH	Thyroid stimulating hormone
WBC	White Blood Cells

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

CF and COPD are chronic respiratory disorders characterised by airflow obstruction. Cystic fibrosis is a lethal, inherited, multi-organ disease due to exocrine gland dysfunction that predominantly affects the lower respiratory tract and pancreas leading to chronic respiratory failure and pancreatic insufficiency. Despite recent advances, over 90% of patients surviving the neonatal period will develop pulmonary involvement and at least 90% will die due to pulmonary complications [P96-3855]. The median age of death remains below 40 years old [R15-5546]. COPD prevalence is still rising due to increased smoking, particularly among women and adolescents. Only smoking cessation has been proven to alter the course of disease and 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. By 2030, COPD will be the third leading cause of death worldwide [R15-3034].

BI 443651 has been observed to inhibit acetylcholinesterase with augmented effects in non-clinical acetylcholine (ACh) / methacholine (MCh) challenge guinea pig models, demonstrating an increase in pulmonary resistance compared to the prior challenge [c02337864]. This effect is not related to the primary target i.e., it is an off target effect for BI 443651. A rapid return to baseline after challenge was observed both with, and without administration of BI 443651. No effect of BI 443651 administered in isolation (without ACh/MCh challenge) was observed on pulmonary resistance in this guinea model. In addition, no adverse respiratory effects were detected in the 4-week toxicology studies in rats and dogs or in the safety pharmacology studies at doses of up to 7,750 µg/ kg in dogs.

Airway hyper-responsiveness (AHR) to methacholine challenge is a marker of airway hyper-reactivity associated with alteration in vagal tone. Patients with asthma have increased AHR to methacholine. The airway hyper reactivity and narrowing is caused by several mechanisms, but is primarily driven by the bronchial smooth muscle. Throughout normal ventilation bronchoconstriction is thought to be at least partially under the control of the cholinergic system [P92-1976]. Asthmatic patients have increased basal airway smooth muscle tone [Hashimoto A, 1996] which may result from increased basal activity of pulmonary parasympathetic cholinergic nerves i.e. increased cholinergic tone, although the degree to which cholinergic tone contributes to airway narrowing in asthmatics is unclear. Proposed mechanisms for the increased cholinergic tone include increased release of acetylcholine from cholinergic nerve endings P17-01614 and reduced levels of neuromodulators that attenuate cholinergic neurotransmission R17-0519, P09-06255. Inhibition of acetylcholinesterase could alter cholinergic tone by reducing the degradation of acetylcholine, thus leading to bronchoconstriction. The guinea pig ACh/ MCh model represents a sensitive model of cholinergic effects, and although the pre-clinical data suggests there is no safety concern in patients in an unchallenged state, theoretically bronchoconstriction could be observed particularly in patients with heightened cholinergic tone.

Whilst AHR has been observed in patients with CF and COPD [P16-04040, R16-1628, R16-1652], it is not clear whether this is a direct consequence of the disease or concomitant asthma. AHR is not directly correlated with the disease as it is in asthma [R16-1630]. Asthma patients represent the most sensitive population of patients with obstructive airways disease to assess possible adverse effects of acetylcholinesterase inhibition.

In summary, there is an unmet need for treatments in CF and COPD. BI 443651 is expected to improve mucus hydration pulmonary function and reduce exacerbations. An off target

effect of BI 443651, aceylcholinesterase inhibition, has been observed in preclinical studies under challenge conditions only. The current clinical study is designed to understand potential consequences of this effect in a closely monitored sensitive population prior to progressing to larger scale studies.

1.2 DRUG PROFILE

For a detailed review see the investigator brochure [c02337864]

1.2.1 Nonclinical pharmacology

In the CEREP screen, BI 443651 revealed an inhibition of acetylcholine esterase with an IC_{50} value of 1.6 µM. Therefore, BI 443651 was tested in the model of acetylcholine (ACh)-induced bronchoconstriction in anaesthetized guinea pigs. BI 443651 dose-dependently enhanced the magnitude of the ACh-induced bronchoconstriction by 51 and 117% at the doses of 80, and 160 µg/kg (reflecting 3.3 and 5 fold ED_{50}) respectively. The potential reinforcement effect of BI 443651 on the cholinergic pathway tone was also assessed in the model of methacholine (MCh)-induced bronchoconstriction in anaesthetized guinea pigs. As with the ACh, BI 443651 at doses of 80 and 160 µg/kg also enhanced the magnitude of the MCh-induced bronchoconstriction's. Inhalation of ipratropium at 60 µg/kg with Respimat® led to an instantaneous and full inhibition of MCh-induced bronchoconstriction in those studies in which ipratropium was administered

1.2.2 Safety pharmacology

Further details of the safety pharmacology studies are provided in the Investigator Brochure (c02337864).

1.2.3 Toxicology

BI 443651 did not demonstrate systemic adverse effects in repeat-dose toxicity studies in dogs.

In two in-vitro tests and one in-vivo test, BI 443651 was non-genotoxic. BI 443651 was not a locally irritant or and was not phototoxic.

In summary, the non-clinical safety data of BI 443651 support clinical Phase I trials in healthy volunteers or patients with inhaled administration for up to 4 weeks.

1.2.5 Drug product

BI 443651 is delivered via the Respimat® as an inhalation solution contained in a drug reservoir / cartridge inserted into the inhaler. Several solutions, including a placebo solution, with different drug substance concentrations have been developed for use in clinical studies (delivered strengths of 10 µg, 100 µg and 300 µg BI 443651 per actuation ex-mouthpiece). A spray volume of 11.05 µL per actuation is nebulized by the device.

1.2.6 Clinical experience in humans

The safety, tolerability, pharmacokinetics and exploratory pharmacodynamics of BI 443651 have been investigated in a randomised, single-blind and placebo-controlled trial in healthy male subjects, study 1363.1 [c02861250-03]. The First-into-Man (FIM) study is complete with single inhaled doses of 10, 30, 100, 300, 900, 1800, 2700, 3600 µg or their matching placebo administered to 63 healthy male volunteers. Details are provided below for both PK and safety.

Summary of PK data from SRD trial (study 1363.1)

Table 1.2.6:1 Pharmacokinetic parameters and geometric mean (gCV %) of BI 443651 following a single dose administration of 10 to 3600 µg BI 443651 in healthy male subjects in study 1363.1

Summary of clinical safety data from SRD trial (study 1363.1)

Safety, tolerability and pharmacokinetics of BI 443651 have been investigated in a partially randomised (within dose groups), single-blind, placebo-controlled trial (study 1363.1). This First-into-Man study included single inhaled doses of 10, 30, 100, 300, 900, 1800, 2700 and 3600 µg or placebo administered via the Respimat device to 63 healthy male volunteers (47 on BI 443651).

Adverse events were reported by 16 of 47 subjects (34.0 %) following treatment with BI 443651 and 4 of 16 subjects (25.0 %) following treatment with placebo.

Ten of 47 subjects (21.3%) experienced AEs that were regarded by the investigator as possibly related to the administration of study drug, all from the BI 443651 treatment groups. These include cough (7 subjects), throat irritation (2 subjects), dysphoria (1 subject) and headache (1 subject).

All AEs were of mild or moderate intensity and recovered or were sufficiently characterized by follow-up. There were no severe nor serious AEs reported. The most frequently reported AE was headache, observed in 7 of 47 subjects (14.9%) after BI 443651 treatment without dose ordering. One subject reported headache in the placebo group (6.3%).

Cough was reported in 7 subjects (14.9%) receiving BI 443651 in a dose ordered fashion: 1 subject at1800 µg, 3 subjects at 2700 µg and 3 subjects at 3600 µg. No subjects receiving placebo reported cough.

Throat irritation was reported by 3 subjects (6.4%) receiving 1800, 2700 and3600 µg (1 subject in each dose group) of BI 443651, while none in the placebo group.
With respect to the type, incidence and severity of AEs other than described above, there was no notable difference between the dose levels.

In summary, clinical safety data of trial 1363.1 showed that single doses of up 3600 µg BI 443651 were well tolerated. A bitter taste was noted by all volunteers administered the highest concentration (300 µg/inhalation), but not in the corresponding placebo group. A reversible drop in FEV_1 and FVC was observed in some volunteers. No clinically relevant abnormalities were observed in ECG recordings, vital sign or safety laboratories. Adverse events were broadly balanced across treatment and dose group with the exception of cough and throat irritation prominently observed after single doses of BI 443651 equal or higher than 1800 µg.

Further details of this study are provided in the Investigator Brochure (c02337864).

1.2.7 Prediction of human pharmacokinetics

In order to assess expected exposures in a phase I multiple-dose study (1363.2), the preliminary BI 443651 concentration-time data for doses up to 900 µg available were fitted to a single first-order absorption and two-compartment body model for each subject. The modeled data were then used to simulate the planned doses. The predicted exposure data from the preliminary simulations are given in Table 1.2.7:1 below.

2. RATIONALE, OBJECTIVES, AND BENEFIT – RISK ASSESSMENT

2.1 RATIONALE FOR PERFORMING THE TRIAL

This is one of the two first multiple dose administration trials of BI 443651, the other study involving multiple dosing in healthy volunteers, COPD and CF patients. The objective of this study is to investigate the safety and tolerability of BI 443651 in male and female (of non-child bearing potential) subjects with asthma using multiple orally inhaled doses to provide the basis for a potential ongoing clinical development of BI 443651. The study is designed to assess potential drug effects on pulmonary function due to an observed in vitro off target effect of acetylcholinesterase inhibition. Nonclinical assessment in in vivo models demonstrated dose dependent augmentation of pulmonary resistance following acetyl and methacholine challenge (see Section 1.2).

Patients with asthma have increased airway hyper-responsiveness (AHR) to methacholine, with chronic inflammation and increased AHR leading to symptoms such as shortness of breath by variable expiratory airflow limitation R97-1015. Airway hyper reactivity and narrowing is primarily driven by the bronchial smooth muscle, which is at least partially under the control of the cholinergic system [P92-1976]. Asthmatic patients have increased basal airway smooth muscle tone [Hashimoto A, 1996] which may result from increased basal activity of pulmonary parasympathetic cholinergic nerves i.e. increased cholinergic tone, although the degree to which cholinergic tone contributes to airway narrowing in asthmatics is unclear. Proposed mechanisms for the increased cholinergic tone include increased release of acetylcholine from cholinergic nerve endings P17-01614, and reduced levels of neuromodulators that attenuate cholinergic neurotransmission [R17-0519, P09-06255]. Inhibition of acetylcholinesterase could alter cholinergic tone by reducing the degradation of acetylcholine, thus leading to bronchoconstriction. The guinea pig ACh/ MCh model represents a sensitive model of cholinergic effects, and although the pre-clinical data suggests there is no safety concern in patients in an unchallenged state, theoretically bronchoconstriction could be observed particularly in patients with heightened cholinergic tone. Patients would asthma should be specifically sensitive to such effects and would represent a population in which to closely monitor for such effects.

This study will derive pulmonary function data following the administration of methacholine in mild asthma subjects after 3 multiple administration of BI 443651 and will act as an early safety study prior to large scale studies in patients with obstructive airways disease. By performing the study in subjects with asthma, safety information can be obtained in subjects s with hyper-reactive airways disease to fully explore possible induction of bronchoconstriction that may result due to inhibition of acteylcholinesterase as an off target effect of BI 443651. Administration of methacholine to asthmatics is considered to be the most sensitive method of assessing bronchoconstriction effects of an acetylcholinesterase inhibition in humans and will quantify the effects observed in the non-clinical studies.

In summary this study aims to assess any potential deleterious effects on pulmonary function in man prior to large scale clinical trials.

2.2 TRIAL OBJECTIVES

The primary objective of this study is to investigate safety and tolerability of three consecutive administrations, 12 hours apart, at three different dose-levels (100, 400 and 1200 µg) of BI 443651 administered via oral inhalation in male and female mild asthmatic subjects after a bolus methacholine challenge.

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

2.3 BENEFIT - RISK ASSESSMENT

BI 443651 is being developed as a therapy for obstructive airways diseases such as cystic fibrosis and COPD. Participation in this study is without expected (therapeutic) benefit for asthmatic subjects. Their participation in the study is of importance to inform the safety profile of BI 443651 specifically with regard potential adverse effects on lung function prior to progressing to long term clinical studies.

Subjects are exposed to risks related to the study procedures and intake of trial medication as described below.

Procedure-related risks
The use of an indwelling venous catheter for the purpose of blood sampling may be accompanied by mild bruising and also, in rare cases, by transient inflammation of the wall of the vein. In addition, in rare cases a nerve might be injured while inserting the venous catheter, potentially resulting in paresthesia, reduced sensibility, and/or pain for an indefinite period. The same risks apply to venepuncture for blood sampling.

Sampling times and visits may be adapted based on information obtained during trial conduct including addition of samples and visits The total volume of blood to be withdrawn during the entire study will not exceed 500mL (roughly equivalent to a normal blood donation). No study-related risk to study participants is expected from this blood withdrawal over the course of the study.

Methacholine (MCh) challenge is a routine practice in the diagnosis of asthma in the event of an unclear history or investigations. The main risk is of bronchoconstriction. Pulmonary function will be monitored and adverse findings can be reversed. Adverse effects are expected to be reversible with administration of an inhaled anticholinergic agent (ipratropium bromide) if necessary.

Drug-related risks and safety measures
The nature of the target and the mechanism of action of BI 443651, are well documented. The side effect profile is well understood and the adverse events observed in rats following administration of BI 443651 are consistent with the mechanism.
The animal models are believed to be predictive for the effects in

humans.

In study 1363.1, 63 healthy male volunteers have been administered single inhaled doses of BI 443651 up to3600µg. In this study, BI 443651 was found to be well tolerated (see Section

he most sensitive species for these effects was the rat with no relevant effects observed in the dog, even at high doses, on serum or urinary electrolytes. No other systemic safety findings were observed in either the toxicology or safety pharmacology studies.

This translates to a safety margin of approximately 11-fold. The urine cover is regarded as the most relevant exposure for safety based mechanism i.e. serum electrolytes.

BI 443651 does not present a genotoxic hazard. BI 443651 is considered to be low risk for phototoxicity, based on its absorbance pattern and lack of toxicity in 4-week repeat dose studies.

Fertility has not been assessed in nonclinical species, but no adverse effects have been observed on reproductive organs in 4-week toxicity studies in rats and dogs, suggesting that there is a low risk to fertility. At the time this current study is planned to start embryo-fetal development studies of BI 443651 will not yet have been conducted.

Off target inhibition of ACh has been observed with augmented effects in non-clinical ACh/MCh challenge guinea pig models. No adverse effects on pulmonary function were observed in the absence of methacholine or acetylcholine challenge. No adverse respiratory effects were detected in the 4-week toxicology studies or in the safety pharmacology studies at doses of up 7,750 µg/ kg in dog or rat. Exaggerated bronchoconstriction effects may be apparent following methacholine challenge however effects on respiratory function will be monitored and are reversible. Inhaled anticholinergic therapy should reverse these effects if required, as is also used if required for MCh testing.

In summary whilst not all safety effects may be predicted, based on mechanism and systemic toxicological finding the only potential systemic toxicity is changes in serum electrolytes and

particularly increases in serum potassium. Augmented bronchoconstriction may be induced following administration of methacholine. In both cases these changes are easily monitored and treatable if observed. The following safety measures will be applied in this study in order to minimize the risk for the mild asthmatic subjects:

1 This study (1363.7) will only start once healthy volunteers have been safely administered 100 and 400 µg b.i.d. of BI 443651 for 7days in a separate ongoing study (1363.2) i.e. no stopping criteria have been triggered in 1363.2.

2 Only mild, controlled, stable asthma subjects with well-maintained lung function will be included in the study i.e. subjects on prn SABA or low dose inhaled corticosteroid with an FEV_1 ≥70% and no recent respiratory tract infection or exacerbation.

3 The study will be split into two parts (see Section 3.1) with an initial pilot (Part 1) to assess for gross adverse effects of BI 443651 on bronchoconstriction after MCh challenge. In Part 1, subjects will receive BI 443651 in a dose ordered fashion with either placebo **or** the lowest dose first followed by the higher doses and placebo (if not taken first). Individual subjects will not be dosed further if individual stopping criteria (including pulmonary function criteria) are triggered. Stopping criteria are described in detail in Section 3.3.4.

The second part of the study (not necessarily dose ordered) will only proceed if no subjects triggered the first three discontinuation criteria following administration of BI 443651 during Part 1.

4 The subjects will be closely monitored throughout the treatment period with frequent evaluation of pulmonary function following MCh challenge. Subjects may only be discharged from clinic after medical assessment has been conducted. The subject's FEV_1 must have returned to ≥ 90% of the first set of spirometry measurements performed that day before the subject can be discharged from the clinic. Rescue medication will be provided as required.

5 Safety laboratory testing will be performed during the study with a focus on electrolytes (see Flow Chart). The study will be stopped if, during Part 1 (pilot) at least 2 subjects in the current cohort or treatment period on active drug showed serum potassium levels ≥ 5.5mmol/L in non-haemolysed blood (confirmed by repeat). In Part 2 (main study), the study would be stopped if 4 subjects on active drug (independent of dose level) showed serum potassium levels ≥ 5.5mmol/L in non-haemolysed blood (confirmed by repeat).

Although rare, a potential for drug-induced liver injury (DILI) is under constant surveillance by sponsors and regulators. Therefore, this trial requires timely detection, evaluation, and follow-up of laboratory alterations in selected liver laboratory parameters to ensure subjects' safety (see Section 5.3.6.1).

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

This multiple dose, randomised, placebo controlled, trial will be conducted in two parts. The first part (pilot study) will be a single-blind four-way crossover with dose ordered sequences. The second part (main study) will be a double-blind four-way crossover, conducted according to a William's design. In both parts of the study, BI 443651 or placebo equivalent will be administered three consecutive times, 12 hours apart, per dose level. All subjects will receive placebo, 100, 400 and 1200 µg BI 443651 (in Part 1, the dose groups may be altered in case evolving data suggests a change in dosage is required (see below)). Each period will be separated by a washout period of at least 14 days (and not more than 28 days). Two administrations of BI 443651 will be delivered on Day 1 (morning and evening) and a single administration Day 2 (morning). One hour after dosing on Day 2, MCh challenge will be performed. A methacholine challenge will be conducted on Day -2 to Day -1 for each treatment period, (with the Day -2 to Day -1 challenge providing the baseline for each treatment period) at the same time of the day.

The two parts of the study will be conducted as follows:

Part 1: 4 subjects will be included in the first pilot part of the study each being administered three active doses of BI 443651 and placebo, with the active doses investigated being in ascending order of dose strength. Placebo administered given in a single-blinded manner in any order relative to the active treatment as per Table 3.1:1.

Table 3.1:1 Sequences for pilot part of the study

Treatment Period 1	Treatment Period 2	Treatment Period 3	Treatment Period 4
Placebo	100 µg	400 µg	1200 µg
100 µg	Placebo	400 µg	1200 µg
100 µg	400 µg	Placebo	1200 µg
100 µg	400 µg	1200 µg	Placebo

Part 2: 32 subjects will participate in the trial with each subject being administered three active dose levels of BI 443651 and placebo. This part of the study will be fully randomised, double blind. The decision to proceed to Part 2 will be based upon the safety and tolerability data of Part 1. Part 2 will only be conducted if, in the opinion of the investigator, no safety concerns arose in Part 1 and if none of the pre-specified trial-specific stopping criteria were met (see Section 3.3.4.2).

Table 3.1:2 Sequences for main part of the study

Treatment Period 1	Treatment Period 2	Treatment Period 3	Treatment Period 4
Placebo	100 µg	400 µg	1200 µg
100 µg	Placebo	1200 µg	400 µg
400 µg	1200 µg	Placebo	100 µg
1200 µg	400 µg	100 µg	Placebo

The first pilot part of the study will not be started until data from an ongoing multiple rising dose study (1363.2) in healthy volunteers is available from the first two dose groups (100 and 400 µg b.i.d. BI 443651). Only if BI 443651 has been safely administered in study 1363.2 and no stopping criteria have been met, will this study (1363.7) be started.

In Part 1, dose groups will be investigated consecutively in ascending order of doses with a dose escalation review between each treatment period. Data from each treatment level will be reviewed prior to progression to the next treatment level. Only if the previous dose of BI 443651 is safe and well tolerated, without meeting any stopping criteria in subjects administered BI 443651 (see Section 3.3.4.1), will the subsequent dose be administered (Table 3.1:1).

In addition a documented Safety Review by the Coordinating Investigator (or an authorised deputy) and appropriate personnel from the Sponsor must take place prior to initiation of Part 2 of the study. Only if BI 443651 is safe and well tolerated in all subjects in the pilot part without the specified number of subjects meeting any individual stopping criteria (see Section 3.3.4.1), will the transition to Part 2 occur.

An unscheduled safety review meeting can be requested anytime for any reasonable cause by the Principal Investigator (or an authorised deputy) or the sponsor of the study, e.g. because of any unforeseen adverse events, etc. Dose escalation or transition to Part 2 will only be permitted if no safety concerns exist in the opinion of the Principal Investigator (or an authorised deputy) and the Trial Clinical Monitor (or an authorised deputy).The minimum data set for review consists of the following data:

- Results from spirometry in all subjects included in the initial pilot part of the study
- AEs in all subjects including in the initial pilot part of the study, up to at least 48h post dosing (including clinically relevant findings from ancillary safety testing listed below) (Note: AEs may be ongoing at the time of Safety Reviews and AE information may be subject to change prior to Database Lock)
- Check of criteria for stopping subject treatment as per Section 3.3.4.1

The decision to escalate the dose during the pilot study or transition to Part 2 of the study will be made jointly by the Co-ordinating Investigator (or an authorised deputy) and appropriate personnel from the Sponsor company after in-depth analysis of all available safety data, especially SAEs (if occurred), AEs and out-of-range laboratory results (if considered clinically significant). Safety Reviews can be conducted face-to-face or by video/telephone conference. The Trial Clinical Monitor is responsible for organization and minutes of the reviews. Minutes will be signed off by the Co-ordinating Investigator (or an authorised deputy) and filed in the ISF and TMF.

In the pilot study (Part 1), the investigator is allowed to alter the scheduled dose levels (e.g. add an intermediate dose level) within the planned and approved dose range on the basis of experience gained during the study. In this case, subjects may be required to participate in additional treatment periods or additional subjects may be enrolled. The investigator and/or the sponsor should stop dose escalation in case the safety evaluation leads to concerns that would not allow higher dosing.

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

3.1.1 Administrative structure of the trial

The trial is sponsored by Boehringer Ingelheim (BI). A Coordinating Investigator has been appointed. The tasks and responsibilities of the coordinating investigator are defined in a contract.

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

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 SOPs,
- direct the clinical trial team in the preparation, conduct, and reporting of the trial,
- ensure appropriate training and information of local clinical monitors (CML), Clinical Research Associates (CRAs), and Investigators.

The organisation of the trial will be performed by the respective local BI-organisation (Operating Unit, OPU) in accordance with applicable regulations and internal SOPs.

Data Management and Statistical Evaluation will be done by BI according to BI SOPs.

The review of data generated in Part 1 of the study and confirmation of dose escalation procedures will be performed in accordance with relevant SOPs.

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

Central and local laboratory services will be used in this trial. Details will be provided in ISF.

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

For MCh challenge studies, the crossover design described in Section 3.1 is commonly employed to increase sensitivity due to the within subject comparison. An active comparator is not appropriate for this assessment and a placebo comparison is required as a negative control to quantify the nature of any response observed.

Subjects will be allowed to continue inhaled low dose corticosteroid and SABA use provided washout is undertaken prior to MCh challenge. The subjects will be on standard of care treatment for the severity of their disease and thus the use of placebo in this setting is considered acceptable.

The study will be conducted in two parts: Part 1 in 4 subjects in a dose escalating design and Part 2 in which doses may be administered according to a William's crossover design (i.e. highest may be administered first). Three multiple dose levels of BI 443651 are included, to assess for a dose-effect relationship as observed in the nonclinical studies and also, in part one of the study to allow for effects to be assessed at lower doses prior to subjects being exposed to the highest dose as the initial dose (as may be allowed in Part 2 of the study). For the pilot part (Part 1), it is planned to include 4 asthma subjects. The planned sample size is not based on a power calculation. This sample size is considered sufficient for the initial evaluation of safety post MCh challenge prior to allowing patients to be administered the highest dose of BI 443651 as the first dose level.

For the main part (Part 2), it is planned to include a total of 32 (8 per sequence) subjects with mild asthma, because this sample size is considered sufficient to achieve the aims of this exploratory trial. For more details refer to Section 7.7.

The cumulative bolus dose approach to MCh challenge is used during the treatment phases as the primary outcome is based on drop in FEV1 for a given dose rather than dose of MCh required to achieve a fall in FEV1.

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

Please refer to Section 8.3.1 for the documentation requirements pertaining to the inclusion and exclusion criteria.

3.3.2 Inclusion criteria

1. Male or female subjects must have a diagnosis of asthma by a physician at least 3 months prior to screening (Visit 1). The diagnosis of asthma must meet the following spirometric criteria:
    a. Pre-bronchodilator clinic measured FEV_1 ≥70% of predicted normal (calculated by the Global Lung Function Initiative equation (GLI)) [R15-0845] measured ≥ 8 hours after the last use of short acting bronchodilator at the screening visit (Visit 1) and on the day of randomisation (Visit 2 i.e: Treatment Period 1 – Day 1)).
2. Age ≥ 18 ≤ 60 years. Subjects must be within the eligible age range on the day of signing informed consent.
3. Diagnosis of asthma must have been made before the subject's age of 40.

    or

    If the subject is ≥ 40 years and the diagnosis has not yet been recorded in the subject's medical files, the investigator should assess whether the subject's medical history (e.g. symptoms and prescribed medications) confirms the subject suffered from asthma since before the age of 40. If so, this subject may be considered for inclusion after consultation with the sponsor.
4. ACQ value < 1.5 at the screening visit (Visit 1).
5. PD20 (Provocative dose causing at least a 20% decline in FEV_1) at the screening visit (Visit 1) of methacholine ≤ 1mg
6. Body mass index (BMI) ≥ 18.5 and ≤ 32.0 kg/m^2 at the screening visit (Visit 1)
7. Subjects must be able to perform all study related procedures and assessments, including pulmonary function tests, as required by the protocol.

3.3.3 Exclusion criteria

In order to be eligible for inclusion in the study, the subject must not present with any of the following:

1. Significant pulmonary diseases other than asthma (up to GINA treatment step 2) or other medical conditions* (as determined by medical history, examination** and clinical investigations at screening) that may, in the opinion of the investigator result in any of the following:
    a) Put the subject at risk because of participation in the study

b) Influence the results of the study

c) Cause concern regarding the subject's ability to participate in the study.

*e.g: cardiovascular, gastro-intestinal, hepatic, renal, metabolic, immunological, dermatologic, neurological, haematological, oncological, hormonal and psychiatric. A malignancy treated by resection, radiation or chemotherapy within the past 5 years. Subjects with treated basal cell carcinoma or fully cured squamous cell carcinoma are allowed to participate in the study.

** includes clinically relevant abnormal blood pressure, pulse rate or ECG findings.

2. Respiratory tract infection or asthma exacerbation in the 4 weeks prior to the screening visit (Visit 1). Subjects can be rescreened 4 weeks after resolution of the infection or exacerbation.
3. Hospitalisation for asthma exacerbation within 3 months or intubation for asthma within 3 years of the screening visit (Visit 1).
4. History of relevant orthostatic hypotension, fainting spells, or blackouts.
5. Major surgery (major according to the investigator's assessment) performed within 12 weeks prior to randomisation.
6. Clinically relevant (in the opinion of the investigator) abnormal baseline haematology, blood chemistry or urinalysis at the screening visit (Visit 1).
7. Serum potassium measurement above the ULN at the screening visit (Visit 1). Any value about the ULN excludes the subject irrespective of clinical relevance.
8. A history of significant alcohol or drug abuse within the last 2 years
9. Blood donation (more than 100mL within 30 days prior to the administration of trial medication or intended during the trial)
10. Subjects who have been treated with any of the following asthma medications in the given interval prior to Visit 1 (see Section 4.2.2) :
    - Non-approved asthma therapies such as methotrexate,
    - Intravenous, intramuscular or oral corticosteroids
    - Inhaled corticosteroids (iCS) other than low dose iCS (defined as equivalent to equal to, or less than 250 µg fluticasone / day)
    - A long acting beta agonist or anticholinergic bronchodilator (Visit 1), including fixed dose beta agonist/inhaled corticosteroid combinations and oral bronchodilators.

      Note: Withdrawal of bronchodilators or reduction in iCS dose is not acceptable unless for medical reasons.
    - A biological based antagonist therapy including Omalizumab, or immune modulators
    - Asthma controller medications (e.g: leukotriene modifier, methylxanthines, nedocromil or cromolyn sodium)
    - Mucolytics

- Systemically available immunomodulatory treatments for allergic rhinitis or atopic dermatitis.

11. Use of any diuretics (including loop diuretics or potassium sparing diuretics (such as amiloride), renin-angiotensin antihypertensive drugs in the 28 days prior to the screening visit (Visit 1)

12. Use of drugs that might reasonably influence the results of the trial or that might prolong the QT/QTc interval within 10 days prior to the randomisation visit (Visit 2 i.e: Treatment Period 1- Day 1).

13. A marked baseline prolongation of QT/QTcF interval (such as QTcF intervals that are repeatedly greater than 450 ms in males or repeatedly greater than 470 ms in females) or any other relevant ECG finding at screening and prior to randomisation

14. A history of additional risk factors for Torsades de Pointes (such as heart failure, hypokalemia, or family history of Long QT Syndrome)

15. Inability to comply with medication or dietary restrictions (see Section 4.2.2).

16. Intake of drugs with a long half-life (more than 24 hours) within at least 1 month of the screening visit (Visit 1) or less than 10 half-lives of the respective drug prior administration (except asthma or atopic disease modification and permitted concomitant medications as described in Table 4.2.2.1:1)

17. Currently enrolled in another investigational device or drug study, or less than 30 days since receiving another investigational treatment(s)

18. History of relevant allergies/hypersensitivities (including allergy to the trial medication or its excipients)

19. Pregnant or nursing women or a positive serum pregnancy test at the screening visit (Visit 1)

20. Women of childbearing potential

    All female subjects (and female partners of male subjects) are regarded as being of childbearing potential unless they are either post-menopausal or permanently sterilised. Post-menopausal is defined as having had, at least 12 months spontaneous amenorrhea with an appropriate clinical profile (age, vasomotor symptoms etc). Females may have been permanently sterilised by means of hysterectomy, bilateral salpingectomy, confirmed tubal occlusion or tubal ligation.

21. Male subjects who do not agree to minimise the risk of female partners becoming pregnant (including sperm donation) from the first dosing day until 3 months after the trial medication treatment has finished.

Male subjects with female partners of child bearing potential must use condoms plus any one other acceptable method of contraception together with their partners, from first dose until 3 months after the last dose of IMP. Alternatively, true heterosexual abstinence is also acceptable (this must be due to subject's lifestyle choice i.e. the subject should not become abstinent just for the purpose of study participation; withdrawal or calendar methods are not considered acceptable).

Acceptable methods of contraception for male subjects with female partners of childbearing potential include:

- Condoms
- Established hormonal contraception
- Intrauterine device (IUD)/intrauterine hormone-releasing system (IUS).

Male subjects with pregnant partners are excluded. Male subjects must not donate sperm until 3 months after the last dose of IMP.

22. Current smokers or ex-smokers who have given up smoking for < 12 months and / or have a smoking pack history of > 5 pack years (1 pack year = 20 cigarettes per day for 1 year of 5 cigarettes per day for 4 years)

23. Previous participation in this trial

3.3.4 Removal of subject from therapy or assessments

3.3.4.1 Removal of individual subjects

An excessive withdrawal rate can have a severe negative impact on the scientific value of the trial. Every effort should be made to keep subjects in the trial as scheduled. This includes careful subject selection and appropriate explanation of the trial requirements and procedures prior to enrolment as well as an explanation of the consequences of premature withdrawal.

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

a	**FEV_1 falls ≥ 45% post methacholine challenge from post diluent value** If the subject is symptomatic requiring SABA the study physician must be informed and the appropriate assessments taken, regardless of time-point. The PI should be informed of the situation as soon as possible and a decision will then be made by the PI as to whether the subject is to continue to receive MCh challenges at any further visits or be withdrawn.
b	The subject has a confirmed increase in serum potassium of ≥ 5.5 mmol/L in non-haemolysed blood.

c	The subject shows relevant individual QT prolongation, i.e. a QTcF increase of greater 60 ms from baseline (pre-dose Day 1 of each Treatment Period)) in connection with absolute QT or QTcF greater than 500 ms, which has been confirmed by a repeat ECG recording.
d	The subject has an asthma exacerbation.
e	The subject withdraws consent for trial treatment or trial participation, without the need to justify the decision.
f	The subject needs to take concomitant drugs that interfere with the investigational product or other trial medication
g	The subject can no longer be treated with trial medication for other medical reasons (such as surgery, adverse events, other diseases, or pregnancy)
h	The subject has repeatedly shown to be non-compliant with important trial procedures and, in the opinion of both, the investigator and sponsor representative, is not willing or able to comply with the trial requirements in the future.

If the subject agrees, he/she will undergo the procedures for early treatment discontinuation and follow up as outlined in the Flow Chart (FC) and Section 6.2.3.

For all subject the reason for withdrawal (e.g. adverse events) must be recorded in the CRF. 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 overall or at a particular trial site at any time for the following reasons:

1	Failure to meet expected enrolment goals overall or at a particular trial site
2	Emergence of any efficacy/safety information invalidating the earlier positive benefit-risk assessment that could significantly affect the continuation of the trial.
3	Violation of GCP, the CTP or the contract disturbing the appropriate conduct of the trial
4	New toxicological findings or serious adverse events invalidate the earlier positive benefit-risk assessment. More specifically, the trial will be terminated if two subjects have, at least, possibly related SAE or in case of the occurrence of three, at least, possibly related severe AEs. No further dosing, dose escalation or inclusion of any further

	subjects (independent of dose level) will occur without approval of a substantial amendment.
5	**Part 1 (pilot study):** At least 2 subjects* in the current cohort or treatment period on active drug showed serum potassium levels ≥ 5.5mmol/L in non-haemolysed blood (confirmed by repeat). **Part 2 (main study):** At least 4 subjects* on active drug (independent of dose level) showed serum potassium levels ≥ 5.5mmol/L in non-haemolysed blood (confirmed by repeat). * These are proposed thresholds for potential trial discontinuation however any and all individual occurrences of serum potassium levels ≥ 5.5mmol/L in non-haemolysed blood will be reviewed by the PI and sponsor medical team.
6	At least 2 subjects independent of dose level on active drug showed relevant individual QT prolongation, i.e. a QTcF increase of greater 60 ms from baseline in connection with absolute QT or QTcF greater than 500 ms, which has been confirmed by a repeat ECG recording* . *These are proposed thresholds for potential trial discontinuation however any and all individual occurrences of QT prolongations will be reviewed by the PI and sponsor medical team

The Investigator / 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

A ‘completed’ subject is defined as a subject who has completed all treatment periods and procedures including MCh challenge. Subjects who do not complete all treatment periods must be replaced. A replacement subject will be assigned a unique study subject number. In part I of the study, the replacement subject will only undergo the treatment periods not completed by the subject he/she replaces. In part II of the study, a replacement subject will be assigned to the same treatment sequence as the subject he/she replaces. The method to include these replacement patients in the analysis will depend on the time point of inclusion of the new patient in the study.

4 TREATMENTS

4.1 INVESTIGATIONAL TREATMENTS

The study medication below will be supplied by Boehringer Ingelheim Pharma GmbH & Co. KG

1 mg BI 443651 (MW 571.12 g/mol) equals 1.26 mg BI 443651 salt form (MW 721 g/mol). The doses given below refer to the respective free base.

4.1.1 Identity of the Investigational Medicinal Products

Table 4.1.1: 1 Test product 1

Substance:	BI 443651
Pharmaceutical formulation:	Solution for inhalation
Source:	BI Pharma GmbH & Co. KG, Germany
Unit strength:	100µg/actuation, 300µg/ actuation
Posology:	Depending on dose group
Route of administration:	Oral inhalation
Device:	RESPIMAT A5
Duration of use:	Multiple dose

Table 4.1.1: 2 Test product 2

Substance:	Placebo
Pharmaceutical formulation:	Solution for inhalation
Source:	BI Pharma GmbH & Co. KG, Germany
Unit strength:	Not applicable
Posology:	Depending on dose group
Route of administration:	Oral inhalation
Device:	RESPIMAT A5
Duration of use:	Multiple dose

For exact amounts and units to be administered per treatment and trial part please refer to Section 4.1.4.

4.1.2 Selection of doses in the trial

Orally inhaled doses in the range of 100 µg to 1200 µg have been selected in order to assess the safety, tolerability and pharmacokinetics of BI 443651 in asthma subjects. The doses were selected as follows (C02337864):

In the pilot study (Part 1), the investigator can decide at any time to discontinue dosing or to decrease the dose escalation by adding intermediate doses in case of intolerability or due to safety concerns. The site will follow relevant local SOPs.

4.1.3 Method of assigning subjects to treatment groups

Subjects are randomised to a treatment sequence at Visit 2 (i.e: Treatment Period 1). After assessment of all inclusion and exclusion criteria, each eligible subject will be assigned the lowest available medication number at the time of randomisation. Note that the medication number is different from the subject number (the latter is assigned directly after informed consent was obtained). Site personnel will enter the medication number in the eCRF.

4.1.4 Drug assignment and administration of doses for each subject

The treatments to be evaluated are administered as outlined in Table 4.1.4:1 below.

Table 4.1.4: 1 Treatment overview

Treatment	Formulation, dose regimen	Treatment Administration*					Posology distribution over the treatment period
		Route	Number of actuations	Unit strength [µg]	Total dose [µg]	Total no. of placebo	
1 (100 µg)	Inhalation solution, three administrations 12 hours apart	Oral inhalation	1	100	100	3	**Day 1:** a.m. and p.m. **Day 2:** a.m. only
2 (400 µg)	Inhalation solution, three administrations 12 hours apart	Oral inhalation	4	100	400	0	**Day 1:** a.m. and p.m. **Day 2:** a.m. only
3 (1200µg)	Inhalation solution, three administrations 12 hours apart	Oral inhalation	4	300	1200	0	**Day 1:** a.m. and p.m. **Day 2**: a.m only
Placebo	Inhalation solution, three administrations 12 hours apart	Oral inhalation	-	-	-	4	**Day 1:** a.m. and p.m. **Day 2:** a.m only

*Four separate devices will be used in each treatment administration to maintain blinding. Placebo devices will be used to make a total of four administrations per dosing.

Each newly assembled RESPIMAT Inhaler has to be primed by qualified, trained, unblinded study personnel, e.g. pharmacist at the trial site under the responsibility of the investigator, who is not involved in the conduct of the trial. Except those devices used for training, priming should NOT take place in the same room where the subject is inhaling trial medication The inhaler should be primed by actuating it until an aerosol is visible plus three additional actuations. For detailed priming instructions please refer to the RESPIMAT Inhaler handling instructions in Appendix 10.1.

Both the study drug as well as the placebo treatment (depending on randomisation) will be inhaled with the RESPIMAT in a sitting or standing position under supervision of the investigating physician or an authorised designee (see section 4.3). Inhalation of study drug should NOT take place in the same room where the blood samples are taken, to prevent contamination of samples from airborne drug. If more than one actuation is needed, planned time 0:00h will always be the first actuation. If more than one actuation will be needed, the duration from first to last actuation will be recorded. After study drug inhalation, subjects will drink 250 mL of water.

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

4.1.5 Blinding and procedures for unblinding

4.1.5.1 Blinding

In the pilot part of the study (Part 1), site staff dosing the subjects will be unblinded. Unblinded site staff will not conduct any study assessments.

The main part of the study (Part 2) will be double-blind and subjects, investigators and everyone involved in trial conduct or analysis or with any other interest in this trial will remain blinded with regard to the randomised treatment assignments until after database lock.

The randomisation code will be kept secret by Clinical Trial Support up to database lock.

The randomisation codes will be provided to bioanalytics prior to the last subject out date to allow for the appropriate analyses of pharmacokinetic (PK) samples taken from different dose strengths. Bioanalytics will not disclose the randomisation code or the results of their measurements until the trial is officially unblinded.

The trial will only be unblinded after locking of the database.

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.

Due to the requirements to report Suspected Unexpected Serious Adverse Reactions (SUSARs), it may be necessary for a representative from Boehringer Ingelheim's Pharmacovigilance group to access the randomisation code for individual subjects during trial conduct. The access to the code will only be given to authorised Pharmacovigilance representatives and not be shared further.

4.1.6 Packaging, labelling, and re-supply

The investigational products will be provided by BI or a designated CRO. They will be packaged and labelled in accordance with the principles of Good Manufacturing Practice (GMP).

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

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.

4.1.8 Drug accountability

The investigator /pharmacist /investigational drug storage manager will receive the investigational drugs delivered by the sponsor when the following requirements are fulfilled:

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

The investigator /pharmacist /investigational drug storage manager must maintain records of the product's delivery to the trial site, the inventory at the site, the use by each subject, and the return to the sponsor or warehouse / drug distribution centre or alternative disposal of

unused products. If applicable, the sponsor or warehouse / drug distribution centre will maintain records of the disposal.

These records will include dates, quantities, batch / serial numbers, expiry (‘use- by’) dates, and the unique code numbers assigned to the investigational product and trial subjects. The investigator / pharmacist / investigational drug storage manager will maintain records that document adequately that the subjects were provided the doses specified by the CTP and reconcile all investigational products received from the sponsor. At the time of return to the sponsor and/or appointed CRO, the investigator / pharmacist / investigational drug storage manager must verify that all unused or partially used drug supplies have been returned by the clinical trial subject and that no remaining supplies are in the Investigator’s possession.

4.2 OTHER TREATMENTS, EMERGENCY PROCEDURES

The study population is restricted to subjects with mild asthma who do not have other significant medical conditions. They have controlled asthma treated adequately with SABA and /or low dose iCS (see Table 4.2.1 for equipotent doses). It is not foreseen that subjects will require other concomitant medications.

Table 4.2: 1 Estimated Equipotent Daily Doses of (low dose) Inhaled Glucocorticosteroids according to GINA 2015 P15-03654.

Drug	**Low Dose (µg)**
Beclomethasone dipropionate	200-500
Budesonide	200-400
Ciclesonide	80-160
Flunisolide	500-1000
Fluticasone propionate	100-250
Mometasone	200-500
Triamcinolone acetonide	400-1000

4.2.1 Other treatments and emergency procedures

There are no special emergency procedures to be followed.

4.2.1.1 Rescue medication

Administration of rescue medication can occur at any point during the study. Open label salbutamol and /or atrovent MDI will be provided as rescue medication, at screening visit.

If rescue medication is administered during clinic visits (Visits 2– 5), the 24-hour clock time of rescue medication, total number of inhalations of rescue medication used, visit number, date and the name, route and dosage of any additional rescue medication will be recorded on the Rescue Medication eCRF page.

The use of rescue medication during Visits 2 -5 does not necessitate discontinuation of the visit. The subject should remain in the clinic in order to complete the remaining other procedures (see 4.2.2.2).

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

No concomitant therapy will be allowed except for treatments as specified in Section 4.2.1 above and a low dose of inhaled corticosteroid as defined by GINA guidance [P15-03654], paracetamol or medication for atopic conditions. However, in case of adverse events therapy according to the judgment of the investigator will be permitted. All concomitant therapies and/or rescue therapies will be recorded on the appropriate pages of the case report forms (CRFs). Concomitant medications have to be washed out as defined in Section 3.3.2.

Table 4.2.2.1:1 Overview of Permitted and Restricted Medications

Class	**Permission / Restriction and explanation**
Inhaled corticosteroids*	**Permitted** provided equal to or less than 250 µg fluticasone equivalent daily and corticosteroids have been stabilized at least 6 weeks prior to randomisation (Visit 2 i.e Treatment Period 1 Day 1) and will continue to be used during the trial at a stable dose
Paracetamol	**Permitted**
Intravenous, intramuscular or oral corticosteroids	**Not permitted** 6 weeks prior screening visit (Visit 1) and during the trial
Oral and patch β-adrenergics	**Not permitted** 4 weeks prior screening visit (Visit 1) and during the trial
Long acting inhaled β-adrenergics (including fixed dose beta-agonist/ inhaled corticosteroid combinations)[1]	**Not permitted** 6 weeks prior screening visit (Visit 1) and during the trial.
Short acting inhaled β-adrenergics	**Not permitted except for supplied rescue medication.** Regarding restrictions for forced spirometry bronchodilators see Section 4.2.2.2.
Long acting inhaled anticholinergics (e.g. Tiotropium, Aclidinium) (including fixed dose beta- agonist	**Not permitted** 6 weeks prior screening visit (Visit 1) and during the trial

/inhaled corticosteroid combinations)[1]	
Short acting inhaled anticholinergics (inhalation aerosol, nasal spray)	**Not permitted except for supplied rescue medication.** Regarding restrictions for forced spirometry bronchodilators see Section 4.2.2.2
Antihistamines	**Not permitted** 4 weeks prior screening visit (Visit 1) and during the trial
Cromolyn sodium / nedocromil sodium	**Not permitted** 4 weeks prior screening visit (Visit 1) and during the trial
Mucolytics	**Not permitted** 4 weeks prior screening visit (Visit 1) and during the trial
Beta blockers	**Permitted** provided that beta blockers have been stabilized at least 6 weeks prior to randomisation (Visit 2 i.e: Treatment Period 1 Day 1) and will continue to be used during the trial in a stable manner
Investigational drugs	**Not permitted**, see exclusion criterion number 17
Antileukotrienes	**Not permitted** 4 weeks prior screening visit (Visit 1) and during the trial
Theophylline, Aminophylline	**Not permitted** 4 weeks prior screening visit (Visit 1) and during the trial
A biological based antagonist therapy including Omalizumab, or immune modulators	**Not permitted** within 6 months of the screening visit (Visit 1)
Non-approved asthma therapies such as methotrexate	**Not permitted** within 3 months of the screening visit (Visit 1)
Systemically available immunomodulatory treatments for allergic rhinitis or atopic dermatitis.	**Not permitted**
Medications that may lead to alterations in serum electrolytes (particularly potassium) including but not limited to diuretics**, angiotensin	**Not permitted** 4 weeks prior screening visit (Visit 1) and during the trial

convertase/ angiotensin receptor inhibitors***, nonsteroidal anti-inflammatory drugs (NSAIDs)****, cyclosporine or tacrolimus, Pentamidine, Trimethoprim-sulfamethoxazole, Heparin, Ketoconazole and Metyrapone	

*	Intranasal steroids for atopic condition and topical treatments for eczema are allowed
**	includes spironolactone, amiloride
***	includes Captopril, Zofenopril, enalapril, 52nalyzin, Quinapril, Perindopril, Lisinopril, Benazepril, Imidapril, Trandolapril, Fosinopril, Cilazapril;
****	includes ibuprofen, diclofenac, naproxen, celecoxib, mefenamic acid,etoricoxib, indomethacin, aspirin (doses > 600 mg)

[1] Withdrawal of bronchodilators or reduction in iCS dose is not acceptable unless for medical reasons.

4.2.2.2 Medication Restrictions (for Pulmonary Function Testing)

An 8-hour minimum washout period for inhaled short-acting bronchodilators (such as salbutamol and ipratropium) must be maintained. The morning dose of inhaled corticosteroids should not be taken in the 1-hour period prior to test-day (Day 1 and Day 2) pre-dose PFT.

Even if subjects violate these restrictions, as a general rule, scheduled procedures (including further dosing and methacholine challenge) should neither be postponed nor skipped. Regarding diet and lifestyle restrictions for forced spirometry testing please see Section 4.2.2.3.

4.2.2.3 Restrictions on diet and life style

Grapefruits, Seville oranges and their juices, dietary supplements (including vitamins and garlic supplements) and herbal products are not permitted from 7 days before day 1 and until last PK of the study.

Alcoholic beverages are not permitted from 48 hours prior to and during all visits.

Intake of coffee, tea, chocolate, cola, energy drinks and other methylxanthine-containing drinks or foods and ice-cold beverages are not allowed for a period of 8 hours prior to clinic visits and during in-house confinement at the study site. Decaffeinated beverages are allowed.

Standardised meals will be provided during in-house confinement at the study site. Subjects are restricted from consuming any foods or drinks than those provided by the staff.

Excessive strenuous physical activity should be avoided for 72 hours prior to screening (Visit 1). Strenuous exercise should be avoided for 48 hours prior to and during all other visits (Visits 2-6).

4.2.2.4 Restrictions regarding women of childbearing potential

Women of childbearing potential are excluded from participation in this study.

4.3 TREATMENT COMPLIANCE

Each subject will be trained in the correct use of the Respimat® inhaler using the training Respimat® inhaler with inserted placebo cartridge. Please refer to Appendix 10.1

5. VARIABLES AND THEIR ASSESSMENT

5. 1 TRIAL ENDPOINTS

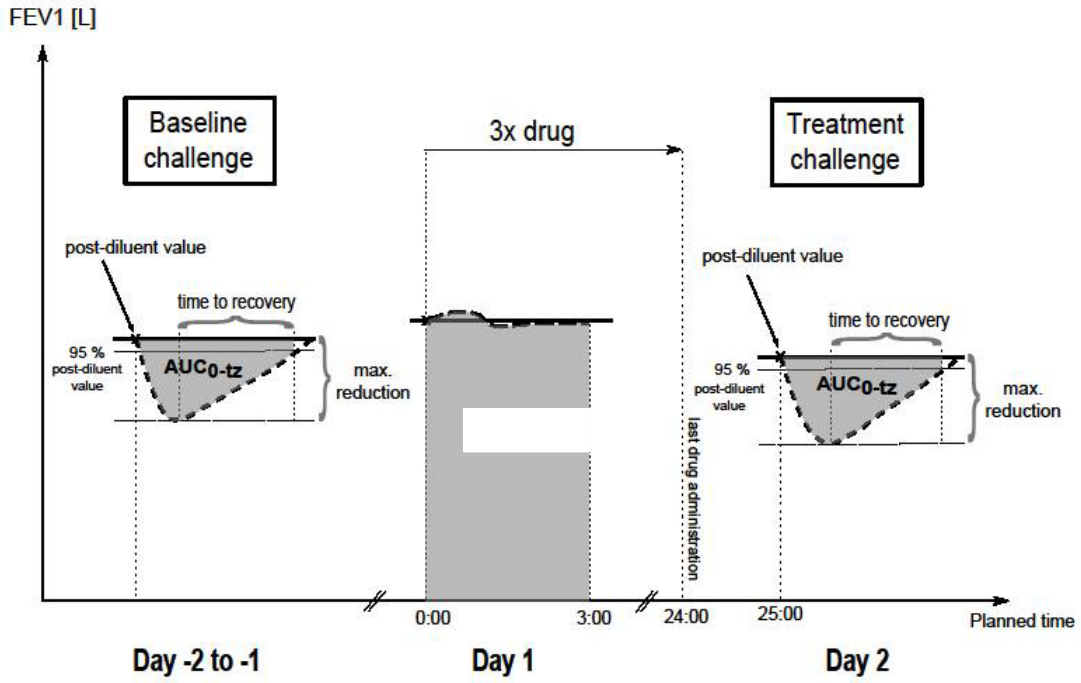

Figure 5.1: 1 Illustration of endpoints based on spirometry measurements (FEV_1 as example).

The figure displays measurements during one treatment period that is during the baseline bolus challenge prior to drug administration, during drug administration and during the treatment challenge on Day 2.

In the following baseline refers to the measurement obtained from the baseline bolus MCh challenge prior to administration of trial medication within each period.

5.1.1 Primary Endpoint(s)

The primary endpoint for the study to assess safety of BI 443651 is

- Absolute change from baseline in maximum FEV_1 reduction following MCh challenge.

The primary endpoint will be compared to placebo for each dose level of BI 443651.

For a visualization of the endpoint refer to Figure 5.1 :1, a detailed description of the primary endpoint and the primary statistical analysis is provided in Section 7.

5.1.2 Secondary Endpoint(s)

The following secondary endpoints will be assessed:

- Relative change from baseline in FEV_1 $AUC_{0\text{-}tz}$ following bolus MCh challenge
- Time to recovery of FEV_1 to within 95% of post-diluent value

The secondary endpoints will be compared to placebo for each dose level of BI 443651.

For a visualization of the endpoints refer to Figure 5.1:1, a detailed description of the secondary endpoints including statistical analysis is provided in Section 7.

5.2 ASSESSMENT OF EFFICACY

There are no efficacy assessments in this study

5.3 ASSESSMENT OF SAFETY

5.3.1 Physical examination

A physical examination will be performed at Screening (Visit 1) and on completion of the study. A targeted physical examination focussing on heart and lungs will be performed at the start of each treatment period (Visits 2 – 5).

All clinically significant findings at screening (Visit 1) will be recorded on the Medical History/Baseline Conditions in the eCRF.

New clinically significant findings or worsening of screening findings detected at the follow up visit (Visit 6) will be recorded as adverse events on the appropriate eCRF page.

An explanation of the aetiology of clinically significant abnormal physical findings must be made on the eCRF. All relevant (in the opinion of the investigator) abnormal physical findings have to be followed up until normalised or sufficiently characterised.

5.3.2 Vital Signs

Pulse rate, systolic and diastolic blood pressure will be measured and recorded at the screening visit (Visit 1) and at subsequent visits at selected timepoints. Measurements will be obtained with the subject supine and rested for at least 5 minutes.

5.3.3 Safety laboratory parameters

For the assessment of laboratory parameters, blood will be collected by the trial site at the time points indicated in the Flow Chart after the subjects have fasted for at least 10h (prior to the Screening Visit (Visit 1)) Subjects may drink water during the fasting period.

Subjects do not need to fast prior to laboratory testing at subsequent visits (i.e: after Visit 1)

If safety laboratory measurement is performed at the same time as other blood collection, e.g. PK sampling, safety laboratory measurement will always be performed first, preferably without any tourniquet.

The parameters that will be determined are listed in Table 5.3.3:.1 Reference ranges will be provided in the ISF.

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

Table 5.3.3:1 Routine laboratory tests

Category	Test name	A	B
Haematology	Haematocrit	x	x
	Haemoglobin	x	x
	Red blood cells (RBC)	x	x
	White blood cells (WBC)	x	x
	Platelets	x	x
	Reticulocytes	x	x
Automatic WBC differential (relative and absolute)	Neutrophils	x	x
	Eosinophils	x	x
	Basophils	x	x
	Monocytes	x	x
	Lymphocytes	x	x
Manual differential WBC (if automatic differential is abnormal)	Polymorphnuclear neutrophils (segs), band neutrophils (stabs), eosinophils, basophils, monocytes, lymphocytes		
Coagulation	Activated partial thromboplastin time (aPTT)	x	x
	Prothombin Time (Quick and INR)	x	x
Enzymes	Alanine aminotransferase (ALT/GPT, SGPT)	x	x
	Alkaline phosphatase	x	x
	Gamma-glutamyl transferase (GGT)	x	x
	Lactate dehydrogenase	x	x

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

A: Parameters to be determined at screening examination and during the study (refer to Flow Chart for time points)
B: Parameters to be determined during the follow-up visit

The laboratory tests will be performed by a central laboratory.

Instructions for the processing, storage and shipment of samples to the central laboratory will be provided to the site.

Where local laboratory results are also used, central laboratory results will take precedence in the interpretation of the results. Local laboratory results will take precedence for dosing decisions (e.g: $K^{+)}$. Local laboratory values will not be entered into the database.

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

5.3.4 Electrocardiogram

A standard 12-lead ECG will be performed on all subjects at the screening visit (Visit 1) and during treatment period (Visits 2-5). ECG will be performed with the subject supine and rested for at least 5 minutes. At Visit 1, significant findings must be recorded on the Medical History/Baseline Condition page. Any clinically relevant (according to the investigator's opinion) changes in the ECG during the study (after Visit 1) should be documented on the AE page of the eCRF.

5.3.5 Other safety parameters

Not applicable

5.3.6 Assessment of adverse events

5.3.6.1 Definitions of Aes

Adverse event

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

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

Adverse reaction

An adverse reaction is defined as a response to a medicinal product which is noxious and unintended. Response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility. Adverse reactions may arise from use of the product within or outside the terms of the marketing authorisation or from occupational exposure. Conditions of use outside the marketing authorization include off-label use, overdose, misuse, abuse and medication errors.

Serious adverse event

A serious adverse event (SAE) is defined as any AE which:

- results in death,
- is life-threatening, this refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if more severe.
- requires inpatient hospitalisation or
- prolongation of existing hospitalisation,
- results in persistent or significant disability or incapacity, or
- 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 jeopardise the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions.

Medical and scientific judgement should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalisation but might jeopardise the patient or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation or development of dependency or abuse. Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

Aes considered "Always Serious"

Cancers of new histology and exacerbations of existing cancer must be reported as a serious event regardless of the duration between discontinuation of the drug and the occurrence of the cancer.
In accordance with the European Medicines Agency initiative on Important Medical Events, Boehringer Ingelheim has set up a list of further Aes, which by their nature, can always be considered to be "serious" even though they may not have met the criteria of an SAE as given above.

The latest list of "Always Serious Aes" can be found in the RDC system.

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, please see above.

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

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

Intensity 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

The definition of an adverse reaction implies at least a reasonable possibility of a causal relationship between a suspected medicinal product and an adverse event. An adverse reaction, in contrast to an adverse event, is characterised by the fact that a causal relationship between a medicinal product and an occurrence is suspected.

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

Arguments that may suggest that there is a reasonable possibility of a causal relationship could be:
- The event is consistent with the known pharmacology of the drug
- The event is known to be caused by or attributed to the drug class.
- A plausible time to onset of the event relative to the time of drug exposure.
- Evidence that the event is reproducible when the drug is re-introduced
- No medically sound alternative aetiologies that could explain the event (e.g. pre-existing or concomitant diseases, or co-medications).

- The event is typically drug-related and infrequent in the general population not exposed to drugs (e.g. Stevens-Johnson syndrome).
- An indication of dose-response (i.e. greater effect size if the dose is increased, smaller effect size if dose is diminished).

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

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

5.3.6.2 Adverse event collection and reporting

AE Collection

The Investigator shall maintain and keep detailed records of all Aes in their patient files. The following must be collected and documented on the appropriate CRF(s) by the Investigator:

- From signing the informed consent onwards through the Residual Effect Period (REP), until an 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 patient for Aes but should only report relevant SAEs and relevant AESIs of which the Investigator may become aware of.

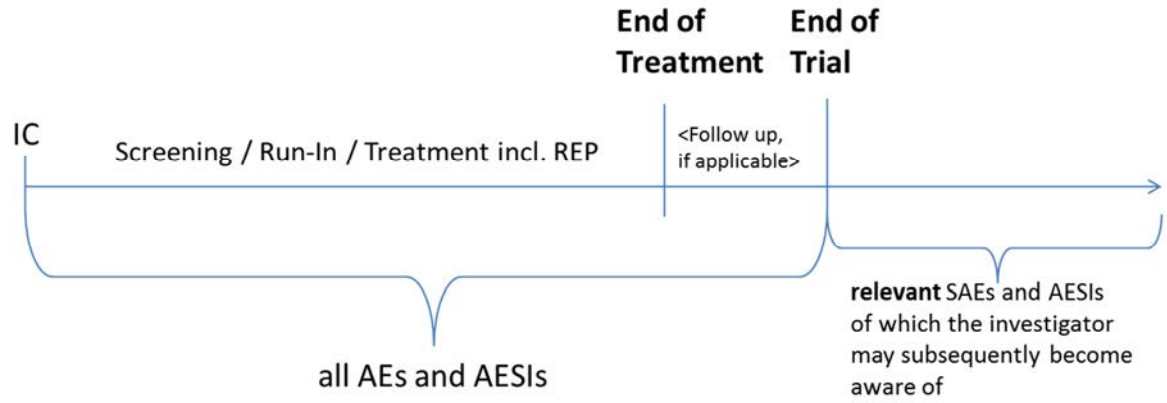

Figure 5.3.6.2: 1 Illustration of Safety Reporting Requirements.

The REP is defined as after the last trial medication application. All Aes which occurred through the treatment phase and throughout the REP will be considered as on treatment (see Section 7.3.4). Events which occurred after the REP and before next drug intake or trial termination date (whatever occurs first) will be considered as follow-up 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 CRF pages and the BI SAE form. The Investigator should determine the causal relationship to the trial medication.

The following should also be recorded as an (S)AE in the CRF and 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 characterised, or no further information can be obtained.

Pregnancy
In rare cases, pregnancy might occur in a clinical trial. Once a patient has been enrolled in the clinical trial and has taken trial medication, the investigator must report any drug exposure during pregnancy in a trial participant immediately (within 24 hours) by means of Part A of the Pregnancy Monitoring Form to the sponsor's unique entry point.

Similarly, potential drug exposure during pregnancy must be reported if a partner of a male trial participant becomes pregnant. This requires a written consent of the pregnant partner.

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

The ISF will contain the Pregnancy Monitoring Form for Clinical Trials (Part A and 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

5.5 ASSESSMENT OF BIOMARKER(S)

Not applicable

5.6 OTHER ASSESSMENTS

There will be no additional assessments

5.7 APPROPRIATENESS OF MEASUREMENTS

All measurements performed in this trial are standard measurements to monitor safety aspects in an appropriate way. The primary and

secondary endpoints are standard and accepted for evaluation of safety, tolerability, and are widely used in this kind of study.

The bolus MCh challenge method (see Section 6.2) has been chosen as this provides a consistent degree of muscarinic receptor excitation between treatment levels, allowing investigation of the effect of regular dosing with a therapeutic agent on both methacholine induced bronchoconstriction and subsequent recovery.

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

The trial consists of a screening period (Visit 1), pilot and main study periods (Visit 2 to 5) and end of study period (Visit 6). The pilot and main study each consist of four separate treatment periods. For administrative reasons, each of these four treatment periods within the pilot and main studies is referred to as a 'Visit' and each 'Visit' will consist of up to 3 days of procedures. The procedures conducted at each of the treatment period 'Visits' (Visit 2 to 5) are the same. A more detailed overview is provided in the Flow Chart.

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

Methacholine (MCh) challenge

The single methacholine concentration according to Table 6.2.1 (column 4) will be administered at both Day -1 or Day -2 and Day 2 of each treatment period. This concentration needed to administer this dose considers the cumulative dose administered during the incremental challenge at the screening visit (see Table 6.2.1). Single FEV_1 measurements (FEV1 only) are then made at 30 and 90 seconds, followed by duplicate FEV_1 and FVC measurements at 5, 10, 20, 30, 45 minutes, 1, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 2.75 and 3 hours on Day -2 or Day -1, with additional timepoints at 3.5, 4.0, 4.5, 5.0, 6.0, 7.0 and 8.0 hours hours on Day 2.

Table 6.2.1: Incremental and bolus MCh challenge dosing schedule.

Dose Number	Methacholine Concentration during Incremental Challenge (mg/ml)	Cumulative Dose (mg) (rounded to 4 d.p. max)	Methacholine Concentration to be used to administer the Bolus Challenge (mg/ml) (only highest dose number administered at Visit 1)
1	0.03125	0.0014	0.03125
2	0.03125	0.0028	0.0625
3	0.0625	0.0056	0.125
4	0.125	0.0113	0.25
5	0.25	0.0225	0.5
6	0.5	0.045	1.0
7	1.0	0.09	2.0
8	2.0	0.18	4.0
9	4.0	0.36	8.0
10	8.0	0.72	16.0
11	16.0	1.44	32.0

Spirometry

Spirometry will be performed according to ATS/ERS guidelines for pulmonary function testing [P05-12782] in order to characterise the study population, to monitor individuals' safety in regard to asthma and as an exploratory assessment of drug effect. The subject must qualify by demonstrating a pre-bronchodilator clinic measured FEV_1 ≥70% of predicted normal. FEV1 normal predicted values will be calculated according to GLI [R15-0845] measured ≥ 8 hours after the last use of short acting bronchodilator at the screening visit (Visit 1) and treatment period 1 Day 1.

Equipment and techniques should conform to American Thoracic Society (ATS) criteria [P05-12782].

Spirometry will be conducted with the subject in a seated position. It is preferable that the same trained individual performs the PFTs for a given subject. Unless otherwise specified in methacholine challenges, the best of three efforts will be defined as the highest FEV_1 and the highest FVC each obtained on any of three blows meeting the ATS criteria (with a maximum of eight attempts). FEV_1, FVC, will be measured as indicated in the Flow Chart and recorded in the eCRF. The best of the three pre-dose FEV_1 measurements will be defined as trough FEV_1. The 24-hour clock time of the first manoeuvre for each PFT time point will be recorded.

Screening and run-in period(s)

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

6.2.1 Treatment period(s)

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

All subjects will attend the trial site (see Flow Chart) after formal assessments and confirmation of their fitness by the investigator or designee.

For details on time points and procedures for collection of plasma samples for PK analysis (see Flow Chart).

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

6.2.2 End of Trial Period

For AE assessment, laboratory tests, recording of ECG and vital signs, physical examination, see Sections 5.3.1

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

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

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

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 STATISTICAL DESIGN – MODEL

The primary objective of the study is to investigate safety and tolerability of three consecutive administrations, 12 h apart, at three different dose-levels (100, 400 and 1200 µg) of BI 443651 administered via oral inhalation in male and female mild asthmatic subjects after a bolus MCh challenge.

For the main part, the primary endpoint absolute change in maximum reduction of FEV_1 and the secondary endpoint relative change in $AUC_{0\text{-}tz}$ as described in Section 5.1 will be analysed using a mixed effects model on the original and logarithmic-scale, respectively, taking the crossover design of the trial into account. The models will include treatment and period as fixed effects, subject as a random effect and period baseline as well as subject baseline as covariates. The subject baseline will be obtained by calculating the mean of period baselines for each subject. Active doses will be compared to placebo for both endpoints. For investigation of the secondary endpoint time to recovery to within 95% of post-diluent value a Cox proportional hazards model will be used to estimate the hazard ratio of BI 443651 vs. Placebo.

For the pilot part, the primary and secondary endpoints as described in Section 5.1 will be analysed using descriptive statistics. No inferential statistics are planned for this part of the trial.

7.2 NULL AND ALTERNATIVE HYPOTHESES

Safety and tolerability of 3 different dose strengths of BI 443651 are to be determined on the basis of the investigated parameters in comparison to placebo. It is not planned to test any statistical hypotheses with regard to these variables in a confirmatory sense. Instead, they will be described in their entirety and evaluated by descriptive statistical methods.

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

7.3 PLANNED ANALYSES

All individual data will be listed.

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

The statistical analysis will be based on the following analysis sets based on the actual treatment the subject receives.

- Enrolled set (ES): This subject set includes subjects that signed informed consent and underwent screening procedures.
- Randomised set (RS): This subject set includes all randomised subjects, whether treated or not.
- Treated set (TS): The treated set includes all subjects who were randomised and treated with at least one dose of study drug. The treatment assignment will be determined based on the first treatment the subjects received.
- Methacholine set (MCS): This subject set includes all subjects in the treated set who provide at least one pair (baseline and end of treatment) of evaluable measures of spirometry parameters that were not excluded due to use of rescue medication within 3 hours after start of MCh challenge.

7.3.1 Primary endpoint analyses

The primary endpoint absolute change from baseline in maximum reduction in FEV_1 (refer to Section 5.1.1) is defined as the difference between the maximum reduction in FEV_1 obtained during the treatment challenge and during the baseline challenge.
The primary endpoint will be investigated using descriptive statistics for both trial parts separately and combined.
For the main part of the trial (part II), this primary endpoint will be analysed using a mixed effects model based on the MCS:

$$y_{imj} = \mu + \pi_m + \tau_j + \gamma b_{im} + \gamma' b_i' + s_i + e_{imj},$$

where i = subject 1,…, N, m = period 1,…,4, j = treatment 1,…,4

y_{imj}	CfB in maximum FEV_1 reduction for the i^{th} subject and the m^{th} period, receiving randomised treatment j
μ	overall intercept,
π_m	m^{th} period effect,
τ_j	j^{th} treatment effect,
b_{im}	baseline value for subject i in period m (period baseline),
γ	associated covariate effect of period baseline,
b_i'	the subject baseline value (mean of period baselines) for subject i,
γ'	associated covariate effect of subject baseline,
s_i	the random effect of subject i,
e_{imj}	the random error associated with subject i who received treatment j in period m.

The treatment comparisons will be the contrast between active dose and placebo at the endpoint visit. Adjusted means (Least Squares Means) as well as 2-sided 90% Cis will be provided.

Further details will be provided in the TSAP.

7.3.2 Secondary endpoint analyses

The secondary endpoint relative change from baseline in FEV_1 $AUC_{0\text{-}tz}$ (see Section 5.1.2) is defined as the ratio of FEV_1 $AUC_{0\text{-}tz}$ obtained during the treatment challenge and during the baseline challenge. During each challenge, the area above the curve of the absolute change in FEV_1 from post-diluent value will be calculated from time 0 to tz using the trapezoidal rule (refer to 001-MCG-163). The time tz refers to the last time point before recovery of FEV_1 to within 95% of post-diluent value.

This secondary endpoint will be investigated using descriptive statistics for both trial parts separately and combined.

For the main part of the trial (part II), this secondary endpoint will be analysed using a mixed effects model on the logarithmic scale based on the MCS:

$$y_{imj} = \mu + \pi_m + \tau_j + \gamma b_{im} + \gamma' b'_i + s_i + e_{imj},$$

where i = subject 1,…, N, m = period 1,…,4, j = treatment 1,…,4

y_{imj}	Logarithm of CfB in FEV_1 $AUC_{0\text{-}tz}$ consideration for the i^{th} subject and the m^{th} period, receiving randomised treatment j
μ	overall intercept,
π_m	m^{th} period effect,
τ_j	j^{th} treatment effect,
b_{im}	Logarithm of baseline value for subject i in period m (period baseline),
γ	associated covariate effect of period baseline,
b'_i	Logarithm of the subject baseline value (mean of period baselines) for subject i,
γ'	associated covariate effect of subject baseline,

s_i the random effect of subject i,
e_{imj} the random error associated with subject i who received treatment j in period m.

To this end, the endpoint will be log-transformed (natural logarithm) prior to fitting the model given above. The difference between the expected means for log(Active)-log(Placebo) will be estimated by the difference in the corresponding adjusted means (Least Squares Means), and a two-sided 90% confidence interval based on the t-distribution will be computed. These quantities will then be back-transformed to the original scale to provide the point estimate and 90% Cis for each endpoint.

The secondary endpoint time to recovery of FEV_1 within 95% of post-diluent value (see Section 5.1.2) is defined as the time from maximum reduction to last time before recovery to within 95% of pre-MCh challenge during each challenge. The time obtained from the treatment challenge represents the endpoint, while the time obtained from the baseline challenge will be used for the baseline correction in the analysis.
This secondary endpoint will be investigated using descriptive statistics for both trial parts separately and combined, if applicable.

Kaplan-Meier (KM) curves will be plotted for the recovery of FEV_1 within 95% of post-diluent value by treatment irrespective of the period it is administered in, for both trial parts separately as well as combined, if applicable.

For part II of the trial, this endpoint will be analysed using a Cox proportional hazards model as given below based on the MCS. The model includes the treatment effect and an effect for subject baseline. Thereby, the subject baseline is calculated as median of all period baselines per subject. Breslow's method for handling ties will be used.

The hazard function for the i^{th} subject is assumed to be

$$\lambda_i(t) = \lambda_0(t) \cdot \exp\{\beta_1 X_{1i} + \beta_2 X_{2i} + \beta_3 X_{3i}\},$$

where i = 1,…, N,
$\lambda_0(t)$ is the unspecified, non-negative, baseline hazard function

- $\beta_{1,2,3}$ are the unknown regression coefficients
- X_{1i} represents the treatment group
- X_{2i} represents the subject baseline (median of period baselines)
- X_{3i} represents the period

For treatment comparisons the hazard ratios of BI 443651 vs. Placebo and asymptotic 95% Wald confidence intervals will be estimated. A hazard ratio of greater than one means that BI 443651 is not inferior to placebo.

Further details will be provided in the TSAP.

7.3.5 Safety analyses

Safety will be assessed for the further safety parameters of interest listed in Section 5.1.3 based on the TS. Safety analyses will be descriptive in nature and will be based on BI standards.

Treatments will be compared in a descriptive way. The active treatment groups will be compared to the placebo group in a descriptive way. Tabulations of frequencies/proportions will be used for the evaluation of categorical (qualitative) data, and tabulations of descriptive statistics will be used to analyse continuous (quantitative) data.

The analyses will be done by 'treatment at onset'.

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

Therefore, measurements planned or Aes recorded prior to first intake of trial medication will be assigned to 'screening', those between first trial medication intake until next intake or end of REP will be assigned to the preceding treatment, and all Aes occurring between the end of REP and next treatment intake or trial termination date respectively will be assigned to 'follow-up'. In case of two or more treatments, the follow-up will be summarized according to the previous treatment. These assignments including the corresponding time intervals will be defined in detail in the TSAP. Please note that Aes occurring after the last per protocol contact but entered before database lock will be reported to drug safety only and will not be captured in the trial database.

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 follow-up intervals).

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Frequency, intensity and causal relationship of Aes will be tabulated by treatment, primary system organ class and preferred term. SAEs, AESIs (see Section 5.3.6) and other significant Aes (according to ICH E3) will be listed separately.

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

Vital signs, physical examinations, or other safety-relevant data observed at screening, baseline, during the course of the trial and at the end-of-trial evaluation will be assessed with regard to possible changes compared to findings before start of treatment.

7.4 INTERIM ANALYSES

No inferential statistical interim analysis is planned. However, after part 1 the investigator (or his deputy) is allowed to postpone progression to part 2 until a preliminary safety review (see Section 3.1) of the data already obtained has been performed. For handling of treatment blinding refer to Section 4.1.5.

7.5 HANDLING OF MISSING DATA

7.5.1 Safety

For evaluation of primary and secondary endpoints a measurement obtained at baseline and on-treatment per period is required. Further details will be provided in the TSAP.

Handling of drop-outs is described in Section 3.3.5.

With respect to further safety evaluations (refer to Section 7.3.4), it is not planned to impute missing values.

7.6 RANDOMISATION

For each trial part, subjects will be randomised to one of four treatment sequences (see Section 3.1) in a 1:1:1:1 ratio. The block size will be documented in the CTR.

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

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

7.7 DETERMINATION OF SAMPLE SIZE

For the pilot part, it is planned to include 4 otherwise healthy asthma subjects. The planned sample size is not based on a power calculation. This sample size is considered as sufficient for the exploratory evaluation of safety after multiple doses in this study population.

For the main part, it is planned to include a total of 32 (8 per sequence) completed otherwise healthy asthma subjects (non-completed subjects will be replaced, see Section 3.3.5) to achieve the aims of this exploratory trial with the following assumptions:

- The primary endpoint is normally distributed
- Two-sided significance level $\alpha = 10\%$
- Considered relevant change: -0.2 L
- The treatment difference between the means of BI 443651 and placebo is expected to be -0.06 L [data on file]
- The within-subject standard deviation (SD) for the difference is expected to be 0.24 L [data on file]

Assuming a within-subject SD of 0.24 L for BI 443651 and given the chosen sample size of N=32 subjects, the precision of the two-sided 90% confidence interval of the difference will be approximately 0.112 (upper confidence limit (UL) – point estimate of the difference (Diff)); for a greater within-subject SD of 0.3, the precision would still be approximately 0.14.

Increasing the sample size by 4 (N=36) results in a precision of approximately 0.105 and 0.131, respectively. Table 7.7: 1 provides an overview of the 90% confidence intervals that are expected with 95% tolerance probability, for possible scenarios of the SDs and intra-subject differences (active drug – placebo).

Table 7.7: 1 Precision that can be expected with 95% tolerance probability and illustrative two-sided 90% confidence intervals around the treatment differences for different SDs and varying sample sizes in a 4x4x4 crossover

N	SD within	Precision (UL-Diff)	Diff (active – placebo)				
			-0.1	-0.05	0	0.05	0.1
32	0.24	0.112	(-0.21,0.01)	(-0.16, 0.06)	(-0.11, 0.11)	(-0.06, 0.16)	(-0.01, 0.21)
32	0.3	0.14	(-0.24, 0.04)	(-0.19, 0.09)	(-0.14, 0.14)	(-0.09, 0.19)	(-0.04, 0.24)
36	0.24	0.105	(-0.20, 0.00)	(-0.15, 0.05)	(-0.10, 0.10)	(-0.05, 0.05)	(-0.00, 0.20)
36	0.3	0.131	(-0.23, 0.03)	(-0.18, 0.08)	(-0.13, 0.13)	(-0.08, 0.18)	(-0.03, 0.23)

The calculation was performed as described by Julious [R11-5230] using R Version 3.2.2.

8. INFORMED CONSENT, TRIAL RECORDS, DATA PROTECTION, PUBLICATION POLICY

The trial will be carried out in accordance with the Medical Devices Directive (93/42/EEC) and the harmonised standards for Medical Devices (ISO 14155, current version).

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), relevant BI Standard Operating Procedures (SOPs), the EU regulation 536/2014, the Japanese GCP regulations (Ministry of Health and Welfare Ordinance No. 28, March 27, 1997) and other relevant regulations.

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

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 Boehringer Ingelheim transparency and publication policy can be found on the following web page: trials.boehringer-ingelheim.com. The rights of the Investigator and of the sponsor with regard to publication of the results of this trial are described in the Investigator contract. As a 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 patients, and is stored in the ISF (Investigator Site File).

8.1 TRIAL APPROVAL, SUBJECT INFORMATION, INFORMED CONSENT

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

Prior to 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 patient or the subject's legally accepted representative."
The Investigator must give a full explanation to trial subjects based on the subject information form. A language understandable to the subject should be chosen, technical terms and expressions avoided, if possible. The subject must be 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.
The consent and re-consenting process should be properly documented in the source documentation.

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) for individual patients 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

In accordance with regulatory requirements the Investigator should prepare and maintain adequate and accurate source documents and trial records that include all observations and other data pertinent to the investigation on each trial subject. Source data as well as reported data should follow good documentation practices and be attributable, legible, contemporaneous, original and accurate. Changes to the data should be traceable (audit trail). Data reported on the CRF must be consistent with the source data or the discrepancies must be explained.

The current medical history of the subject may not be sufficient to confirm eligibility for the trial and the Investigator may need to request previous medical histories and evidence of any

diagnostic tests. In this case the Investigator must make three documented attempts to retrieve previous medical records. If this fails a verbal history from the subject, documented in their medical records, would be acceptable.

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

If the subject is not compliant with the protocol, any corrective action e.g. re-training must be documented in the patient file.
For the CRF, data must be derived from source documents, for example:

- Subject identification: gender, date or year of birth (in accordance with local laws and regulations)
- Subject participation in the trial (substance, trial number, patient number, date subject was informed)
- Dates of Subject's visits, including dispensing of trial medication
- Medical history (including trial indication and concomitant diseases, if applicable)
- Medication history
- Adverse events and outcome events (onset date (mandatory), and end date (if available))
- Serious adverse events (onset date (mandatory), and end date (if available))
- Concomitant therapy (start date, changes)
- Originals or copies of laboratory results and other imaging or testing results, with proper documented medical evaluation (in validated electronic format, if available)
- Completion of Subject's Participation in the trial" (end date; in case of premature discontinuation document the reason for it).
- Prior to allocation of a subject to a treatment into a clinical trial, there must be documented evidence in the source data (e.g. medical records) that the trial participant meets all inclusion criteria and does not meet any exclusion criteria. The absence of records (either medical records, verbal documented feedback of the subject or testing conducted specific for a protocol) to support inclusion/exclusion criteria does not make the subject eligible for the clinical trial.

Direct access to source data and documents

The sponsor will monitor the conduct of the trial by regular on-site monitoring visits and in-house data quality review. The frequency of on-site monitoring will be determined by assessing all characteristics of the trial, including its nature, objective, methodology and the degree of any deviations of the intervention from normal clinical practice.
The Investigator /institution will allow on-site trial-related monitoring, audits, IRB / IEC review and regulatory inspections. Direct access must be provided to the CRF and all source documents/data, including progress notes, copies of laboratory and medical test results, which must be available at all times for review by the CRA, auditor and regulatory inspector (e.g. FDA). The CRA and auditor may review all CRFs and informed consents. The accuracy of the data will be verified by direct comparison with the source documents described in Section 8.3.1. The sponsor will also monitor compliance with the protocol and ICH GCP.

An adaptive approach to clinical trial monitoring will be utilised. The sponsor will perform a risk assessment of the trial to determine the extent and nature of monitoring required in order to ensure the reliability and robustness of the results. Regular review of risk reports will provide sponsor oversight during trial conduct and direct monitoring activities to the areas of greatest risk which have the most potential impact to subject safety and data quality.

The Investigator /institution will allow on-site trial-related monitoring, audits, IRB / IEC review and regulatory inspections. Direct access should be granted to all source documents (paper and e-records) including progress notes, copies of laboratory and medical test results. The CRA and auditor may review all CRFs and informed consents. The accuracy of the data will be verified by direct comparison with the source documents described in Section 8.3.1. The sponsor will also monitor compliance with the protocol and ICH GCP.

The Investigator /institution will allow on-site trial-related monitoring, audits, IRB/IEC review and regulatory inspections. Direct access should be granted to all source documents (paper and e-records) including progress notes, copies of laboratory and medical test results The CRA and auditor may review all CRFs and informed consents. The accuracy of the data will be verified by direct comparison with the source documents described in Section 8.3.1. The sponsor will also monitor compliance with the protocol and ICH GCP.

Storage period of records

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

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

8.4 EXPEDITED REPORTING OF ADVERSE EVENTS

BI is responsible to fulfil their legal regulatory reporting obligation and in accordance to the requirements defined in this CTP.

8.5 STATEMENT OF CONFIDENTIALITY AND SUBJECT PRIVACY

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

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

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.

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

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

- A Quality Management System has been implemented to ensure the adherence with the Principles of Good Clinical Practice as outlined in 'Note For Guidance On Good Clinical Practice' (CPMP/ICH/13 5/95)
- The BI-internal facilities storing and 82nalyzing biological samples and data from clinical trial participants as well as the laboratories' activities for clinical trials sponsored by Boehringer Ingelheim are regularly audited. The analytical groups and the banking facility are therefore assessed to be qualified for the storage and use of biological samples and data collected in clinical trials.
- Samples and data are used only if an appropriate informed consent is available.

8.6 TRIAL MILESTONES

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

The end of the trial is defined as the date of the last visit of the last subject in the whole trial ("Last Subject Out"). The "**Last Subject Drug Discontinuation"** (LSDD) date is defined as the date on which the last subject at an individual trial site ends trial medication (as scheduled per protocol or prematurely). Individual Investigators will be notified of SUSARs occurring with the trial medication until 30 days after LSDD at their site. **Early termination of the trial** is defined as the premature termination of the trial due to any reason before the end of the trial as specified in this protocol.

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

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

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

A final report of the clinical trial data will be written only after all subjects have completed the trial in all countries (EU or non-EU) to incorporate and consider all data in the report. The sponsor will submit to the EU database a summary of the final trial results within one year from the end of a clinical trial as a whole, regardless of the country of the last subject (EU or non-EU).

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9.2 UNPUBLISHED REFERENCES

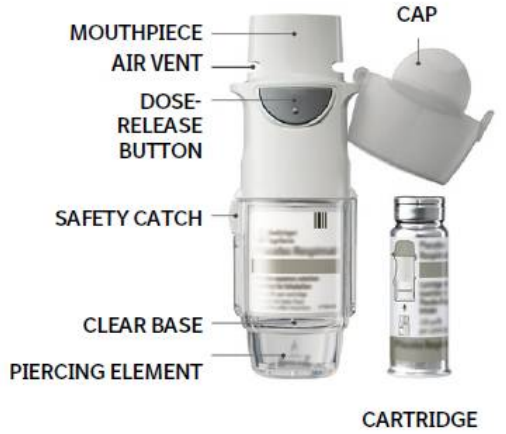
C02337864	Investigator's Brochure
C02861250-03	1363.1 Protocol
001-MCG-163	Statistics and Data Management Respiratory Standards
001-MCS-36-472	Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamic

10. APPENDICES

10.1 HANDLING INSTRUCTIONS FOR RESPIMAT® INHALER FOR USE IN BI 443651 CLINICAL TRIALS

These instructions explain generally the use of BI 443651 RESPIMAT inhaler. Depending on the clinical study, the product is administered under direct medical supervision or used by patients at home. Depending on the situation, the Instructions can be adapted to the specific situation as need be.

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



How to store BI 443651 RESPIMAT

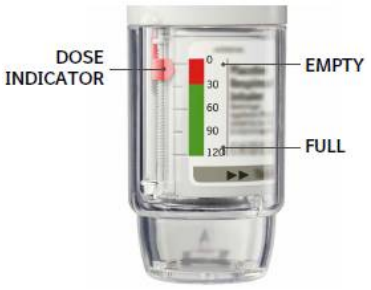
- Keep BI 443651 RESPIMAT out of the sight and reach of children.
- Do not freeze BI 443651 RESPIMAT. For further storage conditions, please refer to product label.
- If BI 443651 RESPIMAT has not been used for more than 1 day, repeat steps 4 to 6 under ‘Prepare for first Use’ until a cloud is visible. Then repeat steps 4 to 6 three more times.
- Do not use BI 443651 RESPIMAT after the expiry date

How to care for BI 443651 RESPIMAT

Clean the mouthpiece including the metal part inside the mouthpiece with a damp cloth or tissue only, at least once a week.

Any minor discoloration in the mouthpiece does not affect BI 443651 RESPIMAT inhaler performance.

When to get a new BI 443651 RESPIMAT



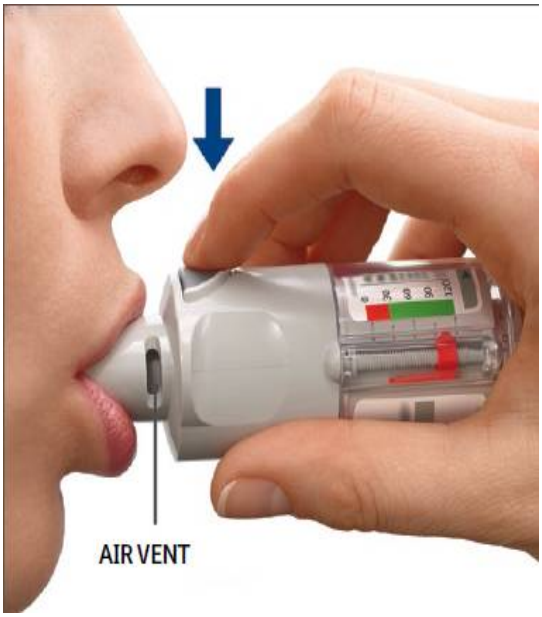
- BI 443651 RESPIMAT inhaler contains 120 puffs if used as indicated.
- The dose indicator shows approximately how much medication is left.
- When the dose indicator enters the red area of the scale, get a new BI 443651 RESPIMAT from the investigational site; there are approximately 30 puffs left.
- Once the dose indicator reaches the end of the red scale, BI 443651 RESPIMAT locks automatically – no more doses can be released. At this point, the clear base cannot be turned any further. The inhaler should not be discarded; it should be returned to investigational site.

Prepare for first use

1. Remove clear base • Keep the cap closed. • Press the safety catch while firmly pulling off the clear base with your other hand.	
2. Insert cartridge • Insert the narrow end of the cartridge into the inhaler. • Place the inhaler on a firm surface and push down firmly until it snaps into place.	

3. Replace clear base • Put the clear base back into place until it clicks.	
4. Turn • Keep the cap closed. • Turn the clear base in the direction of the arrows on the label until it clicks (half a turn).	
5. Open • Open the cap until it snaps fully open.	
6. Press • Point the inhaler toward the ground • Press the dose-release button. • Close the cap. • Repeat steps 4-6 until a cloud is visible. • After a cloud is visible, repeat steps 4-6 three more times.	

Daily use

TURN • Keep the cap closed. • TURN the clear base in the direction of the arrows on the label until it clicks (half a turn).	
OPEN • OPEN the cap until it snaps fully open.	
PRESS • Breathe out slowly and fully. • Close your lips around the mouthpiece without covering the air vents. • While taking a slow, deep breath through your mouth, PRESS the dose-release button and continue to breathe in. • Hold your breath for 10 seconds or for as long as comfortable. • Repeat Turn, Open, Press for a total of 2 puffs.	

Answers to Common Questions

It is difficult to insert the cartridge deep enough.

Did you accidentally turn the clear base before inserting the cartridge? Open the cap, press the dose-release button, then insert the cartridge.

Did you insert the cartridge with the wide end first? Insert the cartridge with the narrow end first.

I cannot press the dose-release button.

Did you turn the clear base? If not, turn the clear base in a continuous movement until it clicks (half a turn).
Is the dose indicator on BI 443651 RESPIMAT pointing to zero? BI 443651 RESPIMAT inhaler is locked after 120 puffs. Prepare and use a new BI 443651 RESPIMAT inhaler.

I cannot turn the clear base.
Did you turn the clear base already? If the clear base has already been turned, follow steps "OPEN" and "PRESS" under "Daily Use" to get your medicine.

Is the dose indicator on the BI 443651 RESPIMAT pointing to zero? The BI 443651 RESPIMAT inhaler is locked after 120 puffs. Prepare and use your new RESPIMAT inhaler.

The dose indicator on the BI 443651 RESPIMAT reaches zero too soon.

Did you turn the clear base before you inserted the cartridge? The dose indicator counts each turn of the clear base regardless whether a cartridge has been inserted or not.
Did you spray in the air often to check whether the BI 443651 RESPIMAT is working? Once you have prepared BI 443651 RESPIMAT, no test-spraying is required if used daily.
Did you insert the cartridge into a used RESPIMAT? Always insert a new cartridge into a **NEW** RESPIMAT.
BI 443651 RESPIMAT sprays automatically.
Was the cap open when you turned the clear base? Close the cap, then turn the clear base.

Did you press the dose-release button when turning the clear base? Close the cap, so the dose-release button is covered, then turn the clear base.

Did you stop when turning the clear base before it clicked? Turn the clear base in a continuous movement until it clicks (half a turn).

BI 443651 RESPIMAT doesn't spray.

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

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

Is the dose indicator on BI 443651 RESPIMAT pointing to 0? If the dose indicator points to 0, you have used up all your medication and the inhaler is locked.

Once BI 443651 RESPIMAT is assembled, do not remove the clear base or the cartridge. Always insert a new cartridge into a **NEW** RESPIMAT.

Further information

BI 443651 RESPIMAT inhaler must not be disassembled after inserting the cartridge and replacing the clear base.

Do not touch the piercing element inside the base.

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11. DESCRIPTION OF GLOBAL AMENDMENT(S)

"This is the original protocol."

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