CLINICAL TRIAL PROTOCAL

	Document Number:	**c25762461-03**
EudraCT No. **EU Trial No.**	Not Applicable	
BI Trial No.	0205-0541	
BI Investigational Medicinal Product(s)	Tiotropium Respimat® (Spiriva® Respimat®)	
Title	A randomized, open-label, two-way crossover study to compare patient acceptability/preference of Tiotropium Respimat® with Tiotropium Handihaler® in patients with moderate to severe chronic obstructive pulmonary disease (COPD).	
Lay Title	A study on whether patients prefer the Spiriva® Respimat® or the Spiriva® Handihaler® for treating their chronic obstructive pulmonary disease (COPD)	
Clinical Phase	Phase IV	
Trial Clinical Monitor	[redacted]	
Coordinating Investigator	[redacted]	
Status	Final Protocol (Revised Protocol based on global amendment 2)	
Version and Date	**Version: 3.0**	**Date: 23 Mar 2020**

CLINICAL TRIAL PROTOCOL SYNOPSIS

Company name	Boehringer Ingelheim
Protocol date	08 Oct 2018
Revision date	23 Mar 2020
BI trial number	0205-0541
Title of trial	A randomized, open-label, two-way crossover study to compare patient acceptability/preference of Tiotropium Respimat® with Tiotropium Handihaler® in patients with moderate to severe chronic obstructive pulmonary disease (COPD).
Coordinating Investigator	[redacted]
Trial site(s)	Multi-center trial
Clinical phase	Phase IV
Trial rationale	The purpose of this study is to evaluate the patient acceptability/preference of Tiotropium Respimat® comparing with Tiotropium Handihaler® in patients with chronic obstructive pulmonary disease (COPD). The validated Patient satisfaction and preference questionnaire（PASAPQ）will be applied to evaluate the outcomes. Based on the previous studies, Tiotropium Respimat® showed better patient acceptability/preference compared with two DPIs, Diskus or Turbuhaler using PASAPQ as measurement. However, no studies have been done to compare the patient acceptability/preference between Tiotropium Respimat® and Tiotropium Handihaler®. The Tiotropium Safety and Performance in Respimat® (TIOSPIR) [P13-11053] study showed the efficacy of tiotropium via Respimat® or Handihaler® was similar in terms of lung function improvement and COPD exacerbation prevention. In real-life practice, the effectiveness might be influenced by different factors. The patient's acceptability/preference on the inhalers can impact the adherence to therapy, and then possibly control of disease. Therefore, we consider it is of clinical importance to investigate the patient acceptability/preference between Tiotropium Respimat® and Tiotropium Handihaler®, so that Health care professionals（HCPs）can refer to this trial to make appropriate decision on the choice between these two devices.
Trial objective(s)	The objective of this study is to investigate the patient acceptability/preference of Tiotropium Respimat® compared with Tiotropium Handihaler® in patients with moderate to severe chronic obstructive pulmonary disease (COPD) to demonstrate the superiority of Tiotropium Respimat®.
Trial endpoints	**Primary endpoints:** Performance domain of PASAPQ; **Secondary endpoints:** • PASAPQ total score;

	• Proportion of patients indicating preference; • Overall Satisfaction Question Score from PASAPQ; • Score on willingness to continue after treatment.
Trial design	Multicentre, randomised, open-label, two-way cross-over study
Total number of patients randomised	71 entered
Number of patients on each treatment	71
Diagnosis	COPD
Main in- and exclusion criteria	**Main inclusion criteria:** • Clinical diagnosis COPD (post-bronchodilator FEV1/FVC<70%) • GOLD Stage II/III COPD (30%<post-bronchodilator FEV1<80% of predicted) • Male or female, age: 40-80 years • Written informed consent provided by the patient **Main exclusion criteria:** • Had visual, cognitive, or motor impairment that, as judged by the investigator, did not allow the patient to independently read and complete the PASAPQ questionnaire • Patients have any previous experience of using Tiotropium Respimat® or Tiotropium Handihaler® within one year prior to screening • Exacerbations during 6 weeks prior to screening.
Test product(s)	Tiotropium Respimat® (Spiriva® Respimat®)
dose	5 µg once daily, given as 2.5µg, two puffs.
method and route of administration	inhalation
Comparator product(s)	Tiotropium Handihaler® (Spiriva®)
dose	18µg once daily
method and route of administration	inhalation
Duration of treatment	• Screening period: 1 week • Treatment period: 8 weeks (2*4 weeks treatment periods)
Statistical methods	Primary endpoint will be analysed using Restricted Maximum Likelihood Estimation based Mixed-effects Model for Repeated Measures analysis to obtain adjusted means for the treatment groups. This model will include treatment and period as fixed effects and patient as a random effect. Compound symmetry will be used as a covariance structure for within-patient variation. Secondary endpoints will be analysed using the same model as the primary endpoint. Chi-squared test will be performed to analyse proportion of patients indicating preference. Descriptive statistics will be used for safety analysis.

FLOW CHART

Trial Periods	Screening Period	Randomization	Randomised Treatment Period		Follow-up Period
Visit	**1**	**2**	**3[5]**	**4**	**5[2]**
Weeks	**-1**	**0**	**4**	**8**	**12**
Days	**-7**	**1**	**28**	**56**	**84**
Visit window (days)	**-7 days**	**N/A**	**±1 day**	**±1 day**	**±2 days**
Informed consent	X				
Demographics	X				
Medical history	X				
Rescue Medication Training	X				
Tiotropium Respimat® Training		X	X		
Tiotropium Handihaler® Training		X	X		
Physical examination (with Vital signs)	X			X[1]	
Laboratory tests−Blood and urine	X			X[1]	
12 lead-ECG	X			X[1]	
pregnancy testing (urine)	X			X	
Screening/Qualifying Pulmonary Function Test (FEV1 and FVC), seated[6]	X				
Smoking Status	X				
Review of in-/exclusion criteria	X	X			
Randomization		X			
Dispense trial medication		X	X		
Dispense rescue medication	X[3]	X[3]	X[3]		
Dispense patient diary	X	X	X		
Dispense trial identification card (TIC)	X				
Collect Respimat® or Handihaler®			X	X[1]	
Collect Rescue Medication		X[4]	X[4]	X[4]	
Collect and review patient diary		X	X	X[1]	
Adverse events		X	X	X[1]	X
Compliance check			X	X	
Concomitant therapy	X	X	X	X[1]	X[1]
PASAPQ: question 1-14			X	X	
PASAPQ: question 15-16				X	
Conclusion of Patient participation				X[1]	

1. To be completed by all patients including those who discontinue early because visit 4 is the end of study treatment.
2. Visit 5 is the end of study visit.
3. To be dispensed from Visit 1 to Visit 3.
4. Rescue medication should be collected at next visit whether the patient use or not.
5. At Visit 3, the investigator will instruct the patient how to use first study drug intake on site. To avoid overdosing, the investigator needs to confirm whether the patient has already taken the medication at home on the day of V3 visit. If so, the patient will not take the first dose of the newly assigned treatment at Visit 3.
6. Historical data from spirometry measurements within the past 6 months either at the site or at the other hospital may be used. If the measurements are not performed at the trial site a signed copies of the measurement printouts must be provided to the trial site for source data verification. In case several qualifying spirometry measurements are available, the most recent one should be referred to as long as it was not performed during an exacerbation. Patients may not be randomised to the study without the availability of spirometry data at the actual study site.

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ABBREVIATIONS

AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine Aminotransferase
AST	Aspartate Transaminase
BAC	Benzalkonium Chloride
BI	Boehringer Ingelheim
[redacted]	[redacted]
CA	Competent Authority
CI	Confidence Interval
COPD	Chronic Obstructive Pulmonary Disease
CRA	Clinical Research Associate
CRF	Case Report Form, paper or electronic (sometimes referred to as “eCRF”)
CTM	Clinical Trial Manager
CTP	Clinical Trial Protocol
DBL	Database Lock
DPIs	Drypowder Inhalers
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
[redacted]	
eDC	Electronic Data Capture
EDTA	Ethylenediaminetetraacetic Acid
FC	Flow Chart
FEV	Forced Expiratory Volume
FUP	Follow Up
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HCG	Human Chorionic Gonadotropin
HCPs	Health care professionals
IB	Investigator’s Brochure
ICH	International Council on Harmonization

IEC	Independent Ethics Committee
IMPs	Investigational Medicinal Products
IPVs	Important Protocol Violations
IRB	Institutional Review Board
ISF	Investigator Site File
IUD	Intrauterine Device
LRTI	Lower respiratory tract infection
MCID	Minimal Clinically Important Difference
MDIs	Metered-dose Inhalers
MedDRA	Medical Dictionary for Drug Regulatory Activities
MMRM	Mixed effect repeated measures model
PASAPQ	Patient satisfaction and preference questionnaire
PFT(s)	Pulmonary function test(s)
pMDIs	Pressurized Metered Dose Inhalers
PRN	As needed
REP	Residual Effect Period
SAE	Serious Adverse Event
SABA	Short-acting β Agonist
SAMA	Short-acting Muscarinic Antagonist
SGOT	Serum Glutamic-oxaloacetic Transaminase
SGPT	Serum Glutamic-pyruvic Transaminase
SMI	Soft Mist Inhalers
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reactions
TMF	Trial Master File
TIC	Trial Identification Card
TIOSPIR	Tiotropium Safety and Performance in Respimat®
ULN	Upper Level of Normal
URI	Upper Respiratory Infection
WHO	World Health Organization
WOCBP	Woman of childbearing potential

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

Chronic obstructive pulmonary disease (COPD) is a complex disease with increasing morbidity and mortality [P13-09537]. It is estimated that by year 2020, COPD will be the third leading cause of mortality worldwide [R18-2760]. COPD represents a significant societal and economic burden throughout the world [P13-09537], [P18-08335]. Current strategy for the management of COPD recommends the use of inhaled medication for relieving symptoms and preventing complications and exacerbations [P13-09537].

Despite advancement in medical treatment, poor adherence remains a major challenge in the management of COPD [R15-5710], and adversely impacts health outcomes, quality of life, and healthcare expenditures [R18-2759]. Between 40% and 60% of patients with COPD do not adhere to the prescribed regimen [P13-04349]. Factors impacting adherence in COPD may be associated with patients (health beliefs, cognitive ability, co-morbidities, and psychological condition), drug treatment (method of drug administration, dosing regimen, polypharmacy, and side effects), and societal factors (access to medication, social support, device training, and follow-up) [P13-04349].

Efficient delivery of inhaled medication is essential for the success of COPD therapy [P13-09537], [P05-02701]. The inhaler device may contribute to optimal drug delivery [P06-04747] and also impact patient adherence [P10-05294]. A wide range of inhaler devices are available, including pressurized metered dose inhalers (pMDIs), drypowder inhalers (DPIs), nebulizers, and soft mist inhalers (SMI) [P10-05294]. Each type of device has its own advantages and disadvantages [P06-04748].

When considered independently of drug class, choice of inhaler device depends on availability and cost of inhalation treatment, clinical setting, age of the patient, dosing regimen, physician and patient acceptability/preference, and ability of the patient to use the inhaler[P05-02701], [P10-05294], [P06-04749]. Patient satisfaction, and consequently adherence, largely depend on the patients' attitude towards the inhaler and their ability to use the device [P05-02701], [R18-2765].

Patient satisfaction with their inhaler is an acknowledged predictor of treatment adherence [R07-1426], [R18-2768], [R18-2761], [R18-2764]. In a large, multinational, cross-sectional, real-world survey reported by Chrystyn et al [R18-2764], patient satisfaction with their inhaler was closely linked to treatment compliance and loosely associated with fewer exacerbations and lower utilization of health-care resources [R18-2761]. Reporting of patient satisfaction with inhalers is therefore gaining increasing attention and is now recognized as an important patient-reported outcome in clinical trials involving patients with COPD or asthma [R18-2763].

1.2 DRUG PROFILE

Tiotropium:

Tiotropium is a non-chiral, quaternary, ammonium compound developed as a long-acting anticholinergic bronchodilator for treatment of bronchospasm and dyspnoea in patients with COPD. It is two to four-times more potent than ipratropium bromide and has a slower onset of action. The duration of action for tiotropium exceeds 24 hours compared to 6 hours for ipratropium bromide. As with other inhaled quaternary anticholinergic agents, tiotropium does not cross the blood-brain barrier to any significant extent. It has low oral bioavailability.

Inhalation Device: Handihaler®
Handihaler® belongs to the single dose dry powder inhalers (DPIs). The drug powder is stored in the capsules which is placed in the centre chamber of the device and is by pressing the pierced button.

Inhalation Device: Tiotropium Respimat® inhaler

The Tiotropium Respimat® is a multi-dose inhaler that differs from currently marketed dry powder and pressurized metered-dose inhalers (MDIs) in several ways. It relies on a spring, rather than propellants, to generate a slow-moving cloud from a solution of medication contained in the cartridge. The energy from turning the transparent base to the right (half a turn) compresses a spring, which draws a pre-defined, metered volume of solution through the capillary tube and into a micro-pump. When the dose-release button is pressed, the energy released forces the solution through the unblock; this produces a slow-moving cloud over approximately 1.5 seconds. The total delivered volume is 22.1 μL per dose (i.e. 2 actuations), and the fine particle fraction around 60%. The Tiotropium Respimat® also offers technological advances that enhance the proper use by the patient (e.g. a dose indicator and a locking mechanism that prevent tail-off of dosing after the declared number of doses)

1.3 RATIONALE FOR PERFORMING THE TRIAL

The purpose of this study is to evaluate the patient acceptability/preference of Tiotropium Respimat® comparing with Tiotropium Handihaler® in patients with chronic obstructive pulmonary disease (COPD). The validated PASAPQ will be applied to evaluate the outcomes. Based on the previous studies, Tiotropium Respimat® showed better patient acceptability/preference compared with two DPIs, Diskus or Turbuhaler using PASAPQ as measurement. However, no studies have been done to compare the patient acceptability/preference between Tiotropium Respimat® and Tiotropium Handihaler®. The TIOSPIR study showed the efficacy of tiotropium via Respimat® or Handihaler® was similar in terms of lung function improvement and COPD exacerbation prevention. In real-life practice, the effectiveness might be influenced by different factors; including the use of inhalers. The patient's acceptability/preference on the inhalers can impact the adherence to therapy, and then possibly the control of disease. Therefore, we consider it is of clinical importance to investigate the patient acceptability/preference between Tiotropium Respimat® and Tiotropium Handihaler®, so that HCPs can refer to this trial to make appropriate decision on the choice between these two devices.

1.4 BENEFIT - RISK ASSESSMENT

Tiotropium HandiHaler® (18 µg inhalation capsules) and tiotropium inhalation solution 5 µg (2 × 2.5 µg) delivered via the Respimat® Inhaler are both widely approved for the maintenance treatment of patients with COPD (including chronic bronchitis and emphysema). Both products are effective drugs for the maintenance treatment of COPD and have demonstrated benefits to patients on multiple clinical endpoints including lung function, health-related quality of life, and exacerbations.

All classes of maintenance respiratory medications are permitted throughout this trial. Only non-study drug inhaled anticholinergics will need to be discontinued. Patients will have access to all available treatments. Exacerbations may be treated with oral steroids and antibiotics according to medical need and the trial medication may be continued throughout the treatment period or after the episode at the discretion of the patient and the investigator. Safety will be monitored at site visits.

2. TRIAL OBJECTIVES AND ENDPOINTS

2.1 MAIN OBJECTIVES, PRIMARY AND SECONDARY ENDPOINTS

2.1.1 Main objectives

The objective of this study is to investigate the patient acceptability/preference of Respimat® compared with Handihaler® in patients with moderate to severe chronic obstructive pulmonary disease (COPD) to demonstrate the superiority of Respimat®.

2.1.2 Primary endpoint(s)

The primary endpoint of the study is the performance domain of the Patient satisfaction and preference questionnaire (PASAPQ) after 4 weeks of treatment.

The PASAPQ is a two-part questionnaire. Part I consists of 14 questions. The first 13 questions generate the Performance domain (7 questions) and the Convenience domain (6 questions), which form a Total Score (all 13 questions). Question 14 asks for overall satisfaction with the device used in the study. Part II consists of stand-alone questions concerning a subject's device preference (question 15) and willingness to continue use (question 16). The first 14 questions in PASAPQ have Likert-type response options of 1 (very dissatisfied) to 7 (very satisfied). Question 15 ask for a response to indicate the preference for the trial device. Question 16 asks for a response between 0 and 100 with 0 indicating not willing to continue using the trial device and 100 indicating definitely willing to continue.

The performance domain score is the sum of 7 questions within the domain (Q1, Q2, Q3, Q4, Q5, Q10 and Q11) and then transformed to a 0 (least) to 100 (most) point scale.

2.1.3 Secondary endpoint(s)

1. PASAPQ total score after 4 weeks of treatment. Total score is the sum of 13 questions (Q1-Q13) and then transformed to a 0 (least) to 100 (most) point scale.
2. Proportion of patients indicating preference which will be administered at Week 8.
3. Overall Satisfaction Question Score from PASAPQ will be administered at week 4 and 8.
4. Score on willingness to continue will be administered at week 8.

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

This is a multicentre, randomised, open-label, two-way cross-over study to compare the patient acceptability/preference between Tiotropium Respimat® and Tiotropium Handihaler®.

Following an initial screening assessment, eligible patients will be randomized to the open-label phase of the trial during which one group of patients will received 5µg tiotropium (2 puffs of 2.5µg) administered once daily by Respimat® (T1), the other group will receive 18µg tiotropium once daily by Handihaler® (T2) for 4 weeks. After the first 4-week treatment, these two groups of patients will be switched to the second period treatment.

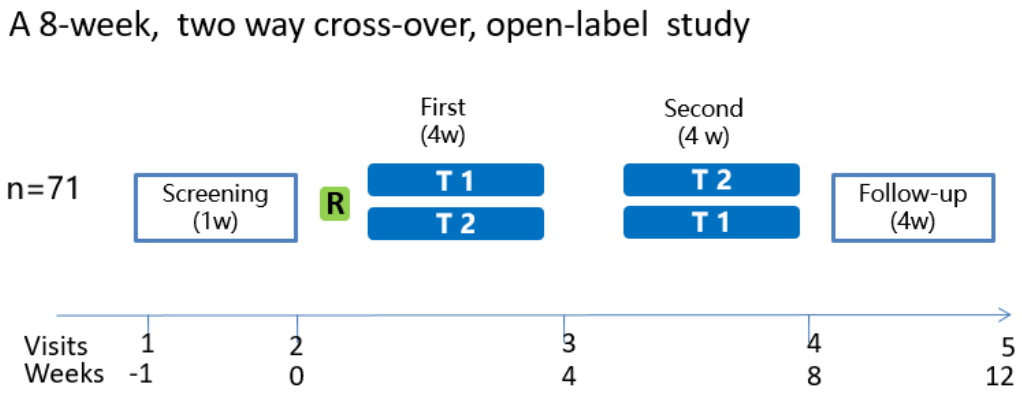

Figure 3.1:1 A 8-week, two way cross-over, open-label study

Patients who withdraw prematurely from the randomised treatment period will be followed up regarding COPD exacerbations, SAEs and vital status until their predicted normal exit date from the trial.

Refer to the Flow Chart (FC) for an overview of procedures to be done at each visit.

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

A cross-over design is appropriate for the evaluation of patients' assessment on their acceptability/preference with the inhalers. Four-week treatment with inhalers would suffice for patients to evaluate the inhalers. As efficacy endpoints are not evaluated in this trial, no wash-out period is required.

3.3 SELECTION OF TRIAL POPULATION

A sufficient number of patients (approximately 71) will be randomized to ensure that a minimum of 60 patients of either sex, 40 years of age or older, with a diagnosis of COPD will

complete the 8-week treatment study. Approximately 7 sites will be initiated in mainland China. Each site is expected to enter approximately 10 patients within 6 months after study initiation.
Screening of patients for this trial is competitive, i.e. screening for the trial will stop at all sites at the same time once a sufficient number of patients has been screened. Investigators will be notified about screening completion and will then not be allowed to screen additional patients for this trial.

A log of all patients enrolled into the trial (i.e. who have signed informed consent) will be maintained in the Investigator Site File (ISF) irrespective of whether they have been treated with investigational drug or not.

If a patient is enrolled in error (does not meet all inclusion criteria or meets one or more exclusion criteria on the day of enrolment), the sponsor should be contacted immediately.

3.3.1 Main diagnosis for trial entry

Patients of either sex, 40 years of age or older, with a diagnosis of COPD will be selected as subjects for the trial.

Please refer to Section 8.3.1. (Source Documents) for the documentation requirements pertaining to the in- and exclusion criteria.

3.3.2 Inclusion criteria

1. All patients must have a diagnosis of COPD and must meet the following spirometric criteria at Visit 1 (Screening).

- Relatively stable, moderate to severe airway obstruction with a post-bronchodilator 30% ≤FEV_1 ≤80% of predicted normal and FEV_1/FVC <70%. Spirometry should be done at baseline and approximately 1/2 hour following 4 inhalations of albuterol.

  Male = exp [−10.61669 + 2.27078 × ln (− in cm) + 0.06622 × ln (age in year) + Mspline]
  Female = exp [−9.69716 + 2.09385 × ln (− in cm) + 0.02006 × ln (age in year) + Mspline]

  Historical data from spirometry measurements within the past 6 either at the site or at the other hospital may be used. If the measurements are not performed at the trial site a referral letter and signed copies of the measurement printouts must be provided to the trial site for source data verification. In case several qualifying spirometry measurements are available, the most recent one should be referred to as long as it was not performed during an exacerbation. Patients may not be randomised to the study without the availability of spirometry data at the actual study site.

2. Male or female, age: 40-80 years
3. Patients must be current or ex-smokers with a smoking history of ≥ 10 pack years. (Patients who have never smoked cigarettes must be excluded).

$$\text{Pack Years} = \frac{Number\ of\ cigarettes/day}{20\ cigarettes/pack} \times \text{year of smoking}$$

4. Signed and dated written informed consent in accordance with International Council on Harmonization (ICH) ICH-GCP and local legislation prior to admission to the trial
5. Patients must be able to inhale medication from the Tiotropium Respimat® and Tiotropium HandiHaler®
6. Patients must be able to perform all study related procedures, and must be able to maintain records (patient diary) during the study period as required by the protocol

3.3.3 Exclusion criteria

1. Had visual, cognitive, or motor impairment that, as judged by the investigator, did not allow the patient to independently read and complete the PASAPQ questionnaire
2. Patients have any previous experience of using Respimat® or Handihaler® or generic Handihaler within one year prior to screening.
3. Patients with significant diseases other than COPD will be excluded. A significant disease is defined as a disease or condition which, in the opinion of the investigator, may put the patients at risk because of participation in the study or may influence either the results of the study or the patient's ability to participate in the study.
4. All patients with an Aspartate Transaminase (AST) (serum glutamic-oxaloacetic transaminase, SGOT) >80 IU/L, Alanine Aminotransferase (ALT) (Serum Glutamic-pyruvic Transaminase, SGPT) >80 IU/L, Bilirubin >2.0 mg/dL or Creatinine >2.0 mg/dL will be excluded regardless of the clinical condition. Repeat laboratory evaluation will not be conducted in these subjects.
5. Patients with a recent history (i.e., one year or less) of myocardial infarction.
6. Patients who have been hospitalized or being treated for heart failure within the past year.
7. Patients with any unstable or life-threatening cardiac arrhythmia requiring intervention or change in drug therapy during the last year.
8. Patients with a history of cancer, other than treated basal cell carcinoma, within the last five years.
9. Known active tuberculosis.
10. Patients with a history of asthma, cystic fibrosis, bronchiectasis, interstitial lung disease, or pulmonary thromboembolic disease
11. History of thoracotomy with pulmonary resection. Patients with a history of thoracotomy for other reasons should be evaluated as per exclusion criterion 3.
12. Patients with any respiratory tract infection or COPD exacerbation in the 6 weeks prior to the initial screening visit (Visit 1).

13. Patients with known symptomatic prostatic hypertrophy or bladder neck obstruction. Patients whose symptoms are controlled on treatment may be included.
14. Patients with known narrow-angle glaucoma.
15. Use of systemic corticosteroid medication at unstable doses (i.e., less than six weeks on stable dose) or at doses in excess of the equivalent of 10 milligrams (mg) prednisolone per day.
16. Patients who regularly use daytime oxygen therapy for more than 1 hour per day and in the investigator's opinion will be unable to abstain from the use of oxygen therapy.
17. Pregnant or nursing women or women of childbearing potential not using a medically approved means of contraception (i.e., oral or injectable contraceptives, intrauterine devices (IUD) or diaphragm with spermicide, or Norplant®).
18. Significant alcohol or drug abuse within the past 12 months
19. Known hypersensitivity to anticholinergic drugs, lactose, benzalkonium chloride (BAC), ethylenediaminetetraacetic acid (EDTA) or any other components of the HandiHaler® or Respimat® inhalation solution delivery system.
20. Patients currently in any pulmonary rehabilitation program or scheduled to participate in any such program during the study period.
21. Previous participation in this study. (The patient cannot re-enroll into this study.)
22. Patients who are currently participating in another interventional study.

3.3.4 Withdrawal of patients from treatment or assessments

Patients may potentially be withdrawn from trial treatment or from the trial as a whole ("withdrawal of consent") with very different implications, please see sections 3.3.4.1 and 3.3.4.2 below.

Every effort should be made to keep the randomised patients in the trial.
Measures to control the withdrawal rate include careful patient selection, appropriate explanation of the trial requirements and procedures prior to randomization, as well as the explanation of the consequences of withdrawal.

Patients who fail to complete all treatment and PASAPQ as required in the protocol, will not be considered complete. The decision to withdraw from trial treatment or from the whole trial as well as the reason must be documented in the patient files and Case Report Form (CRF).

3.3.4.1 Discontinuation of trial treatment

An individual patient will discontinue trial treatment if:

- The patient wants to discontinue trial treatment, without the need to justify the decision.
- The patient has repeatedly shown to be non-compliant with important trial procedures and, in the opinion of both, the investigator and sponsor representative, is not willing or able to adhere to the trial requirements in the future.

- The patient needs to take concomitant medication that interferes with the investigational medicinal product or other trial treatment.
- The patient can no longer receive trial treatment for medical reasons (such as surgery, adverse events, other diseases, or pregnancy).

In case of a temporary reason, trial treatment should be restarted if medically justified, please see Section 4.1.4.

Even if the trial treatment is discontinued, the patient remains in the trial and, given his/her agreement, will undergo the procedures for early treatment discontinuation and follow up as outlined in the Flow chart and section.

3.3.4.2 Withdrawal of consent to trial participation

Patients may withdraw their consent to trial participation at any time without the need to justify the decision.

If a patient wants to withdraw consent, the investigator should be involved in the discussion with the patient and explain the difference between trial treatment discontinuation and withdrawal of consent to trial participation, as well as explain the options for continued follow up after trial treatment discontinuation, please see Section 3.3.4.1 above.

3.3.4.3 Discontinuation of the trial by the sponsor

Boehringer Ingelheim reserves the right to discontinue the trial 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 Good Clinical Practice (GCP), the trial protocol, or the contract impairing the appropriate conduct of the trial.

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

4. TREATMENTS

4.1 INVESTIGATIONAL TREATMENTS

4.1.1 Identity of the Investigational Medicinal Products (IMPs)

The test product Tiotropium Respimat® (Spiriva® Respimat®), and the comparator product Tiotropium Handihaler® (Spiriva®) will be supplied by Boehringer Ingelheim Pharma GmbH & Co. KG, Germany. The composition of the drugs is described as follow:

Table 4.1.1:1 Test product: Tiotropium Respimat® (Spiriva® Respimat®)

Substance:	Tiotropium
Pharmaceutical formulation:	inhalation solution
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG, Germany
Unit strength:	2.5µg per puff, 60 puffs with 1 Respimat® Inhaler
Posology:	5 µg once daily, given as 2.5µg per puff, two puffs
Method and route of administration:	Oral Inhalation via Respimat®

Table 4.1.1:2 Comparator products: Tiotropium Handihaler® (Spiriva®)

Substance:	Tiotropium
Pharmaceutical formulation:	Inhalation Powder
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG, Germany
Unit strength:	30 capsules with 1 Handihaler® device
Posology:	18µg once daily
Method and route of administration:	Oral Inhalation via Handihaler®

Tiotropium Respimat® and Tiotropium Handihaler® both have the same active ingredient in the medicine: tiotropium bromide.
Tiotropium Respimat® delivers a very slow-moving mist that is designed to help the patient inhale the medicine easier. The amount of medicine the patient takes in does not depend on how fast they are able to inhale. Patients receive one dose per day, which lasts for 24 hours.

The medicine in Tiotropium Handihaler® comes in a dry powder contained in a capsule that is put into a special inhaler. The patient takes the medicine by breathing in two inhalations through the Handihaler®. The medicine lasts for 24 hours, so patients take one dose (two inhalations) of Tiotropium Handihaler® per day in the morning. Patients use a new capsule for each dose.

4.1.2 Selection of doses in the trial and dose modifications

Tiotropium Respimat® and Tiotropium Handihaler® have been available on the market, so dose selection please follow the local package inserts, that is, randomized patients will receive tiotropium 5 µg inhalation solution from the Respimat® inhaler or tiotropium inhalation capsules 18 µg delivered by the HandiHaler®.

4.1.3 Method of assigning patients to treatment groups

Technical and statistical features of the process of treatment sequence allocation are provided in Section 7.

Each patient will get a patient number when informed consent is signed at Visit 1and a randomization number at Visit 2, which will be recorded in the electronic case report form (eCRF).

Since the medication dispensed to the patient is one device of Respimat® or Handihaler® each time, only the device type will be recorded in the eCRF and there will be no medication number.

After assessment of all in- and exclusion criteria, each eligible patient will be randomised to the open-label phase of the trial (Visit 2) during which one group of patients will received 5µg tiotropium (2 puffs of 2.5µg) administered once daily by Respimat® (T1), the other group will receive 18µg tiotropium once daily by Handihaler® (T2) for 4 weeks.

Randomisation of patients to treatment sequence is based on randomization envelope at visit 2. After the first 4-week treatment, these two treatment groups of patients will switch to the Tiotropium Respimat® and Tiotropium Handihaler® vice versa. The appropriate randomization number and correspondent device type will be assigned by randomization envelope at Visit 2. Note that there is no medication number exists during the study and medication device type should be recorded in eCRF.

4.1.4 Drug assignment and administration of doses for each patient

At Visit 1, all patients should be trained on the use of rescue medication Salbutamol Sulphate Aerosol (pMDI).

At Visit 2 and Visit 3, patients will be assigned to one of the two treatment groups. At each of these visits, patients will be trained on how to use the Tiotropium Respimat® or Handihaler® properly.

4.1.4.1 Instructing the patient

Detailed written instructions and training for the use of the Respimat®, Handihaler® and Salbutamol Sulphate Aerosol will be given to the patient at Visit 2 and 3 (see Section 10.1, 10.2 and 10.3).

The Respimat® inhalers and cartridges will be dispensed to patients unassembled and packaged in one box (each box containing one Tiotropium Respimat® inhaler and one Tiotropium Respimat® cartridge), and patients will be instructed on how to prepare the inhaler for use, including inserting the cartridge into the inhaler and priming the unit, and on using the Tiotropium Respimat® inhaler.

Note: Patients who are randomized to Tiotropium Respimat® must follow the instructions for this inhaler in Section 10.1. These patients must be instructed to take two puffs of Tiotropium Respimat® one time a day.

Patients who are randomized to Tiotropium Handihaler® must follow the instructions for this product according to Section 10.2. These patients must take one capsule of tiotropium bromide once daily with the HandiHaler® device at the same time of day.

Table 4.1.4.1: 1 Dosage and treatment schedule

Treatment	Visit Number	Tiotropium Respimat®	Tiotropium Handihaler®
		µg/daily	
1	Visit 2 - Visit 3 (Week 0-4)	5µg (2 puffs of 2.5µg)	-
	Visit 3 - Visit 4 (Week 4-8)	-	18µg (one capsule)
2	Visit 2 - Visit 3 (Week 0-4)	-	18µg (one capsule)
	Visit 3 - Visit 4 (Week 4-8)	5µg (2 puffs of 2.5µg)	-

The Tiotropium Respimat® contains 60 puffs per cartridge and 2.5µg tiotropium per puff, with drug concentration of 0.2262 mg/ml (calculated as tiotropium) after preparing the inhaler for first use. There is enough medicine for 30 days when it is used as two puffs of Tiotropium Respimat® one time a day.

Each Tiotropium Handihaler® contains 30 capsules with the HandiHaler® device. Each capsule contains 18µg (as tiotropium, equivalent to 22.5µg tiotropium bromide monohydrate), enough for 30 days if used as one capsule once daily with the HandiHaler® device.

Two treatment groups of patients will be assigned to therapy with either Tiotropium

Respimat® or Tiotropium HandiHaler® for 4 weeks respectively before completing the PASAPQ at a single visit to the study site.

4.1.4.2 Trial medication administration at home

Patients will be instructed to refer to the detailed written inhaler directions provided at either Visit 2 or Visit 3, or to phone the site if they have questions.

The patient will record whether he/she took the daily doses (number of puffs orcapsule) of the medication in a patient diary. If a patient misses a dose, he/she should take the next dose at the next scheduled time and make a note of the missed dose in his/ her patient diary.

4.1.4.3 Trial medication return

All used and unused trial medication, used device will be returned to the clinic at the next treatment visit.
Any inhaler that is reported to have malfunctioned by the patient or study staff should be returned to BI for further investigation. Please see the ISF for specific instructions regarding the procedure to return such devices.

Note: Tiotropium HandiHaler® capsules are to be used only with the HandiHaler® device. Tiotropium Respimat® cartridges are to be used only with the Respimat® inhaler.

4.1.5 Blinding and procedures for unblinding

Not applicable.

4.1.6 Packaging, labelling, and re-supply

The investigational products will be provided by BI. They will be labelled in accordance with the principles of Good Manufacturing Practice (GMP). Re-supply to the sites will be managed via site staff and CRA, which will also monitor expiry dates of supplies available at the sites.

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

4.1.7 Storage conditions

Trial medication must be stored under the recommended storage conditions indicated on the drug information leaflets.

- Tiotropium Respimat®: Do not freeze. Store in a safe place out of the reach of children!
- Tiotropium Handihaler®: Do not store above 25°C. Do not freeze. Store in a safe place out of the reach of children!
- Salbutamol Sulphate Aerosol: Store under 30°C. Keep away from light and avoid freezing and direct sunlight.

A temperature log must be maintained by the site to make certain that the drug supplies are stored at the correct temperature. If the storage conditions are found to be outside the

specified range, the Clinical Trial Manager (CTM) for the study should be contacted immediately.

Trial medication must be stored securely at the study sites, out of reach of children and be protected from freezing, e.g. in a locked cupboard or at a pharmacy. It may only be dispensed to trial patients fulfilling the inclusion and exclusion criteria by authorized study personnel as documented in the ISF. Receipt, usage, and return of the study medication must also be documented on the respective forms in the ISF.

4.1.8 Drug accountability

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

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

IMPs are not allowed to be used outside the context of this protocol. They must not be forwarded to other investigators or clinics. Patients should be instructed to return unused IMPs.

The investigator or designee must maintain records of the product's delivery to the trial site, the inventory at the site, the use by each patient, 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, medication device type and trial patients. The investigator or designee will maintain records that document adequately that the patients were provided the doses specified by the Clinical Trial Protocol (CTP) and reconcile all IMPs received from the sponsor. At the time of return to the sponsor, the investigator or designee must verify that all unused or partially used drug supplies have been returned by the clinical trial patient and that no remaining supplies are in the investigator's possession.

4.2 OTHER TREATMENTS, EMERGENCY PROCEDURES, RESTRICTIONS

4.2.1 Other treatments and emergency procedures

- **Rescue medication(s)**

Salbutamol Sulphate Aerosol (pMDI) will be provided as rescue medication. Administration of rescue medication can occur at any time during the study. The number of puffs used for rescue will be recorded by the patient in the Patient Diary. In the case of potentially life-

threatening COPD exacerbations, any and all therapies and interventions deemed medically necessary by the treating physician could be prescribed.

The following medications are allowed to control acute exacerbations as medically necessary during the treatment period.

1. As needed (PRN) Salbutamol Sulphate Aerosol (pMDI) (provided by [redacted] and to be recorded on the Patient Diary).
2. Temporary of nebulised short-acting β agonist (SABA) and/or short-acting muscarinic antagonist (SAMA) can be allowed during exacerbation.
3. Temporary increases in the dose of theophylline preparations of up to 7 days each are allowed during the study. Temporary increases in the dose or addition of, oral steroids of up to 7 days each are allowed during the study.
4. The use of antibiotics is not restricted and may be used as medically necessary for exacerbations and other infections.

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

Table 4.2.2.1:1 Restrictions for concomitant treatment

Drug class	Screening period	Treatment period
Oral corticosteroids[1] (≤ 10 mg prednisone per day)	Permitted	Permitted
Inhaled corticosteroids[1]	Permitted	Permitted
Theophylline[1]	Permitted	Permitted
Mucolytics[1]	Permitted	Permitted
Antihistamines, Antilerkotrienes, Cromolyn[1]	Permitted	Permitted
Inhaled long-acting-beta-adrenergics[1]	Permitted	Permitted
Oral beta-adrenergics[1]	Permitted	Permitted
Inhaled short-acting-beta-adrenergics	PRN as supplied for study only - recorded in patient Diary	PRN as supplied for study only - recorded in patient Diary

Inhaled short-acting-anticholinergics	Only for exacerbation treatment.	Only for exacerbation treatment.
Inhaled long-acting-anticholinergics	Not permitted	Trial medication

1. If stabilized for 6 weeks before screening (visit 1)

The following inhalation devices or medications are **not allowed** during the screening period or the treatment period.

- Inhalation devices other than the investigational devices which have not been stably used for 6 weeks prior to the screening period.
- Use of systemic corticosteroid medication at unstable doses (i.e., less than six weeks on stable dose) or at doses in excess of the equivalent of 10 milligrams (mg) prednisolone per day.
- Long-acting anticholinergic drugs other than the investigational drugs during the randomization treatment period.

4.2.2.2 Restrictions on diet and life style

No restrictions on diet or life style.

4.2.2.3 Contraception requirements

For tiotropium, no clinical data on exposed pregnancies are available. Preclinical studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal / foetal development, parturition or postnatal development.

Clinical data from nursing women exposed to tiotropium are not available. Based on lactating rodent studies, a small amount of tiotropium is excreted into breast milk. Therefore, tiotropium should not be used in pregnant or nursing women unless the expected benefit outweighs any possible risk to the unborn child or the infant. Pregnant and nursing women are generally excluded from tiotropium clinical trials.

Clinical data on fertility are not available for tiotropium. A non-clinical study performed with tiotropium showed no indication of any adverse effect on fertility.

Woman of childbearing potential (WOCBP) (for the definition please refer to Section 3.3.3.) and men able to father a child must use two medically approved methods of birth control throughout the trial, and for a period of at least 30 days after last trial drug intake. They must use one barrier method, i.e. condom or occlusive cap with spermicide, or vasectomized partner, and one highly effective non-barrier method including oral, injected or implanted hormonal contraceptives, intrauterine device or system.

Male patients:
Men whose partner is a WOCBP must use a condom during the study, and for a period of at least 30 days after the last dose of study drug.

Female patients:
WOCBP must use a highly effective method of birth control per ICH M3 (R2) that results in a low failure rate of less than 1% per year when used consistently and correctly during the study, and for a period of at least 30 days after the last dose of study drug.

Acceptable methods of birth control for this trial are:

- Combined (estrogen and progestogen containing) hormonal birth control that prevents ovulation (oral, intravaginal, transdermal).
- Progestogen-only hormonal birth control that prevents ovulation (oral, injectable, implantable).
- Intrauterine device (IUD) or intrauterine hormone-releasing system (IUS).
- Bilateral tubal occlusion
- Vasectomised sexual partner with documented absence of sperm.

Or

Patients must abstain from male-female sex. This is defined as being in line with the preferred and usual lifestyle of the patient. Periodic abstinence e.g. calendar, ovulation, symptothermal, post-ovulation methods; declaration of abstinence for the duration of exposure to study drug; and withdrawal are not acceptable.

4.3 TREATMENT COMPLIANCE

The patient will enter, in the Patient Diary, the number of puffs or capsules of study medication taken. The investigator/study staff will review these records with the patient at each study visit to assess treatment compliance. The investigator / study staff should also examine the inhalers used since last visit. The Tiotropium Respimat® dose indicator should concur with the patient diary. And the residual of Tiotropium Handihaler® should be in accord with the patient diary. If compliance rate is not between 80-120%, site staff will explain to the patient the importance of treatment compliance, and the reason of non-compliance should be recorded in the source document. CTM should be notified if patients continue to be non-compliant. Patients will be asked to return all used and unused study medication to the clinic at each scheduled visit and at the end of study.

The study site must transfer data regarding study medication use and rescue medication from Patient Diary to the eCRF within 1 week after each visit.

5. ASSESSMENTS

5.1 ASSESSMENT OF EFFICACY

5.1.1 Primary endpoint

The primary endpoint for patient preference is the performance domain of the Patient Satisfaction and Preference Questionnaire (PASAPQ).

The PASAPQ is a two-part questionnaire. Part I consists of 14 questions. The first 13 questions generate the Performance domain (7 questions) and the Convenience domain (6 questions), which form a Total Score (all 13 questions). Question 14 asks for overall satisfaction with the device used in the study. Part II consists of stand-alone questions concerning a subject's device preference (question 15) and willingness to continue use (question 16). The first 14 questions in PASAPQ have Likert-type response options of 1 (very dissatisfied) to 7 (very satisfied). Question 15 ask for a response to indicate the preference for the trial device. Question 16 asks for a response between 0 and 100 with 0 indicating not willing to continue using the trial device and 100 indicating definitely willing to continue.

The performance domain score is the sum of 7 questions within the domain (Q1, Q2, Q3, Q4, Q5 Q10 and Q11) and then transformed to a 0 (least) to 100 (most) point scale.

5.1.2 Secondary endpoints

Total score of PASAPQ:

Total score domain containing 13 questions will be evaluated at Visit 3 (week 4) and Visit 4 (week 8).

The proportion of patients indicating preference:

Preference for either inhalation device will be evaluated at Visit 4 (week 8).

Overall Satisfaction Question Score from PASAPQ:

The answer to the PASAPQ question "Overall, how satisfied are you with your inhaler" measured using a 7-point Likert scale (1 meaning very dissatisfied and 7 means very satisfied) at Visit 3 (week 4) and Visit 4 (week 8).

Willingness to continue:

Question 16 asks for a response between 0 and 100 with 0 indicating not willing to continue using the trial device and 100 indicating definitely willing to continue, which will be evaluated at Visit 4 (week 8).

5.2 ASSESSMENT OF SAFETY

5.2.1 Physical examination

A full physical examination will be completed on all patients at screening (Visit 1) and Visit 4.All clinically relevant abnormal findings at the screening visit will be recorded on the Medical History/Baseline Conditions eCRF page. Clinically relevant new abnormal findings or worsening of baseline conditions detected at follow-up physical examinations will be recorded as AEs on the appropriate eCRF page. All (S)AEs, including those persisting after individual patient's end of trial must be followed up until they have resolved, have been assessed as 'chronic' or 'stable', or no further information can be obtained.

5.2.2 Vital signs

Pulse rate and blood pressure will be measured and recorded at screening Visit 1 and Visit 4.

Vital Status for patients who discontinue early:

The objective of obtaining vital status is to ascertain information on health status in patients who withdraw prematurely from randomized treatment up to the previously projected exit date from the trial. Depending on the time of discontinuation, there will be 1 or 2 calls made to the patients to assess their vital status. The site must make at least 2 attempts to contact the patient at each projected time point. The following information should be obtained during these phone calls: 1) date of follow up; 2) status (alive, deceased or lost to follow up); if lost to follow up, last date known alive, if patient is deceased the date and cause of death must be recorded. In this case the site must complete and forward an SAE form to [redacted].and the reason for lost to follow up should be recorded.

5.2.3 Safety laboratory parameters

Clinical laboratory testing will be conducted on all patients at the Screening Visit (Visit 1) and (Visit 4).

Laboratory specimens (blood and urine) will be collected in the morning with the patient having fasted for at least 8 hours. The patient may have a light snack after blood collection on these pulmonary function test-days.

Hematology testing will include hemoglobin, hematocrit, erythrocytes, platelets, total leukocyte count with differential (neutrophils, lymphocytes, monocytes, eosinophils, and basophils), and absolute eosinophil count. Serum chemistry testing will include albumin, alkaline phosphatase, calcium, chloride, creatinine, glucose, inorganic phosphorus, LDH, potassium, AST (SGOT), ALT (SGPT), sodium, total bilirubin, total protein, uric acid, urea nitrogen（or urea).

The urinalysis will include specific gravity, pH, glucose, protein, leukocytes and erythrocyte.

A urine pregnancy test will be conducted at the screening visit and visit 4 in all women of child-bearing potential.

All clinical laboratory tests will be performed at local laboratory. Comments should be given for each value considered clinically relevant (for instance, outside the reference range or if any value that differs importantly from previous ones). If the baseline laboratory evaluation is repeated, only the most recent results are used for evaluation of patient participation. The significant abnormality as judged by the investigator will be recorded as adverse events.

5.2.4 Electrocardiogram

A standard 12-lead electrocardiogram (ECG) will be recorded as scheduled in the flowchart. The investigator or a designee will evaluate whether the ECG is normal or abnormal and whether it is clinically relevant, if abnormal.

All electrocardiograms should be performed prior to pulmonary function. The interpretation of the ECG will be performed by the investigator or a qualified designee.

The purpose of the baseline ECG (Visit 1) is to obtain information about the patient's baseline condition that may have not been elicited in obtaining the medical history; therefore, any significant findings from this examination are recorded on the Medical History/Concomitant Diagnoses page.

The purpose of the ECG at Visit 4 is to find any new condition or worsening on baseline condition. Clinically relevant abnormal findings should be reported as an adverse event.

If necessary, additional ECGs may be recorded for safety reasons. Dated and signed printouts of ECG with findings should be documented in patient’s medical record.

5.2.5 Other

Medical History
A complete medical history by body system will be performed on all patients at the screening visit. All active and resolved historical disorders for the last 5 years will be recorded on the eCRF.

Record of Investigational Drug
A paper Patient Diary will be kept documenting the administration of the investigational drug during the study.

Concomitant Therapies
All concomitant therapies taken in the 2 months preceding the screening visit and throughout the study (including baseline period) will be recorded on the Concomitant Therapy eCRF page.

Smoking Status
The smoking status (current smoker or ex-smoker) of each patient will be recorded at the screening visit (Visit 1).

5.2.6 Assessment of adverse events

5.2.6.1 Definitions of AEs

5.2.6.1.1 Adverse event

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

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

The following should also be recorded as an AE in the CRF and BI SAE form (if applicable):

- Worsening of the underlying disease or of other pre-existing conditions
- Changes in vital signs, ECG, physical examination and laboratory test results, if they are judged clinically relevant by the investigator.

If such abnormalities already exist prior to trial inclusion, they will be considered as baseline conditions and should be collected in the eCRF only.

5.2.6.1.2 Serious adverse event

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

- results in death,
- is life-threatening, which refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if more severe,
- requires inpatient hospitalisation,
- requires prolongation of existing hospitalisation,
- results in persistent or significant disability or incapacity,
- is a congenital anomaly / birth defect,
- is deemed serious for any other reason if it is an important medical event when based on appropriate medical judgement which may jeopardise the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation or development of dependency or abuse.

5.2.6.1.3 AEs considered “Always Serious”

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

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

The latest list of "Always Serious AEs" can be found in the eDC system. A copy of the latest list of "Always Serious AEs" will be provided upon request. These events should always be reported as SAEs as described above.

5.2.6.1.4 Adverse events of special interest

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

The following are considered as AESIs:

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

- An elevation of AST (aspartate transaminase) and/or ALT (alanine aminotransferase) ≥3 fold Upper Level of Normal (ULN) combined with an elevation of total bilirubin ≥2 fold ULN measured in the same blood draw sample, or
- Aminotransferase (ALT, and/or AST) elevations ≥10 fold ULN.

These lab findings constitute a hepatic injury alert and the patients showing these lab abnormalities need to be followed up according to the "DILI checklist" provided in the ISF. 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.

5.2.6.1.5 Intensity (severity) of AEs

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

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

5.2.6.1.6 Causal relationship of AEs

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

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

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

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

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

5.2.6.2 Adverse event collection and reporting

5.2.6.2.1 AE Collection

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

- From signing the informed consent onwards until the individual patient's end of trial: all AEs (serious and non-serious) and all AESIs.
- After the individual patient's end of trial:
  the investigator does not need to actively monitor the patient for new AEs but should only report any occurrence of cancer and related SAEs and related AESIs of which the investigator may become aware of by any means of communication, e.g. phone call. Those AEs should however not be reported in the CRF.

All adverse events, regardless of causality, will be recorded on the adverse event eCRF page after review of the Patient Daily Record, the paper Patient Diary and discussions with the patient. Information concerning the onset, duration, intensity, severity, medication taken,

action taken with study medication and causality of the adverse event will be collected on the eCRF page. Where relevant (e.g., paradoxical bronchospasm) the temporal relationship (minutes) between the onset of an adverse event and the time of drug administration should be recorded in the comment section of the adverse event eCRF page.

All AE should be recorded in CRF as soon as possibleafter the investigator becomes aware.

Vital Status Data Collection

Patients who discontinue trial medication prematurely, who agree to be contacted further but do not agree to physical visits, should be followed up as described in Section 3.3.4.1 withdrawal from trial treatment. From then on until the individual patient's end of the trial the investigator must report all deaths/fatal AEs regardless of relationship, related SAEs and related AESIs the investigator becomes aware of.

5.2.6.2.2 AE reporting to the sponsor and timelines

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

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

Additionally, serious adverse events leading to death, which is related to IMP, should additionally fax to local PV immediately (contact details will be provided in the ISF).

5.2.6.2.3 Information required

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

5.2.6.2.4 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 well as non-trial specific information and consent for the pregnant partner.

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

5.3 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

Not applicable.

5.4 ASSESSMENT OF BIOMARKER(S)

Not applicable.

5.5 BIOBANKING

Not applicable.

5.6 OTHER ASSESSMENTS

Not applicable.

5.7 APPROPRIATENESS OF MEASUREMENTS

Not applicable.

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

The study will consist of three sequential periods, a Screening period of up to 7 days, a treatment period of 8 weeks and a follow-up period of 4 weeks. The maximum duration is expected to be 93 days.

Following an initial screening, eligible patients will be randomized to enter the first 4-week treatment periods in which they will be given Tiotropium Respimat® or Tiotropium HandiHaler® respectively. Before the treatment phase, patients will be trained to use these two inhalers correctly. After the first treatment period, patients will enter the next 4-week treatment phase and have to switch to the other inhaler. After each of the treatment period, patients will fill-in the performance domain, convenience domain and overall satisfaction. After conclusion of both treatment phases (at visit 4), all patients will indicate their preference and willingness to continue of these two inhalers in the PASAPQ.

Adverse events will be tracked from screening to the follow-up period. All SAEs or any AE associated with trial medication persisting after trial completion must be followed up until they have been resolved or have been fully characterized (have been assessed as “chronic” or “stable”, or no further information can be obtained).

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

6.2.1 Screening period(s)

Written informed consent will be obtained prior to initiating any study-related evaluation. Upon obtaining consent, the patient will be instructed on the medication and other restrictions for the screening test.
All tests for the visits during the study period are detailed in the Flow Chart and completed at local sites.

Screening Period (Visit 1, up to 7 days)

- A complete medical history, including demographic information.
- A complete physical examination including vital sign measurements and 12-lead ECG.
- Smoking status (smoker vs. ex-smoker) will be recorded.
- Concomitant therapy for the two months will be recorded in the CRF.
- Blood and urine samples will be collected for laboratory analysis and determination of eligibility as well as a urine pregnancy for females of child-bearing potential. The patient will perform a baseline pulmonary function test (PFT) that will consist of three manoeuvres and the highest FEV1 and FVC of those manoeuvres will be recorded on the eCRF. The patient will be required to have a post-bronchodilator 30% ≤FEV1 ≤80% of predicted normal and FEV1/FVC ≤70%. Spirometry must be done at baseline and approximately 1/2 hour following 4 inhalations of albuterol. Predicted normal values will be calculated according to the Jinping Zheng’s study [R18-2762]. Historical data from

spirometry measurements within the past 6 months either at the site or at the other hospital may be used. Please refer to flow chart for details.
- Patients will be assessed for the eligibility as per the inclusion and exclusion criteria.
- Patients will be dispensed a Salbutamol Sulphate Aerosol (pMDI) as rescue medication. The usage guidance will be given.
- The Patient Diary will be dispensed to the patient. Directions will be provided on proper completion.
- Trial Identification Card (TIC) with trial information and study Doctor's contact information will be provided for the patient.
- Patients will be instructed on medication restrictions.
- Details of any patient who is screened for the trial but are found to be ineligible must be entered in an enrolment log and documented in the case report form.

6.2.2 Treatment period(s)

Visit 2 (1 day):

This visit will be scheduled for after the completion of the screening period.
The inclusion and exclusion criteria will be reviewed prior to randomization, and if the patient qualifies for the screen period of the trial, patients will be randomized into 2 groups by envelope randomization. When one group (T1) is randomized into Respimat® arm, and another group (T2) will enter into Handihaler® arm for 4-week treatment.

After randomization the following will be performed:

- Rescue medication and patient diary dispensed at Visit 1 need to be collected.
- Adverse events and concomitant therapy since last visit will be reviewed and recorded on the eCRF.
- Patients will be trained by the investigator to use the randomized inhalers, i.e. Respimat® or Handihaler®. The placebo of each inhaler will be provided for the training to patients, which will follow the instructions in the local product information and demonstration video.
- The tiotropium Respimat® or Tiotropium Handihaler® will be provided to the patients. The patient will assemble (Tiotropium Respimat®, only) and prime his/her assigned inhaler(s) in the presence of the trial staff.
- The first dose of trial medication will be administered at the clinic.
- Patients will be provided with rescue medication and a new patient diary. He/she will be instructed to return to the clinic in 29 days for the next scheduled visit = visit 3.

Visit 3 (28 days±1 days): T1 will enter into Handihaler® arm for 4 weeks after the completion of all procedures as listed below; on the contrary, T2 will enter into Respimat® arm for 4 weeks.
- Patients will have to complete the PASAPQ including total score (Q1-13), overall satisfaction (Q14), except for the preference question prior to any other procedures or evaluations.
- Patients' diary will be collected and reviewed for patient compliance.

- Concomitant therapy and any adverse events since last visit will be checked and recorded on the eCRF.
- All trial medication (used and un-used) will be collected.
- Patients will be trained by the investigator in the use of the next randomised inhalers, i.e. Respimat® or Handihaler®. The placebo of each inhaler will be provided for the training to patients, following the instructions in the local product information and demonstration video.
- The first dose of trial medication should be administered at the clinic. To avoid overdosing, the investigator needs to confirm whether the patient has already taken the medication at home on the day of V3 visit. If so, the patient will not take the first dose of the newly assigned treatment at Visit 3.
- The tiotropium Respimat® or Tiotropium Handihaler® will be provided to the patients. The patient will assemble (Tiotropium Respimat®, only) and prime his/her assigned inhaler(s) in the presence of the trial staff.
- The first dose of trial medication will be administered at the clinic.
- Patients will be provided with rescue medication and a new patient diary. He/she will be instructed to return to the clinic in 29 days for the next scheduled visit = visit 4.

Visit 4 (56 days±1 days).

The following trial procedures must be performed by all completed patients at Visit 4 as well as by all patients who discontinue the study prematurely (prior to 8 weeks of treatment).

- Patients should complete PASAPQ, including total score (Q1-13), overall satisfaction (Q14), preference and willingness to continue (Q15 and Q16) prior to any other procedures or evaluations.
- Patients' diary will be collected and reviewed for patient compliance.
- All trial medication (used and un-used) will be collected.
- Patients will receive a complete final physical examination with vitals.
- 12 lead-ECG should be done.
- Blood and urine samples will be collected for laboratory analysis.
- Pregnancy test (urine) will be performed on applicable female patients.
- Adverse events and concomitant therapy since last visit will be reviewed and recorded on the eCRF.
- Conclusion of Patient participation

6.2.3 Follow-up Period (84 days±2 days)

During the follow-up period, the investigator should collect AE&SAE information and concomitant therapy by telephone.

Patients who discontinue study treatment early should complete all assessments as soon as possible, which is the same as visit 4, especially, AE check and safety test, such as 12 lead-ECG, Laboratory tests, and so on.

6.2.3.1 Vital status for patients who discontinue early

Patients who withdraw permanently from the randomized treatment period will be followed up by phone regarding their health status until their projected normal exit date from the trial.

The phone calls should be made at approximately 4 and 8 weeks after the patient is randomized. The site must make at least two attempts to contact the patient.

6.2.4 Removal of patients from therapy assessment

Criteria and rules for stopping subject treatment

To be considered complete, a patient must complete the use of both devices as specified in the protocol without violations of the protocol significant enough to obscure the patient acceptability/preference. Patients who fail to complete all treatment will not be replaced.

Dropouts and Withdrawals

Randomized patients who fail to complete all treatment and all of the testing as specified in the protocol will not be considered complete, may not be enrolled at a later date and will not be replaced. If the investigator feels a subject should be discontinued, the Local Clinical Monitor should be contacted.

A record will be kept of all patients who fail to complete all test-days and their reasons for discontinuation. A final physical examination should be conducted on all discontinued patients. All safety information collected from discontinued patients will be included in the safety analysis of the study.

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

Details of all analyses will be provided in the Trial Statistical Analysis Plan (TSAP).

7.1 STATISTICAL DESIGN - MODEL

This is a multi-center, randomized, open-label, two-way cross-over study to investigate the patient acceptability/preference of Tiotropium Respimat® compared with Tiotropium Handihaler® in patients with moderate to severe chronic obstructive pulmonary disease (COPD).

Based upon these design considerations, the primary endpoint (performance domain of PASAPQ) will be analysed using Mixed-effects Model for Repeated Measures (MMRM), with treatment and period as fixed effects, and patient as a random effect. Compound symmetry will be used as a covariance structure for within-patient variation.

7.2 NULL AND ALTERNATIVE HYPOTHESES

The following hypothesis (two-sided $\alpha = 0.05$) will be tested for the primary endpoint – performance domain of PASAPQ after 4 weeks of treatment:

H_0: mean performance score for Tiotropium Respimat® = mean performance score for Tiotropium Handihaler®
H_a: mean performance score for Tiotropium Respimat® ≠ mean performance score for Tiotropium Handihaler®

7.3 PLANNED ANALYSES

The analysis will be based on the following populations:

- Treated set (TS) is defined as all patients who were dispensed study medication and were documented to have at least one dose of investigational treatment.
- Full analysis set (FAS) is defined as all patients who were randomized to treatment sequence and received at least one dose of one study drug and providing at least one PASAPQ score measurement.

The primary endpoint will be analyzed on the FAS (as the primary analysis). The secondary endpoints will be analyzed on the FAS.
Safety analyses will be performed on the TS.
Demographic and baseline characteristics will be analyzed on the TS using descriptive statistics.

7.3.1 Primary endpoint analyses

In the primary analysis, comparisons between treatment groups for the performance domain of PASAPQ will be based on a mixed effect repeated measures model (MMRM). This model will include treatment and period as fixed effects and patient as a random effect. Compound symmetry will be used as a covariance structure for within-patient variation. The SAS procedure MIXED will be used involving the restricted maximum likelihood estimation and the Kenward-Roger approximation for denominator degrees of freedom (Kenward, 2010). Adjusted mean values as well as treatment contrasts will be presented together with the 95% confidence intervals (CI) and p-values.

7.3.2 Secondary endpoint analyses

Continuous secondary endpoints will be analysed using a similar MMRM model as for the primary endpoint. Chi-squared test will be performed to analyse proportion of patients indicating preference.

[redacted]

7.3.4 Safety analyses

All treated patients will be included in the safety analysis. In general, safety analyses will be descriptive in nature and will be based on BI standards. No hypothesis testing is planned. Adverse events will be coded using the Medical Dictionary for Drug Regulatory Activities (MedDRA). Standard BI summary tables and listings will be produced. All adverse events with an onset between start of and end of the REP, a period of 4 weeks after the last dose of trial medication, will be assigned to the on-treatment period for evaluation.

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

Vital signs (blood pressure and pulse rate), physical examinations, or other safety-relevant data observed at screening, 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.

Laboratory data will be analysed both quantitatively as well as qualitatively. The latter will be done via comparison of laboratory data to their reference ranges. Values outside the reference range as well as values defined as clinically relevant will be summarised. Treatment groups will be compared descriptively with regard to distribution parameters as well as with regard to frequency and percentage of patients with abnormal values or clinically relevant abnormal values.

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

Vital signs (blood pressure and pulse rate), physical examinations, or other safety-relevant data observed at screening, 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.

Laboratory data will be analysed both quantitatively as well as qualitatively. The latter will be done via comparison of laboratory data to their reference ranges. Values outside the reference range as well as values defined as clinically relevant will be summarised. Treatment groups will be compared descriptively with regard to distribution parameters as well as with regard to frequency and percentage of patients with abnormal values or clinically relevant abnormal values.

7.3.5 Pharmacokinetic and pharmacodynamic analyses

No pharmacokinetic analysis is planned for this study.

7.4 INTERIM ANALYSES

No interim analysis is planned.

7.5 HANDLING OF MISSING DATA

Every effort should be made to collect the complete data at the planned time points for this trial.
For PASAPQ, imputation of responses to individual questions will follow the “half-scale rule”. If a patient missed less than four of the seven questions in the Performance domain or less than four of the six questions in the Convenience domain in the PASAPQ, then the missing item in this domain is imputed using the observed mean from the same domain, and then the Total score is calculated as the sum of the 13 items after substitution for missing items at the domain level has taken place. If a patient missed more than three items in either domain, then the domain and the Total score are set to missing and will not be imputed.
The number of patients who cannot be included in the FAS will be summarised by treatment group and period. Sensitivity analyses, in which missing data will be imputed according to the reason they are missing, will be described in the TSAP.

7.6 RANDOMISATION

This is a cross-over study with two treatment groups. After screening, eligible patients will be randomized in equal ratio to one of the two treatment sequences.

BI will arrange for the randomisation and the packaging and labelling of trial medication. The randomisation list will be generated using a validated system, which involves a pseudo-random number generator so that the resulting treatment will be both reproducible and non-predictable. The block size will be documented in the Clinical Trial Report. Access to the codes will be controlled and documented.

7.7 DETERMINATION OF SAMPLE SIZE

Calculations were performed using nQuery Advisor® 6.1 statistical package by [redacted]

The Minimal Clinically Important Difference (MCID) is 8-10 points for PASAPQ assessment which is meaningful to patients (Richard Hodder, 2009). Based on previous studies, the standard deviation of difference between Respimat® versus DPI devices or MDI devices ranges from 18-22 (Schürmann W, 2005) (Gary T Ferguson, 2013) (Price, 2009). The study sample size was based on the calculation that 60 completed patients would be required to have a 85% power to detect a minimum 8-point difference in the mean performance domain score between patients using Respimat® and Handihaler®, and using a two-sided 5% significant level, assuming that the standard deviation for treatment difference is 20.0 using t-test (ANOVA) for difference of means in 2 x 2 crossover design (nQuery Advisor 7.0). To account for 15% potential patients with no evaluable data, a total number of 71 patients were planned.

Table 7.7: 1 Sample size calculation based on t-test (ANOVA) for difference of means in 2X2 crossover design

Treatment Difference	SD for difference	Power		
		90%	85%	80%
6	18	98	84	74
	20	120	102	90
	22	144	124	108
8	18	54	48	42
	20	68	60	52
	22	82	70	62
10	18	38	32	28
	20	46	38	34
	22	54	46	42

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

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 Guideline for Good Clinical Practice (GCP), relevant BI Standard Operating Procedures (SOPs) and other relevant regulations. Investigators and site staff must adhere to these principles.

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

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

The Boehringer Ingelheim transparency and publication policy can be found on the following web page: trials.boehringer-ingelheim.com. The rights of the investigator and of the sponsor with regard to publication of the results of this trial are described in the investigator contract. As a 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.

8.1 TRIAL APPROVAL, PATIENT 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 regulations. The same applies for the implementation of changes introduced by amendments.

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

The investigator or delegate must give a full explanation to trial patients based on the patient information form. A language understandable to the patient should be chosen, technical terms and expressions avoided, if possible.

The patient must be given sufficient time to consider participation in the trial. The investigator or delegate obtains written consent of the patient's own free will with the informed consent form after confirming that the patient understands the contents. The investigator or [redacted] delegate must sign and date the informed consent form. 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

The trial will be conducted in accordance with the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines, local regulations, and the company standard operating procedures (SOPs). The following necessary steps will be taken to ensure accurate, consistent, complete and reliable data.

- An investigator meeting will be held prior to the initiation of the study. The protocol, eCRFs, safety reporting, and GCP / ICH requirements will be reviewed with the investigators and study coordinators.
- Adverse events, concomitant therapies, and diagnoses will be coded using the MedDRA coding system. Coding will be reviewed by the Clinical Monitor for appropriateness and consistency.
- On-site monitoring will be conducted every 6 weeks during the trial.
- Data will be collected using a Remote Data Capture (RDC) system, and will be source verified by the field monitors before the Principal Investigators approve the data in RDC. Training will be provided to all investigators, coordinators and field monitors to ensure consistency and accuracy of the data.
- The data management procedures to ensure the quality of the data are described in detail in the trial data management and analysis plan (TDMAP) available in the CTMF.

8.3 RECORDS

CRFs for individual patients will be provided by the sponsor. For drug accountability, refer to section 4.1.7.

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 patient. Source data as well as reported data should follow the "ALCOA principles" and be **a**ttributable, **l**egible, **c**ontemporaneous, **o**riginal and **a**ccurate. 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 patient 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 patient, documented in their medical records, would be acceptable.

Before sending or uploading those copies of source documents, the investigator must ensure that all patient identifiers (e.g. patient's name, initials, address, phone number, social security number) have properly been removed or redacted from any copy of the patients' source documents.

If the patient 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:

- Patient identification (gender, date of birth)
- Patient participation in the trial (substance, trial number, patient number)
- Dates of Patient's visits
- Dates of ECG tracings
- Medical history (including trial indication and concomitant diseases, if applicable)
- Adverse events (onset date)
- Serious adverse events (onset date)
- Concomitant therapy (onset date, changes)
- Originals or copies of laboratory results (in validated electronic format, if available)
- Patient responses on the Patient Daily and PASAPQ
- Conclusion of Patient's Participation in the trial

8.3.2 Direct access to source data and documents

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

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

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

8.4 EXPEDITED REPORTING OF ADVERSE EVENTS

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

There is no protocol specified exempted events.

8.5 STATEMENT OF CONFIDENTIALITY AND PATIENT PRIVACY

Individual patient data obtained as a result of this trial is considered confidential and disclosure to third parties is prohibited with the exceptions noted in section 8.6.

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

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

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

Not applicable.

8.6 TRIAL MILESTONES

The start of the trial is defined as the date when the first patient in the whole trial signed informed consent.

The end of the trial is defined as the date of the last visit of the last patient in the whole trial ("Last Patient Completed"). The "Last Patient Last Treatment" (LPLT) date is defined as the date on which the last patient in the whole trial is administered the last dose of trial treatment (as scheduled per protocol or prematurely).

Individual investigators will be notified of Suspected Unexpected Serious Adverse Reaction (SUSARs) occurring with the trial medication until 30 days after LPLT at their site. Early termination of the trial is defined as the premature termination of the trial due to any reasons 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.

8.7 ADMINISTRATIVE STRUCTURE OF THE TRIAL

The trial is sponsored by Boehringer Ingelheim (BI).
One coordinating Investigator is responsible to coordinate investigators at the different sites participating in this trial. Tasks and responsibilities are defined in a contract.
Relevant documentation on the participating (Principal) Investigators (e.g. their curricula vitae) will be filed in the (Investigator Site File) ISF.

BI has appointed a Clinical Trial Leader, responsible for coordinating all required activities, in order to

- Manage the trial in accordance with applicable regulations and internal sop.
- Direct the clinical trial team in the preparation, conduct and reporting of the trial.
- Ensure appropriate training and information of Clinical Trial Manager (CTM), Clinical Research Associate (CRA), and investigators of participating countries.

The organisation of the trial in the participating countries will be performed by the respective local or regional BI-organization 9Operationg Unit, OPU) in accordance with applicable regulations and BI SOPs, or by a Contract Research Organisation CRO) with which the responsibilities and tasks will have been agrees and a written contract filed before initiation of the clinical trial. Data Management will be done by a CRO with which the responsibilities and tasks will have been agreed and a written contract filed before initiation of the clinical trial. Statistical Evaluation will be done by BI according to BI SOPs. IRT will not be used for this study. The local laboratory service at each site will be used for this study.

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

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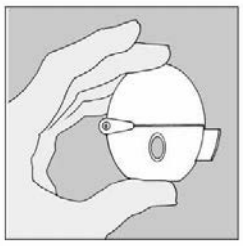
9.2 UNPUBLISHED REFERENCES

Not applicable.

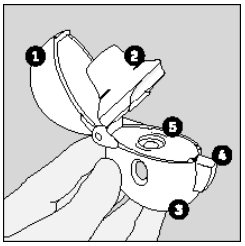
10. APPENDICES

10.1 INSTRUCTIONS FOR THE USE OF THE RESPIMAT®

Instructions for Use:

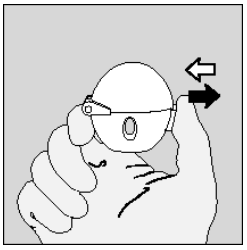


Remember to carefully follow your doctor's instructions for using SPIRIVA®. The HandiHaler® is especially designed for SPIRIVA®. You must not use it to take any other medication. You can use your HandiHaler® for up to one year to take your medication.

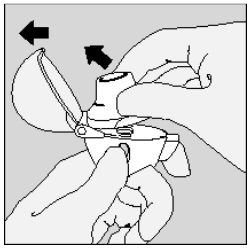


The HandiHaler®

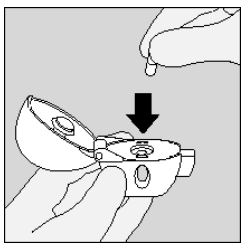
1 Dust cap
2 Mouthpiece
3 Base
4 Piercing button
5 Centre chamber



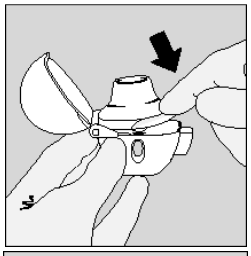
1. To release the dust cap press the piercing button completely in and let go.



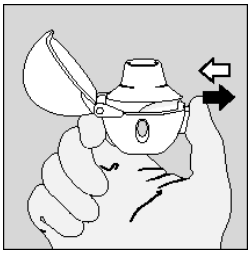
2. Open the dust cap completely by pulling it upwards.
Then open the mouthpiece by pulling it upwards.



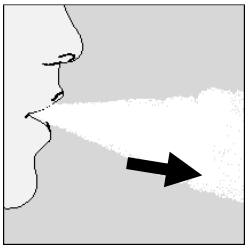
3. Remove a SPIRIVA® capsule from the blister (only immediately before use) and place it in the centre chamber (5), as illustrated. It does not matter which way the capsule is placed in the chamber.



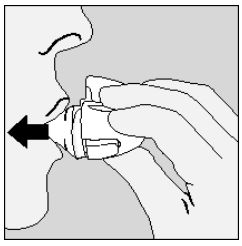
4. Close the mouthpiece **firmly** until you hear a click, leaving the dust cap open.



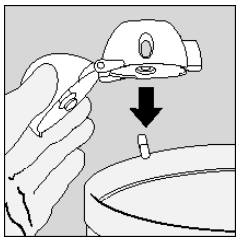
5. **Hold the HandiHaler® device with the mouthpiece upwards and press the piercing button completely in only once, and release.**
This makes holes in the capsule and allows the medication to be released when you breathe in.



6. **Breathe out completely.**
Important: Please avoid breathing into the mouthpiece at any time.

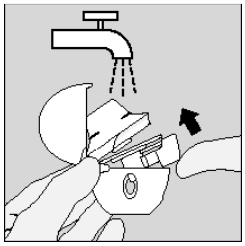


7. Raise the HandiHaler® to your mouth and close your lips tightly around the mouthpiece. Keep your head in an upright position and breathe in slowly and deeply but at a rate sufficient to hear or feel the capsule vibrate.
Breathe in until your lungs are full; then hold your breath as long as comfortable and at the same time take the HandiHaler® out of your mouth. Resume normal breathing.
Repeat steps 6 and 7 once, in order to empty the capsule completely.



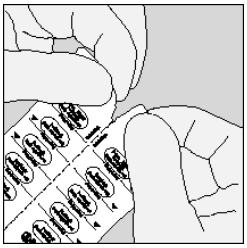
8. Open the mouthpiece again. Tip out the used capsule and dispose. Close the mouthpiece and dust cap for storage of your HandiHaler® device.

Cleaning your HandiHaler®

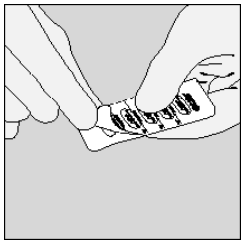


Clean the HandiHaler® once a month. Open the dust cap and mouthpiece. Then open the base by lifting the piercing button. Rinse the complete inhaler with warm water to remove any powder. Dry the HandiHaler® thoroughly by tipping excess of water out on a paper towel and air-dry afterwards, leaving the dust cap, mouthpiece and base open. It takes 24 hours to air dry, so clean it right after you used it and it will be ready for your next dose. If needed, the outside of the mouthpiece may be cleaned with a moist but not wet tissue.

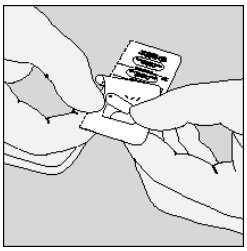
Blister handling



A. Separate the blister strips by tearing along the perforation.



B. Peel back foil (only immediately before use) using the tab until one capsule is fully visible.
In case a second capsule is exposed to air inadvertently this capsule has to be discarded.



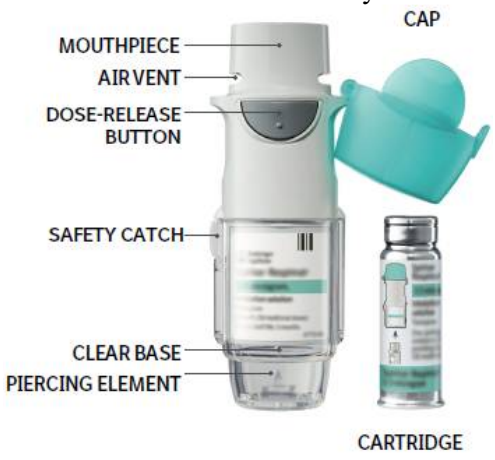
C. Remove capsule.

SPIRIVA® capsules contain only a small amount of powder so that the capsule is only partially filled.

10.2 INSTRUCTIONS FOR THE USE OF THE HANDIHALER®

Instructions for Use

Introduction
It is the product of tiotropium bromide Spray. Read these Instructions for Use before you start using it.
You will need to use this inhaler only ONCE A DAY. Each time you use it take TWO PUFFS.



- If Spiriva® Respimat® has not been used for more than **7 days** release one puff towards the ground.
- If Spiriva® Respimat® has not been used for more than **21 days** 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 touch the piercing element inside the clear base.

How to care for your Spiriva® 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 your Spiriva® Respimat® inhaler performance.

If necessary, wipe the outside of your Spiriva® Respimat® inhaler with a damp cloth.

When to get a new Spiriva® Respimat®

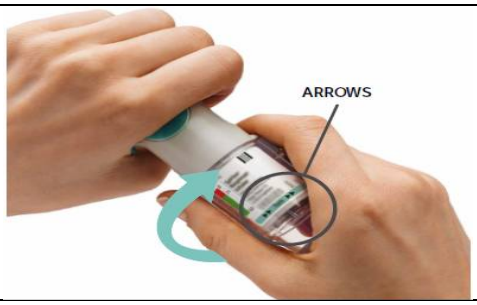
- Your Spiriva Respimat® inhaler contains 60 puffs (30 doses) if used as indicated (two puffs/once daily).
- The dose indicator shows approximately how much medication is left.
- When the dose indicator enters the red area of the scale you need to get a new prescription; there is approximately medication for 7 days left (14 puffs).
- Once the dose indicator reaches the end of the red scale, your Spiriva® Respimat® locks automatically – no more doses can be released. At this point, the clear base cannot be turned any further.
- Spiriva® Respimat® should be discarded three months after you have prepared it for first use, even if it has not been fully used or used at all.

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 clicks into place. • Do not remove the cartridge once it has been inserted into the inhaler.	

3. Replace clear base • Put the clear base back into place until it clicks. • Do not remove the clear base again.	
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. Your inhaler is now ready to use. These steps will not affect the number of doses available. After preparation your inhaler will be able to deliver 60 puffs (30 doses).	

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. • Close the cap until you use your inhaler again.	

10.3 INSTRUCTIONS FOR THE USE OF SALBUTAMOL SULPHATE AEROSOL

Instructions for Use and Handling
The drug in the aerosol is inhaled into the lungs. Shake the inhaler well, place the mouthpiece of the inhaler in the mouth, close the lips, press the actuation button, and do inhale the sprayed drug into lungs while breathing in (see [Guidance for Use]).

[Guidance for Use]

1. Remove the mouthpiece cover by gently squeezing the sides of the cover. Hold the aerosol as shown in Figure 1, check inside and outside of the inhaler including the mouthpiece for the presence of loose objects. Shake the inhaler well to ensure that any loose objects are removed and that the contents of the inhaler are evenly mixed.


Figure 1

2. Breathe out gently until no air can be breathed out of the lungs (Figure 2), and then immediately…

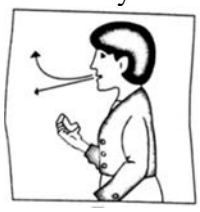


Figure 2

3. Place the mouthpiece in your mouth between your teeth and close your lips around it. Just after starting to breathe in through your mouth press down on the top of the inhaler to release Ventolin® (Figure 3) while still breathing in steadily and deeply.

Figure 3

4. Hold your breath for ten seconds or continue holding your breath for as long as is comfortable, and then slowly breathe out.

Figure 4

5. If you are to take further actuations, wait at least one minute before repeating steps two to four.

6. After use, push and snap the cover back to the mouthpiece.

10.4 PATIENT SATISFACTION AND PREFERENCE QUESTIONNAIRE

10.4.1 PASAPQ at Visit 3

PART 1: RATING OF SATISFACTION WITH INHALER ATTRIBUTES

Instructions: For the following questions, please check the response that best describes how satisfied you are with each of the following items. Please take as much time as you need to answer each question.

	How satisfied are you…	Very Dissatisfied	Dissatisfied	Somewhat Dissatisfied	Neither Satisfied nor Dissatisfied	Somewhat Satisfied	Satisfied	Very Satisfied
1.	With the overall feeling of inhaling your medicine?	☐	☐	☐	☐	☐	☐	☐
2.	With the feeling that the inhaled dose goes to your lungs?	☐	☐	☐	☐	☐	☐	☐
3.	That you can tell the amount of medication left in your inhaler?	☐	☐	☐	☐	☐	☐	☐
4.	That the inhaler works reliably?	☐	☐	☐	☐	☐	☐	☐
5.	With the ease of inhaling a dose from the inhaler?	☐	☐	☐	☐	☐	☐	☐
6.	With the instructions for use?	☐	☐	☐	☐	☐	☐	☐
7.	With the size of your inhaler?	☐	☐	☐	☐	☐	☐	☐
8.	That the inhaler is durable (hard wearing)?	☐	☐	☐	☐	☐	☐	☐
9.	With the ease of cleaning your inhaler?	☐	☐	☐	☐	☐	☐	☐
10.	With using the inhaler?	☐	☐	☐	☐	☐	☐	☐
11.	With the speed at which medicine comes out of the inhaler?	☐	☐	☐	☐	☐	☐	☐
12.	With the ease of holding the inhaler during use?	☐	☐	☐	☐	☐	☐	☐
13.	With the overall convenience of carrying the inhaler with you?	☐	☐	☐	☐	☐	☐	☐
14.	Overall, how satisfied are you with your inhaler?	☐	☐	☐	☐	☐	☐	☐

10.4.2 PASAPQ at Visit 4

PART 1: RATING OF SATISFACTION WITH INHALER ATTRIBUTES

Instructions: For the following questions, please check the response that best describes how satisfied you are with each of the following items. Please take as much time as you need to answer each question.

	How satisfied are you…	Very Dissatisfied	Dissatisfied	Somewhat Dissatisfied	Neither Satisfied nor Dissatisfied	Somewhat Satisfied	Satisfied	Very Satisfied
1.	With the overall feeling of inhaling your medicine?	☐	☐	☐	☐	☐	☐	☐
2.	With the feeling that the inhaled dose goes to your lungs?	☐	☐	☐	☐	☐	☐	☐
3.	That you can tell the amount of medication left in your inhaler?	☐	☐	☐	☐	☐	☐	☐
4.	That the inhaler works reliably?	☐	☐	☐	☐	☐	☐	☐
5.	With the ease of inhaling a dose from the inhaler?	☐	☐	☐	☐	☐	☐	☐
6.	With the instructions for use?	☐	☐	☐	☐	☐	☐	☐
7.	With the size of your inhaler?	☐	☐	☐	☐	☐	☐	☐
8.	That the inhaler is durable (hard wearing)?	☐	☐	☐	☐	☐	☐	☐
9.	With the ease of cleaning your inhaler?	☐	☐	☐	☐	☐	☐	☐
10.	With using the inhaler?	☐	☐	☐	☐	☐	☐	☐
11.	With the speed at which medicine comes out of the inhaler?	☐	☐	☐	☐	☐	☐	☐
12.	With the ease of holding the inhaler during use?	☐	☐	☐	☐	☐	☐	☐
13.	With the overall convenience of carrying the inhaler with you?	☐	☐	☐	☐	☐	☐	☐
14.	Overall, how satisfied are you with your inhaler?	☐	☐	☐	☐	☐	☐	☐

PART 2: RATING OF PREFERENCE AND WILLINGNESS TO CONTINUE WITH INHALER

15. Comparing the two inhalers that you have used during the study, overall, would you prefer to use Respimat® or Handihaler®?

Please check one box

I prefer Respimat® ☐

I prefer Handihaler® ☐

No preference ☐

16. Comparing the two inhalers that you have used during the study, overall, how would you feel about continuing to use Respimat® or Handihaler®?

Please indicate your willingness to continue using each of the inhalers that you used during the study by providing a value between 0 and 100.

0 indicates that you would not be willing to continue using this inhaler and 100 indicates that you would definitely be willing to continue.

Please write in a number in **each** box that is between 0 and 100.

Respimat® ☐

Handihaler® ☐

Both boxes should contain a number between 0 and 100.

10.5 PHARMACOKINETIC METHODS AND ANALYSES

Not applicable.

10.6 TIME SCHEDULE FOR PHARMACOKINETIC (PK) BLOOD SAMPLING

Not applicable.

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

11.1 GLOBAL AMENDMENT 1

Date of amendment		**17 Apr 2019**
EudraCT number **EU number**		**Not applicable**
BI Trial number		**0205-0541**
BI Investigational Medicinal Product(s)		**Tiotropium Respimat® (Spiriva® Respimat®)**
Title of protocol		**A randomized, open-label, two-way crossover study to compare patient acceptability/preference of Tiotropium Respimat® with Tiotropium Handihaler® in patients with moderate to severe chronic obstructive pulmonary disease (COPD).**
Global Amendment due to urgent safety reasons		☐
Global Amendment		☒
Section to be changed		**Clinical Trial Protocol Synopsis：Trial endpoints**
Description of change		Deleted “4 weeks ”
Rationale for change		Revised error in previous version.
Section to be changed		**Flow Chart**
Description of change		• Changed from “PASAPQ question 1-14, question 16” to “PASAPQ question: 1-14”, and added the item into the column of “Visit 4” • Changed from “PASAPQ question 1-16” to “PASAPQ question: 15-16”
Rationale for change		Revised error in previous version.
Section to be changed		**2.1.3 Secondary endpoint(s)**
Description of change		Changed from “Score on willingness to continue after 4 weeks treatment which will be administered at week 4 and 8. “ to “Score on willingness to continue will be administered at week 8.“
Rationale for change		Revised error in previous version.
Section to be changed		**5.1.2 Secondary endpoints：**
Description of change		• Underlined “<u>The proportion of patients indicating preference</u>” • <u>Willingness to continue:</u> changed from“Question 15”to “Question 16”, and deleted “Visit 3 (week 4) and”
Rationale for change		Revised error in previous version.
Section to be changed		**5.2.3 Safety laboratory parameters**

Description of change		Deleted the test for "CO_2"
Rationale for change		Not required
Section to be changed		**6.1 Visit schedule**
Description of change		Revised from"After each of the treatment period, patients will fill-in the performance domain, convenience domain, overall satisfaction and willingness to continue. After conclusion of both treatment phases (at visit 4), all patients will indicate their preference of these two inhalers in the PASAPQ." to "After each of the treatment period, patients will fill-in the performance domain, convenience domain and overall satisfaction. After conclusion of both treatment phases (at visit 4), all patients will indicate their preference and willingness to continue of these two inhalers in the PASAPQ."
Rationale for change		Revised error in previous version.
Section to be changed		**6.2.2 Treatment period(s): Visit 3 (28 days±1 days)**
Description of change		Changed from "Patients will have to complete the PASAPQ including total score (Q1-13), overall satisfaction (Q14) and willingness to continue (Q16), except for the preference question prior to any other procedures or evaluations. " to "Patients will have to complete the PASAPQ including total score (Q1-13), overall satisfaction (Q14), except for the preference question prior to any other procedures or evaluations."
Rationale for change		Revised error in previous version.
Section to be changed		**10.4 Patient satisfaction and preference questionnaire**
Description of change		PASAPQ was divided into two questionnaires.
Rationale for change		Patients only will have to complete PASAPQ question 1-14 at Visit 3 and PASAPQ question 1-16 at Visit4.

11.2 GLOBAL AMENDMENT 2

Date of amendment		**23 Mar 2020**
EudraCT number **EU number**		**Not applicable**
BI Trial number		**0205-0541**
BI Investigational Medicinal Product(s)		**Tiotropium Respimat® (Spiriva® Respimat®)**
Title of protocol		**A randomized, open-label, two-way crossover study to compare patient acceptability/preference of Tiotropium Respimat® with Tiotropium Handihaler® in patients with moderate to severe chronic obstructive pulmonary disease (COPD).**
Global Amendment due to urgent safety reasons		☐
Global Amendment		☒
Section to be changed		**5.2.3 Safety laboratory parameters**
Description of change		Added "urea" and changed to "Serum chemistry testing will include albumin, alkaline phosphatase, calcium, chloride, creatinine, glucose, inorganic phosphorus, LDH, potassium, AST (SGOT), ALT (SGPT), sodium, total bilirubin, total protein, uric acid, urea nitrogen (or urea). "
Rationale for change		Most sites couldn't test urea nitrogen. Because either urea nitrogen or urea can reflect the patient's renal function, urea nitrogen testing or urea testing can be accepted.
Section to be changed		**5.2.3 Safety laboratory parameters**
Description of change		Deleted "hemoglobin" and added "leukocytes and erythrocyte", changed to "The urinalysis will include specific gravity, pH, glucose, protein, leukocytes and erythrocyte."
Rationale for change		Most sites couldn't test hemoglobin. Delete "hemoglobin" and add "leukocytes and erythrocyte" which can also reflect "haemoglobin" to evaluate the patient's body index.
Section to be changed		**5.2.4 Electrocardiogram**
Description of change		Deleted "and one minute rhythm strip will be performed as scheduled in the flowchart." And changed to "A standard 12-lead electrocardiogram (ECG) will be recorded as scheduled in the flowchart. The investigator or a designee will evaluate whether the ECG is normal or abnormal

		and whether it is clinically relevant, if abnormal."
Rationale for change		Most sites couldn't test ECG for one minute rhythm strip. The site can assess the patient's related factor via local ECG result.
		Clinical Trial Protocol Synopsis
Description of change		Deleted "84 enrolled, (assuming a 15%-screening failure rate)" and changed to "Total number of patients randomised: 71 entered"
Rationale for change		Actual screening failure rate is higher than planned screening failure rate. The enrolled number and screening failure rate are not yet determined, so were deleted to avoid subsequent protocol revision.
Section to be changed		**Flow Chart** and **3.3.2 Inclusion criteria**
Description of change		Historical data from spirometry measurements within the past 6 months either at the site or at the other hospital may be used. If the measurements are not performed at the trial site a signed copies of the measurement printouts must be provided to the trial site for source data verification. In case several qualifying spirometry measurements are available, the most recent one should be referred to as long as it was not performed during an exacerbation. Patients may not be randomised to the study without the availability of spirometry data at the actual study site.
Rationale for change		The timeline of spirometry measurements need to be fleshed out in order to instruct the investigator to screen the patient effectively.
Section to be changed		**6.2.1 Screening Period (Visit 1, up to 7 days)**
Description of change		Historical data from spirometry measurements within the past 6 months either at the site or at the other hospital may be used. Please refer to flow chart for details.
Rationale for change		After reviewed the reference, the data within the past 6 months can be accepted.