Clinical Trial Protocol

	Document Number:	**c13020187-03**
BI Trial No.:	1237-0063	
BI Investigational Product(s):	Stiolto®, Tiotropium+olodaterol fixed dose combination – Respimat®	
Title:	A randomized, double-blind, double-dummy, active-controlled, multi-center, parallel group study to show the superiority in lung function of 12 weeks once daily treatment with orally inhaled tiotropium+olodaterol fixed dose combination delivered by the Respimat® inhaler vs. 12 weeks twice daily treatment with orally inhaled fluticasone propionate+salmeterol fixed dose combination delivered by the Diskus® in patients with Chronic Obstructive Pulmonary Disease (COPD) [ENERGITO® 2]	
Lay Title:	The ENERGITO® 2 study compares 2 inhaled medicines for Chronic Obstructive Pulmonary Disease (COPD). One medicine is a combination of tiotropium and olodaterol (Stiolto®) taken using the Respimat® inhaler and the other medicine is a combination of fluticasone and salmeterol taken using the Diskus®	
Clinical Phase:	IV	
Trial Clinical Monitor:	Phone: Fax:	
Coordinating Investigator:	Phone: Fax:	
Status:	Final Protocol (Revised Protocol based on global amendment 2)	
Version and Date:	**Version: 3.0**	**Date: 06 March 2018**

CLINICAL TRIAL PROTOCOL SYNOPSIS

Name of company:		**Boehringer Ingelheim**	
Name of finished product:		Stiolto®	
Name of active ingredient:		Tiotropium+olodaterol (5µg/5µg) fixed dose combination inhalation solution – Respimat®	
Protocol date **09 May 2017**	**Trial number:** **1237-0063**		**Revision date:** **06 March 2018**

Title of trial:	A randomized, double-blind, double-dummy, active-controlled, multi-center, parallel group study to show the superiority in lung function of 12 weeks once daily treatment with orally inhaled tiotropium+olodaterol fixed dose combination delivered by the Respimat® inhaler vs. 12 weeks twice daily treatment with orally inhaled fluticasone propionate+salmeterol fixed dose combination delivered by the Diskus® in patients with Chronic Obstructive Pulmonary Disease (COPD) [ENERGITO® 2]
Coordinating Investigator:	Phone: Fax:
Trial site(s):	Multi-center trial conducted in the US
Clinical phase:	IV
Objective(s):	The primary objective of the trial is to show superiority in lung function of once daily treatment with orally inhaled tiotropium+olodaterol (5µg/5µg) fixed dose combination to twice daily treatment with fluticasone propionate+salmeterol (250µg/50µg) fixed dose combination over 12 weeks in patients with Chronic Obstructive Pulmonary Disease (COPD).
Methodology:	Randomized, double-blind, double-dummy, active-controlled parallel group design
No. of patients:	350 enrolled
Total entered:	288

Name of company:		**Boehringer Ingelheim**	
Name of finished product:		Stiolto®	
Name of active ingredient:		Tiotropium+olodaterol (5µg/5µg) fixed dose combination inhalation solution – Respimat®	
Protocol date **09 May 2017**	**Trial number:** **1237-0063**		**Revision date:** **06 March 2018**

Each treatment:	144
Diagnosis :	Chronic Obstructive Pulmonary Disease (COPD)
Main criteria for inclusion:	Outpatients of either sex, aged ≥ 40 years with a diagnosis of COPD; smoking history >10 pack years, post-bronchodilator 30% ≤ FEV_1 (Forced Expiratory Volume in one second) <80% predicted, post-bronchodilator FEV_1/FVC <70%
Test product(s):	Tiotropium+olodaterol FDC solution for inhalation – Respimat®
Dose:	5µg tiotropium + 5µg olodaterol daily (2.5 µg /2.5 µg per actuation administered as 2 actuations once daily)
Mode of administration:	Oral inhalation (2 inhalations in the morning)
Comparator products:	Fluticasone propionate + salmeterol FDC dry powder for inhalation – Diskus®
Dose:	500µg fluticasone propionate + 100µg salmeterol daily (250 µg /50 µg per actuation administered as 1 actuation twice a day)
Mode of administration:	Inhalation
Duration of treatment:	12 weeks
Endpoints:	Primary endpoint: FEV_1 AUC (Area under the curve) $_{0\text{-}24hours}$ response (change from baseline) [L] after 12 weeks of treatment Secondary endpoints: • FEV_1 AUC $_{0\text{-}12h}$ response (change from baseline) [L] after 12 weeks treatment • Trough FEV_1 response (change from baseline) [L] after 12 weeks treatment

Name of company:		**Boehringer Ingelheim**	
Name of finished product:		Stiolto®	
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Protocol date **09 May 2017**	**Trial number:** **1237-0063**		**Revision date:** **06 March 2018**
	• Peak 0-3h FEV_1 response (change from baseline) [L] after 12 weeks treatment		
Safety criteria:	Adverse Events, Serious Adverse Events, Physical Exam		
Statistical methods:	The primary and secondary endpoints at week 12 will be analyzed using a mixed effects model repeated measures (MMRM) approach. DH exploratory study data will be analyzed separately and analysis will be descriptive only.		

FLOW CHART

Trial Periods	**Screening/ Run-in Period**		**Randomized Treatment Period**			**Follow-up (FU) Period**
Visit	**0**	**1**	**V2**	**V3**	**V4/EOT**	**V5/FU**
Week			**1**	**6**	**12**	**15**
Day[1]		**-28**	**1**	**42**	**84**	**105**
Visit window (days)		**+3**[18]		**±3**	**±3**	**±7**
Informed Consent[2]	x					
Inclusion/ exclusion criteria	x	x	x			
Demographics/Baseline Conditions		x				
Physical examination incl. vital signs[14]		x			x[3]	x[4]
COPD/patient characteristics		x				
Register patient in screening (IRT)	x					
Issue Trial Identification Card	x					
Dispense and explain use of ProAir® HFA (rescue medication)	x	x[13]	x[13]	x[13]		
Dispense Atrovent HFA per investigator discretion[16]	x					
Collect Atrovent HFA, if applicable			X[16]			
Medication washout check[9]		x	x	x	x	
Collect rescue medication[8]		x	x	x	x[3]	
12 lead-ECG[14, 15]		x				
Laboratory tests [14]		x	x			
Pregnancy test[5]		x	x		x[3]	x
Review smoking status		x	x	x	x[3]	
COPD Assessment Test CAT[14]			x		x[3]	
Saint George's Respiratory Questionnaire SGRQ[14]			x		x[3]	
Training in use of Respimat® and Diskus®		x	x[6]	x[6]	x[6]	
PFTs (FEV_1 & FVC)*[14]		x[10]	x[7, 11]	x[7, 12]	x[7, 12]	
Adverse events	x	x	x	x	x[3]	x
Concomitant therapy	x	x	x	x	x[3]	x
Telephone Contact[7]			x	x	x	
Randomization (IRT)			x			
Medication kit allocation (IRT)			x	x		

Trial Periods	**Screening/ Run-in Period**		**Randomized Treatment Period**			**Follow-up (FU) Period**
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Week			**1**	**6**	**12**	**15**
Day[1]		**-28**	**1**	**42**	**84**	**105**
Visit window (days)		**+3**[18]		**±3**	**±3**	**±7**
Drug accountability check[9]			x	x	x[3]	
Medication compliance check[17]				x	x[3]	
Dispense trial medication			x	x		
Administration (dosing) of trial medication at the site			x	x	x	
Collect trial medication				x	x[3]	
Trial medication termination (IRT)					x[3]	
Trial Completion						x

Guidance Notes:

1.	Visit 1 may be scheduled from 1 day to 6 weeks after Visit 0 (depending on medication washout requirements). The visit interval may also be extended for administrative reasons to allow for recovery from respiratory infections (See Section 6.1). If no medication washout is required, Visits 0 and 1 could take place on the same day.
2.	All patients must sign an informed consent consistent with ICH-GCP guidelines prior to participation in the trial, which includes medication washout and restrictions. Re-consenting may become necessary when new relevant information becomes available as should be conducted according to the sponsor's instructions.
3.	For patients who discontinue early, EOT visit should be performed instead of the scheduled visit at time of discontinuation and all indicated procedures are to be performed if possible.
4.	To be performed only if relevant findings at Visit 4.
5.	Women of child-bearing potential: Serum pregnancy test is to be completed at Visit 1. Urine pregnancy test (dipstick) is to be completed at Visits 2, 4, and 5. Pregnancy testing is to be completed prior to study drug administration.
6.	If needed, the patient will be re-instructed/re-educated in the use of the Respimat® and Diskus® devices but the patient should not inhale from the placebo inhaler at

	these visits.
7.	Site staff will telephone the patient 1 – 2 days prior to visits 2, 3 and 4 to remind the patient of medication restriction requirements and that they should not inhale trial medication at home on the morning of a clinic visit.
8.	Collect dispensed rescue medication during the course of the trial (whenever applicable).
9.	Including drug accountability check of dispensed ProAir® HFA rescue medication and Atrovent HFA (if applicable).
10.	Visit 1: Reversibility testing using 400µg albuterol [Note: reversibility is not an inclusion criterion]. See Appendix 10.5
11.	Visit 2*: • Two pre-dose PFTs: One at 1hour pre-dose and a second at 10 minutes prior to inhalation of dose of trial medication. • Post-dose PFTs: 30 min, 1, 2 and 3h post-dose
12.	Visits 3 and 4**: • Pre-dose PFT: 10 minutes prior to dosing • Post-dose PFTs: 30 min, 1, 2, 3, 4, 6, 8, 10, 11h50′ • Inhalation of evening dose of study medication (12:00) • Post evening dose PFTs: 12h30′, 13, 14, 22, 23h and 24h
13.	Dispense rescue medication as needed.
14.	The preferred sequence of procedures is as follows: 1. CAT (where applicable) 2. SGRQ (where applicable) 3. Physical Exam (where applicable) 4. 12-lead ECG (where applicable) 5. Labs (where applicable) 6. Pulmonary Function Test (pre-dose)
15.	ECG: 12-lead ECG recording at screening (Visit 1) for inclusion in the study.
16.	Patients on treatment with a LAMA at study entry will receive open label Atrovent HFA during the run-in period, per Investigator's discretion. **This medication must be collected at Visit 2.**
17.	Medication use: From dose counter on Respimat® and Diskus® devices.
18.	The 4-week screening period (between Visit 1 and Visit 2) may be extended by up to 4 weeks for administrative reasons and/or to meet wash-out requirements. (see Section 6.1).

*** For reversibility testing instructions see Appendix 10.5.**

****Time windows for PFT Measurements:**

PFT Time Windows: Visit 2:
The 1h pre-dose measurement will be obtained at -15 minutes and + 5 minutes of the scheduled time point; the 10 minute pre-dose and the 30 min and 1h post dose measurements will be obtained within ± 5 minutes of the scheduled time point.

The 2h and 3h post- dose measurement will be obtained within ± 10 minutes of the scheduled time point.

PFT Time Windows: Visits 3 and 4
The 10 minute pre-dose measurement will be obtained within ± 5 minutes of the scheduled time point.

The 30 minute and 1h post-dose measurements will be obtained within ± 5 minutes of the scheduled time point. The post dose measurements from 2h through 11h50´ pre evening dose and from 12h30´ through 24 post evening dose measurements will be performed ± 10 minutes of the scheduled time point.

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ABBREVIATIONS

AE	Adverse Event
AESI	Adverse Event of Special Interest
App.	An application, downloaded to patient iPhone
AMP	Auxiliary Medicinal Product
ATS/ERS	American Thoracic Society/European Respiratory Society
AUC	Area under the Curve
BI	Boehringer Ingelheim
b.i.d.	bis in die (twice daily dosing)
CAT	COPD Assessment Test
CCDS	Company Core Data Sheet
CML	Local Clinical Monitor
COPD	Chronic Obstructive Pulmonary Disease
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Contract Research Organization
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
ECSC	European Coal and Steel Community
EDC	Electronic Data Capture
EOT	End of Trial
FAS	Full Analysis Set
FC	Flow Chart
FDC	Fixed Dose Combination
FEV_1	Forced Expiratory Volume in one second
FU	Follow-up
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
GOLD	Global Initiative for Chronic Obstructive Lung Disease
HCG	Human Chorionic Gonadotrophin
IB	Investigator's Brochure
IC	Informed Consent
ICH-GCP	International Council for Harmonisation – Good Clinical Practice
ICS	Inhaled Corticosteroid
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
INN	International Non-proprietary Name
IRB	Institutional Review Board
IRT	Interactive Response Technology

ISF	Investigator Site File
i.v.	Intravenous
L	Liter
LABA	Long-acting β2-agonist
LAMA	Long-acting antimuscarinic antagonist
LPDD	Last Patient Drug Discontinuation
LRTI	Lower Respiratory Tract infection
PRN	Pro re nata (as occasion requires)
q.d.	quaque die (once a day)
q.i.d	quater in die (4 times a day)
REP	Residual effect period, after the last dose of medication with measureable drug levels or pharmacodynamic effects still likely to be present
SABA	Short acting beta agonist
SAE	Serious Adverse Event
SmPC	Summary of Product Characteristics
STORM	Storage conditions for Trial Medications
TCM	Trial Clinical Monitor
TMF	Trial Master File
TSAP	Trial Statistical Analysis Plan
URTI	Upper Respiratory Tract infection
WHO	World Health Organization

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

Chronic obstructive pulmonary disease (COPD) is a chronic and progressive disease characterized by persistent airflow limitation (Global Initiative for Chronic Obstructive Lung Disease 2017 (GOLD) [P16-13658].

Long-acting bronchodilators, such as long-acting muscarinic antagonists (LAMAs) and long-acting beta-agonists (LABAs), are the cornerstone of maintenance therapy for patients with COPD, whose symptoms are not adequately controlled by short-acting bronchodilators alone [P13-05794, P16-13658]. Treatment with inhaled corticosteroids (ICS) is only recommended for patients with a history of exacerbations despite appropriate treatment with long-acting bronchodilators (GOLD group C and D patients) [P16-13658]. In clinical practice, however, ICS/LABA is also commonly used as maintenance treatment for individuals with low exacerbation risk who have less severe COPD, despite a lack of evidence to show that this is the optimal treatment approach for this group.

The rationale for combining bronchodilators with different mechanisms is based on the notion of additive relaxation of airway smooth muscle by direct inhibition of cholinergic activity and functional antagonism of bronchoconstriction through β2-adrenergic pathways, with the expectation of an increase in the degree of bronchodilation for equivalent or lesser side effects. When beta-agonists and muscarinic antagonists with similar or equivalent posologies are combined, the opportunity exists for offering a simpler and more convenient administration regimen with the development of fixed combinations within the same inhaler device. Fixed dose combinations of a short-acting β2-agonist and a short-acting anticholinergic have been developed and have been shown to be safe, efficacious and convenient for the patient (e.g., Combivent®: albuterol+ipratropium bromide; [P94-1346]). The recent interest in the development of LABAs and LAMAs with a once daily posology has presented the opportunity for the development of LABA/LAMA fixed dose combinations with a once daily posology.

The recently completed clinical development program for tiotropium+olodaterol fixed dose combination (FDC) was based on the hypothesis that the combination of the LAMA, tiotropium, and the LABA, olodaterol, inhaled once daily, is superior in improving airflow over 24 hours compared with tiotropium monotherapy once daily and olodaterol monotherapy once daily. In the pivotal studies, this combination has been shown to improve bronchodilation as compared with their respective monotherapies. The addition of a second bronchodilator has been seen to provide additional benefits in terms of enhanced bronchodilation, inspiratory capacity, improved dyspnea, quality of life and a decline in rescue medication use [P15-04531, P15-03349]. Importantly, superiority in lung function improvement with once-daily tiotropium+olodaterol FDC compared to twice-daily salmeterol + fluticasone propionate FDC was demonstrated over the full 24-hour dosing period [P16-01440].

Therefore, the combination of tiotropium+olodaterol in a single Respimat® Inhaler device provides a rational target for optimizing bronchodilator treatment of COPD. In this context and given the increasing number of treatment options available, generating additional evidence may facilitate clinicians´ decision to choose the appropriate approach for individuals who require initiation of maintenance treatment for COPD.

1.2 DRUG PROFILE

Tiotropium+olodaterol combination

Tiotropium+olodaterol FDC (Stiolto® Respimat®) is an aqueous solution of tiotropium and olodaterol contained in a cartridge. It is administered by using the Respimat® inhaler. The same device is used for tiotropium (Spiriva® Respimat®). One cartridge is used per inhaler, which is inserted into the device prior to first use.

In the pivotal studies (1237.5/.6) [c01735218/c01735249] tiotropium+olodaterol FDC showed statistically significant improvements in Forced Expiratory Volume in first second (FEV_1) Area under the curve (AUC_{0-3h}) response and trough FEV_1 response after 24 weeks compared to the mono-components and these improvements were maintained up to 52 weeks. Tiotropium+olodaterol FDC showed statistically significant improvements in health-related quality of life [St. George´s Respiratory Questionnaire (SGRQ)] and dyspnea experienced during everyday activities [Transitional Dyspnea Index (TDI)] after 24 weeks compared to the mono-components. More patients treated with the combination had an improvement in SGRQ total score and TDI focal score greater than the Minimal Clinically Important Difference (MCID). Treatment with tiotropium+olodaterol FDC also resulted in reductions in both daytime and night time rescue bronchodilator use compared to the mono-components. Supportive evidence characterizing the bronchodilating profile of tiotropium+olodaterol FDC over 24- hour dosing interval, with similar 24-hour FEV_1 time profiles and an increased bronchodilatory activity compared to twice daily fluticasone propionate +salmeterol FDC, was provided from a 6-week cross-over trial (1237.11) [P16-01440].

Tiotropium+olodaterol FDC was shown to be safe and well tolerated over 1 year in a moderate to very severe COPD population. The overall incidences of adverse events (AEs), serious adverse events (SAEs), fatal AEs, frequencies for cardiac events and Major adverse cardiovascular event (MACE) in the tiotropium+olodaterol FDC treatment group were similar to the mono-components. The nature and frequency of AEs in general was consistent with the disease under study. There were no results in the clinical development program suggesting the need for absolute contraindications for the combination product.

Based on these observations, marketing authorization for tiotropium+olodaterol (5µg /5µg) FDC (total daily dose) has so far been granted in US, Canada, Australia and in all European countries within the decentralized procedure (DCP) as well as in a number of other countries worldwide.

For a more detailed description of the drug profile refer to the current Summary of Product Characteristics (SmPC) for Stiolto® which is included in the Investigator Site File (ISF).

Boehringer Ingelheim's Respimat® inhaler will be used for administration of study drug. The medication is provided as an aqueous solution in a cartridge, which is inserted into the device prior to first use. A propellant-free device, the Respimat® inhaler generates a soft mist which is released over a period of approximately 1.5 seconds. The fraction of fine particles accessible to the lungs and airways is very high compared with many metered dose aerosols or dry powder devices. The use of the Respimat® inhaler has been shown to be safe with regards to paradoxical bronchoconstriction during chronic use in patients with COPD [P05-08465].

Fluticasone propionate + salmeterol combination

Fluticasone propionate and salmeterol are the constituents in the fixed dose combination product Advair® (Seretide®, Viani®). In the US Advair® (50µg salmeterol and 250µg fluticasone proprionate) given twice daily via the Diskus® inhaler is approved for the maintenance treatment of airflow obstruction and reducing exacerbations in patients with chronic obstructive pulmonary disease (COPD).

More information can be found in the SmPC for US PI for Advair®, included in the Investigator Site File (ISF).

The FDC of fluticasone and salmeterol is registered for the maintenance treatment of patients with severe to very severe COPD and frequent exacerbations in many countries. Despite this labeled indication, the real world use of LABA/Inhaled corticosteroids (ICS) combinations is different and comparable doses to those in the trial are being used from maintenance initiation onwards in the US as well as in many EU countries. Therefore we believe that it is justified to use the comparator product as specified in the trial protocol.

2. RATIONALE, OBJECTIVES, AND BENEFIT - RISK ASSESSMENT

2.1 RATIONALE FOR PERFORMING THE TRIAL

This study will be a randomized, 12 weeks, parallel study to evaluate the lung function and symptom improvements following treatment with tiotropium+olodaterol FDC 5µg/5µg compared to fluticasone + salmeterol FDC 500/100 µg.

In a previous BI study (ENERGITO 1,1237.11), tiotropium+olodaterol FDC 5/5µg was shown to be superior to twice-daily fluticasone + salmeterol FDC 250µg/50µg and 500 µg/50µg with respect to FEV1 AUC_{0-12} response after 6 weeks of treatment. With the growing evidence of once-daily LABA/LAMA FDC having shown superior efficacy vs ICS/LABA FDC in several COPD trials, further assessment of the lung function profile over 24 hours with once daily tiotropium+olodaterol FDC 5/5µg in comparison with a commonly used twice daily ICS/LABA FDC is warranted. This study will use a different formulation of fluticasone+ salmeterol than ENERGITO 1. A 12-week parallel group study was chosen for this trial to avoid repeated washout periods for the patients, which would be necessary in a cross-over trial (design of ENERGITO 1).

There is a specific need for the US to generate further local data on LAMA/LABA vs. LABA/ICS to confirm that LAMA/LABA is significantly superior to LABA/ICS in terms of lung function. In addition, the study will also conduct an initial exploration of the effects of LABA/LAMA compared with LABA/iCS regarding symptom improvement.

2.2 TRIAL OBJECTIVES

The primary objective of the trial is to show superiority in lung function of once daily (2 inhalations) treatment with orally inhaled tiotropium+olodaterol (5µg/5µg) fixed dose combination to twice daily (one inhalation) treatment with fluticasone propionate+salmeterol (250µg/50µg) fixed dose combination over 12 weeks in patients with Chronic Obstructive Pulmonary Disease (COPD).

Safety will be assessed as a further objective.

2.3 BENEFIT-RISK ASSESSMENT

Clinical trials conducted to date have shown tiotropium+olodaterol (5µg/5µg) fixed dose combination to be a safe, well tolerated and efficacious combination therapy according to treatment guidelines in a moderate to severe COPD population. The observed incremental bronchodilator response for the fixed dose combination compared to the individual components translated into benefits that were meaningful for the patient, with improvements in several patient centred outcomes.

Further potential benefits of tiotropium+olodaterol FDC include:

- improved airflow over a complete 24 hour period compared with twice daily treatment with fluticasone propionate+salmeterol FDC

- improved convenience and compliance compared with the free combination of tiotropium and olodaterol

Both tiotropium and olodaterol offer a 24 hour duration of action profile.

Potential risks associated with administration of the combination of tiotropium and olodaterol include the listed (expected) adverse events for tiotropium / olodaterol (5µg/5µg) fixed dose combination. The most frequently reported adverse reactions were nasopharyngitis and cough.

Potential risks associated with administration of tiotropium include the listed (expected) adverse events for tiotropium monoproduct. The most frequently reported adverse reactions were nasopharyngitis, dry mouth and cough.

Potential risks associated with administration of olodaterol include the listed (expected) adverse events for olodaterol monoproduct.

Furthermore, the β_2-mimetic class effects described in the international product information of β_2-agonists such as formoterol [R04-4303, R04-4304, and R04-4305] may also be relevant for olodaterol, both as monoproduct and in combination with tiotropium. As noted in Section 7.1 of the Investigator's Brochure [c01730070-04], careful assessment of cardiovascular function has to be ensured in planned clinical studies of the combination of tiotropium and olodaterol.

The potential benefits for patients outweigh potential risks and justify clinical development of tiotropium+olodaterol FDC.

The fixed-dose combination of fluticasone and salmeterol is registered for the maintenance treatment of patients with severe to very severe COPD and frequent exacerbations in many countries.

Therefore, both treatment regimens are considered options for long-term therapy of COPD and a comparison of both regimens regarding efficacy and safety is of importance for the future treatment of COPD patients.

Women of childbearing potential may be included in clinical trials for tiotropium+olodaterol (5µg/5µg) fixed dose combination provided appropriate precautions are taken to minimise the probability of becoming pregnant. These precautions include pregnancy testing and use of a highly effective method of birth control. Continued testing and monitoring during the trial should be sufficient to ensure compliance with the measures not to become pregnant during the period of drug exposure (which may exceed the length of the study until the follow-up visit at 21 days after discontinuation of the study medication) [R10-5669].

The trial design requires that all eligible patients complete a four week baseline/run-in period in which LABAs, LAMAs and ICS are withdrawn prior to randomization. At the Investigator's discretion, Atrovent® HFA may be provided to patients who are taking a LAMA previous to trial entry for use during the 4 week run-in period; Boehringer Ingelheim (BI) will provide open-label Atrovent® HFA for this purpose.

During the entire course of the trial Boehringer Ingelheim will provide open-label albuterol as PRN rescue medication for all patients who have signed Informed Consent.

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

This is a randomized, double-blind, double-dummy, active-controlled, multi-center, parallel group, Phase IV study to show superiority in lung function of 12 weeks once daily treatment with orally inhaled tiotropium+olodaterol fixed dose combination (5µg/5µg) delivered by the Respimat® inhaler vs. 12 weeks twice daily orally inhaled treatment with fluticasone propionate+salmeterol fixed dose combination (250µg/50µg) delivered by the Diskus® inhaler in patients with Chronic Obstructive Pulmonary Disease (COPD).

The study will consist of a screening and run-in period of at least 4 four week duration, a 12-week randomised treatment period and a three week follow up period.

After signing Informed Consent (IC) at Visit 0 and completing an initial screening visit (Visit 1), patients enter a four-week screening (baseline) period to ensure clinical stability (i.e. no exacerbations). Patients who meet all inclusion criteria and do not present with any of the exclusion criteria will be randomised into the 12-week treatment period (at Visit 2) in which they will be assigned randomly to one of two treatments. An interactive response technology (IRT) system will be used for randomisation to treatment in this trial and for allocation of medication to patients throughout the treatment period. Additional clinic visits will be scheduled after 6 and 12 weeks of treatment (Visits 3 and 4). A follow-up visit (Visit 5) will be scheduled approximately three weeks after the last dose of study medication.

Individual patient participation is concluded when the patient has completed the last planned visit. The “last-patient-last-visit-primary-endpoint” is the last scheduled primary endpoint visit at Week 12 completed by the last patient. The end of the trial is defined as “last patient out”, i.e. last scheduled visit completed by the last patient.

All randomised patients who withdraw prematurely are encouraged to have an end of treatment (EOT) visit and a follow-up visit, three weeks after the EOT visit.

Site staff will contact the patients by telephone approximately one to two days prior to scheduled PFT visits (Visits 2, 3 and 4) to remind them of medication washout and any other requirements in preparation for the visit (see Figure 3.1: 1).

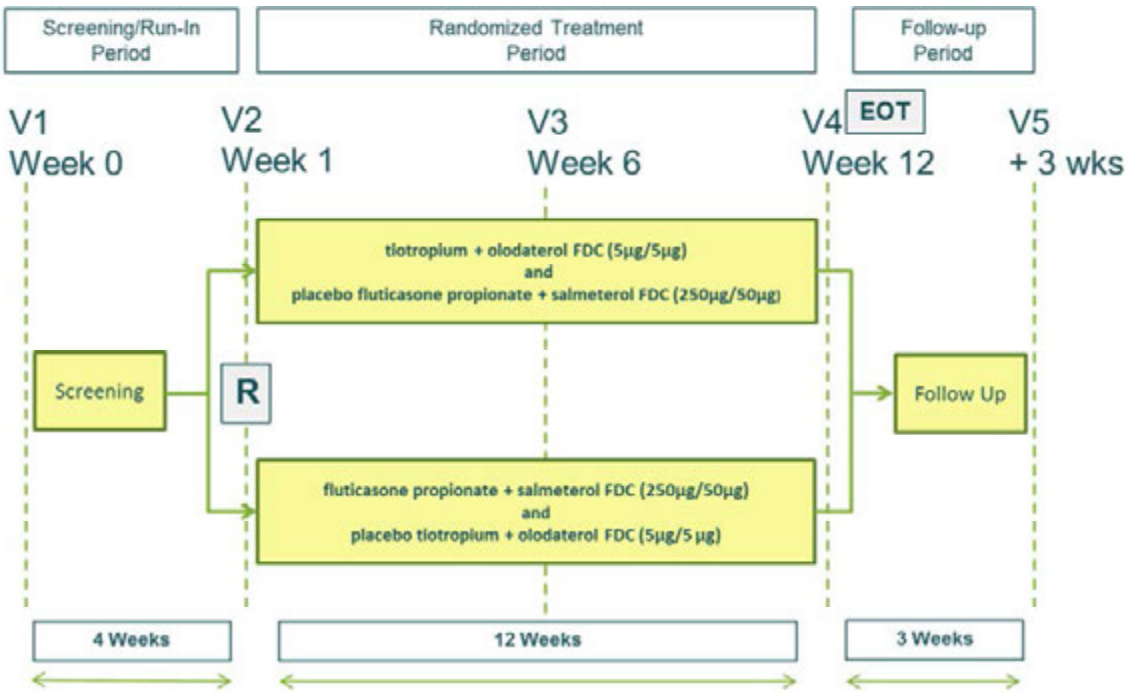

Figure 3.1: 1 Study design flow diagram

Pulmonary function testing (PFT) will be conducted at the screening visit (Visit 1) to determine patient eligibility.

Analysis of clinical laboratory samples will be performed by a Central Lab. Any abnormal laboratory finding at Visit 2, which is considered by the investigator to be clinically relevant, will be recorded as baseline condition.

Adverse events will be documented throughout the trial, i.e. starting with informed consent and ending 21 days after administration of the last dose of trial medication.
Further details of the assessments conducted throughout the study period are provided in the Flow Chart and Section 6.

3.1.1 Administrative structure of the trial

The trial is sponsored by Boehringer Ingelheim (BI).
BI has appointed a Trial Clinical Monitor (TCM), responsible for coordinating all required activities, in order to:

- manage the trial in accordance with applicable regulations and internal SOPs (Standard Operating Procedures).
- direct the clinical trial team in the preparation, conduct, and reporting of the trial,
- ensure appropriate training and information of local clinical monitor (CML), Clinical Research Associates (CRAs), and Investigators.

All study-related documentation will be stored in the BI clinical trial master file (TMF). Trial relevant documentation for the study sites will be filed in the investigator site file (ISF) at the investigational sites.

Boehringer Ingelheim will be responsible for the monitoring of the study. Management of clinical trial supply including an IRT system will be handled by BI and an external vendor.

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

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

Coordinating Investigator: A coordinating investigator is selected by the sponsor. Tasks and responsibilities will be defined in a contract. Relevant documentation on the participating (principal) investigators and other important participants, including their curricula vitae, will be filed in the ISF.

Targeted group of Investigators**:** Pulmonologists/qualified sites with access to the requested patient population. They must have the logistical infrastructure in place to be able to perform 24-hour pulmonary function testing in patients with COPD, including adequate facilities to accommodate overnight stays of patients and site staff over the full course of the study. To facilitate the inclusion of the patients and ease the burden on the study staff, sites might include patients in cohorts, where more than one patient is performing the 24-hour PFT visits at the same day at the same site. This approach requires that adequate site staff and equipment are available during the 24-hour serial spirometry testing days.

The following local facilities/equipment is required at the investigational site:

- scale
- 12-lead electrocardiogram (ECG)
- Barometer for use in calibration of the spirometer

A central laboratory service and vendors for spirometry, and IRT (Interactive Response Technology) will be used in this trial. Details will be provided in the applicable manuals available in the ISF.

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

Patients with COPD with moderate to severe pulmonary impairment will be included in this trial. Pharmacotherapy with long-acting bronchodilators (as single-agent therapy or as combination therapy) is the recommended maintenance treatment for these patients according to various international medical guidelines for the management of this disease [P01-02794, P04-07409].

Since patients may be receiving combination therapy that includes both a long-acting ß-agonist (olodaterol), and a long-acting anti-cholinergic (tiotropium) or a long-acting ß-agonist (salmeterol) and ICS (fluticasone propionate) it is necessary to restrict the use of long-acting ß-agonists (e.g. salmeterol, formoterol, indacaterol), anti-cholinergics (e.g. tiotropium, ipratropium) and inhaled corticosteroids (ICS) during the entire treatment phase. Short-acting ß-agonist medication (salbutamol/albuterol) will be provided to all patients for rescue use (PRN), and appropriate medications will be allowed to control acute exacerbations as medically necessary. A short-acting anticholinergic medication (Atrovent HFA) will be provided for use during the LAMA washout prior to the randomisation visit on investigator's discretion.

Randomisation will be used to avoid any systemic differences between groups with respect to patient characteristics that could affect the outcomes of interest. The double-blind design will be used to ensure that patients, investigators and BI personnel are unaware of each patient's assigned treatment, thus minimizing any potential biases resulting from differences in management, treatment or assessment of patients, or interpretation of results that could arise as a consequence of patient or investigator knowledge of the assigned treatment [R03-2273].

3.3 SELECTION OF TRIAL POPULATION

A sufficient number of patients of either sex, 40 years of age or older, with a diagnosis of COPD will be enrolled in the study to ensure that a minimum of 288 patients are entered (randomized) into the study.

Clinical trials contribute toward reducing health disparities through improved knowledge about treatment among diverse populations. Greater diversity in clinical trial samples allows for broader generalization of trial results, increased minority access to trials, improved standards of care, decreased disparities in disease treatment and outcomes, and improved external validity supported by a more representative sample. Each Investigator should develop a recruitment strategy that ensures the recruitment of a representative patient population and takes into consideration gender, race and ethnicity.

Enrolment will be competitive and conducted at approximately 45 study sites. Additional sites may be initiated and 'non-productive' sites may be closed to ensure sponsor's timelines. It is anticipated that each site will enroll an average of approximately 6 – 8 patients over an approximate 8 month enrollment period.

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

3.3.1 Main diagnosis for trial entry

Outpatients with a history of COPD with moderate to severe pulmonary impairment (according to GOLD guideline [P11-05865]) are eligible for inclusion if they fulfil all the inclusion criteria (Section 3.3.2) and do not present with any of the exclusion criteria (Section 3.3.3).

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

3.3.2 Inclusion criteria

1. All patients must sign an informed consent consistent with FDA regulations prior to participation in the trial, which includes medication washout and restrictions.

2. All patients must have a diagnosis of chronic obstructive pulmonary disease [P11-05865] and must meet the following spirometric criteria:

   Patients with a post-bronchodilator 30% ≤ FEV_1<80% of predicted normal (ECSC, [R94-1408]); and a post-bronchodilator FEV_1/FVC <70% at Visit 1 (see Appendix 10.5 for ECSC predicted normal equations)

3. Male or female patients, 40 years of age or older.

4. Patients must be current or ex-smokers with a smoking history of more than 10 pack years. (see Appendix10.5 for calculation): Patients who have never smoked cigarettes must be excluded.

5. Patients must be able to perform, according to investigator's judgment, all trial related procedures including:
   - Technically acceptable pulmonary function tests (spirometry)
   - Completion of study questionnaires

6. Patients must be able to inhale medication in a competent manner (in the opinion of the investigator) from the Respimat® and Diskus® inhalers (Appendix 10.1 and 10.2) and from a metered dose inhaler (MDI).

3.3.3 Exclusion criteria

1. Patients with a significant disease other than COPD; a significant disease is defined as a disease which, in the opinion of the investigator, may (i) put the patient at risk because of participation in the study, (ii) influence the results of the study, or (iii) cause concern regarding the patient's ability to participate in the study.

2. Patients who have had a COPD exacerbation that required treatment with antibiotics, systemic steroids (oral or intravenous) or hospitalization in the last 3 **months** prior to Visit 1 and/or between Visit 1 and Visit 2.

3. Patients with a history of asthma. For patients with allergic rhinitis or atopy, source documentation is required to verify that the patient does not have asthma. If a patient has a total blood eosinophil count ≥ 600/mm^3, source documentation is required to verify that the increased eosinophil count is related to a non-asthmatic condition.

Patients with any of the following conditions:

4. A diagnosis of thyrotoxicosis (due to the known class side effect profile of $ß_2$-agonists).

5. A diagnosis of paroxysmal tachycardia (>100 beats per minute) (due to the known class side effect profile of $ß_2$-agonists).

6. A history of myocardial infarction within 1 year of screening visit (Visit 1).

7. Unstable or life-threatening cardiac arrhythmia.

8. Hospitalization for heart failure within the past year.

9. Known active tuberculosis.

10. A malignancy for which patient has undergone resection, radiation therapy or chemotherapy within last five years (patients with treated basal cell carcinoma are allowed).

11. A history of life-threatening pulmonary obstruction.

12. A history of cystic fibrosis.

13. Clinically evident bronchiectasis.

14. A history of significant alcohol or drug abuse.

15. Patients who have undergone thoracotomy with pulmonary resection (patients with a history of thoracotomy for other reasons should be evaluated as per exclusion criterion No. 1).

16. Patients being treated with oral or patch β-adrenergics.

17. Patients being treated with oral corticosteroid medication within 6 weeks prior to Visit 1.

18. Patients who regularly use daytime oxygen therapy for more than one hour per day and in the investigator's opinion will be unable to abstain from the use of oxygen therapy during clinic visits.

19. Patients who have completed a pulmonary rehabilitation program in the six weeks prior to the screening visit (Visit 1) or patients who are currently in a pulmonary rehabilitation program.

20. Patients who have taken an investigational drug within one month, six half-lives or (in case the investigational drug (sub) class is listed in Table 4.2.2.1:1) within the wash out period specified in Table 4.2.2.1:1 (whichever is greater) prior to screening visit (Visit 1).

21. Patients with known hypersensitivity to β-adrenergic drugs, BAC, EDTA, or any other component of the Respimat® inhalation solution. In addition, patients with known hypersensitivity to Lactose monohydrate (which contains milk proteins).

22. Pregnant or nursing women.

23. Women of childbearing potential not using a method of birth control classified at least as "acceptable"*. Female patients will be considered to be of childbearing potential unless surgically sterilized by hysterectomy, bilateral salpingectomy, bilateral oophorectomy, or post-menopausal (defined as no menses for 12 months without an alternative medical cause). Tubal ligation is NOT a method of permanent sterilisation.

* as per ICH M3(R2) [R10-5669]: a highly effective method of birth control is defined as those which result in a low failure rate (i.e. less than 1% per year) when used consistently and correctly. As per CTFG Recommendations related to contraception and pregnancy testing in clinical trials (http://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2014_09_HMA_CTFG_Contraception.pdf), sections 2.2.4, 4.1, 4.2 and 4.3, "highly effective" or "acceptable" methods include:

- combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
  - oral
  - intravaginal
  - transdermal
- progestogen-only hormonal contraception associated with inhibition of ovulation :
  - oral
  - injectable
  - implantable
- intrauterine device (IUD)
- intrauterine hormone-releasing system (IUS)
- vasectomised partner
- progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action
- male or female condom with or without spermicide
- cap, diaphragm or sponge with spermicide

24. Patients who have previously been randomized in this study or are currently participating in another study.

25. Patients who are unable to comply with pulmonary medication restrictions prior to randomization.

3.3.4 Removal of patients from therapy

3.3.4.1 Removal of individual patients

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

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

- The patient withdraws consent for trial treatment or trial participation, without the need to justify the decision.
- The patient needs to take concomitant drugs that interfere with the investigational product or other trial medication.
- The patient can no longer be treated with trial medication for other medical reasons (such as surgery, adverse events, other diseases, or pregnancy)
- 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 stick to the trial requirements in the future.

If a patient becomes pregnant or a pregnancy is suspected during the trial, the patient will be permanently discontinued from study treatment and will be followed up until birth or otherwise termination of the pregnancy. For further information on reporting of pregnancy and the outcome of pregnancy, please see Section 5.3.5.2.

Investigators must carefully consider withdrawal from the treatment of an individual patient if any of the following criteria apply:

- More than 3 courses (or increases) of systemic (oral, i.v.) corticosteroids are required to treat a COPD exacerbation
- When, during trial participation, a second hospital admission (at least 2 overnight stays) for a COPD exacerbation occurs
- Clinical deterioration requiring maintenance treatment not allowed per protocol

No patient should be discontinued from the trial for a protocol violation before discussion with the local clinical monitor.

The patient will undergo the procedures for early treatment discontinuation and follow up as outlined in the Flow Chart (FC) and Section 6.2.3.

For all patients the reason(s) for withdrawal (e.g. adverse events) must be recorded in the electronic case report form (e-CRF). These data will be included in the trial database and reported.

3.3.4.2 Discontinuation of the trial by the sponsor

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

1. Failure to meet expected enrolment goals overall or at a particular trial site
2. Emergence of any efficacy/safety information invalidating the earlier positive benefit-risk-assessment that could significantly affect the continuation of the trial
3. Violation of GCP, the CTP, or the contract disturbing the appropriate conduct of the trial

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

After screening, eligible patients will be randomly assigned to one of two study medications for 12 weeks.

1. tiotropium+olodaterol FDC, a once daily dose of 2 actuations of 2.5µg /2.5µg inhalation solution via the Respimat® inhaler.
2. Fluticasone propionate+salmeterol FDC, a twice daily dose of one actuation of 250µg/50µg inhalation powder via the Diskus® inhaler.

- During each treatment the patient will inhale two puffs from the Respimat® inhaler, once daily, in the morning followed by one inhalation from the Diskus® inhaler.
- Each evening the patient will take one inhalation from the Diskus® inhaler only.
- The Respimat® inhaler is not to be used in the evening.

4.1.1 Identity of the investigational medicinal products

Table 4.1.1: 1 Test product 1: tiotropium+olodaterol FDC

Substance:	Tiotropium+olodaterol fixed dose combination
Pharmaceutical formulation:	Inhalation solution
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Unit strength:	2.5 µg / 2.5 µg per actuation
Posology	2 inhalations once daily (a.m. dosing)
Route of administration:	Oral inhalation via Respimat® inhaler

Placebo for test product 1:

Substance:	Tiotropium+olodaterol fixed dose combination
Pharmaceutical formulation:	Inhalation solution
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Unit strength:	NA
Posology	2 inhalations once daily (a.m. dosing)
Route of administration:	Oral inhalation via Respimat® inhaler

Test product 2: Fluticasone propionate+salmeterol FDC

Substance:	Fluticasone propionate+salmeterol fixed dose combination
Pharmaceutical formulation:	Inhalation powder
Source:	GlaxoSmithKline, Zebulon, North Carolina
Unit strength:	250 µg / 50 µg per inhalation
Posology	One inhalation in the morning and evening (a.m. and p.m. dosing)
Route of administration:	Oral inhalation via Diskus®

Placebo for test product 2:

Substance:	Fluticasone propionate+salmeterol fixed dose combination
Pharmaceutical formulation:	Inhalation powder
Source:	GlaxoSmithKline France
Unit strength:	NA
Posology	One inhalation in the morning and evening (a.m. and p.m. dosing)
Route of administration:	Oral inhalation via Diskus®

4.1.2 Selection of doses in the trial

Tiotropium Respimat® 5µg once daily and tiotropium+olodaterol Respimat® 5µg/5µg once daily are approved dose regimens for the treatment of COPD in many countries and these doses were selected for the trial. The clinical trials conducted during the Phase III program for tiotropium+olodaterol FDC 5µg/5µg have shown that this dose is a safe, well tolerated and efficacious combination therapy. The observed incremental bronchodilator response for the combination compared to the individual components translated into benefits that were meaningful to the patient, with improvements in several patient-centered outcomes.

4.1.3 Method of assigning patients to treatment groups

Patients are randomised to treatment at Visit 2. After assessment of all in- and exclusion criteria, each eligible patient will be assigned kits that will have unique medication numbers. Note that the medication number is different from the patient number (the latter is assigned directly after informed consent is obtained). Site personnel will enter the medication number on the case report form.

During visit 2, eligible patients will be randomised to receive tiotropium+olodaterol FDC or fluticasone propionate+salmeterol FDC in a 1:1 ratio according to a randomization plan. The assignment will occur in a blinded fashion via Interactive Response Technology (IRT).

The treatment for each patient is determined by random assignment.

Details on the IRT are provided in the ISF.

4.1.4 Drug assignment and administration of doses for each patient

Dispensing of trial medication

Patients will be randomized at Visit 2 to one of two treatments, tiotropium+olodaterol FDC and placebo fluticasone propionate+salmeterol FDC or fluticasone propionate+salmeterol FDC and placebo tiotropium+olodaterol FDC. At Visit 2 the IRT will assign three Respimat® Kits (two for treatment and one for reserve) and three Diskus® Kits (two for treatment and one for reserve). At Visit 3 the patient will bring in all treatment kits (including the reserve kits) that were dispensed at Visit 2. At Visit 3, two new Respimat® and Diskus® treatment kits will be dispensed in addition to the reserve kit which was previously dispensed at Visit 2. If the reserve kit dispensed at Visit 2 was used by the patient, a new reserve kit will be dispensed as well. Each treatment kit will have a unique medication ID number. Trial medication will be dispensed to the patient by the investigator/pharmacist at these visits. The amount of trial medication dispensed will be recorded on the drug accountability forms.

The reserve kits allow the patient the flexibility of not having to return to the clinic immediately to replace a lost or malfunctioning inhaler. In the event that a patient may need additional inhalers and cartridges due to rescheduled visits, inhaler loss or malfunction, these will be supplied on an 'on demand' basis. Dispensing of these extra inhalers will also be managed via the IRT.

Priming of the Respimat®Inhaler
Each newly assembled Respimat®Inhaler has to be primed. Priming should NOT take place in the same room where the patient is inhaling trial medication. The inhaler should be primed by actuating it until an aerosol is visible plus three additional actuations. All priming actuations should be directed to the ground. For detailed priming instructions please refer to the Respimat®Inhaler handling instructions in Appendix 10.1.

Once assembled, the shelf-life of the Respimat® Inhaler with trial medication is 3 months. Once assembled, the shelf-life of the Respimat® Inhaler with training medication is also 3 months. Therefore it is important to ALWAYS enter the date of the cartridge insertion on the medication label of the Respimat® Inhaler immediately after the cartridge is inserted.

Fluticasone propionate+salmeterol Inhaler - Diskus®
The Diskus® is a dry powder inhaler (DPI) and does not require priming and has no shelf-life restriction other than labelled use-by date. The Diskus® Inhaler should not be used beyond one month after removal from the moisture-protective foil overwrap, or after all blisters have been used (when indicator reads "0"), whichever comes first.

Rescue Medication: ProAir® HFA: Testing of the MDI
Before using for the first time, one actuation should be released into the air to make sure the device is working.

4.1.4.1 Study Medication Administration

Trial medication administration at site visits
Detailed written instructions and training for the use of the Respimat® Inhaler and Diskus® Inhaler will be given to the patient at Visit 1 (see Appendices 10.1 and 10.2). At Visits 2 - 4 detailed instructions on the use of the devices will be repeated if needed, but patients should not inhale from a training device that day. The investigator or qualified study personnel will observe the inhalation procedure and will reinforce a correct inhalation technique.

At each clinic visit and in this order, oral inhalation of two puffs of the trial medication from the assigned Respimat®Inhaler followed by one puff of trial medication from the assigned Diskus® Inhaler (inhaled according to the instructions provided in Appendix 10.1 and 10.2) will be self-administered by the patient under the direct supervision of the investigating physician or designee. In addition, the evening dose of one puff from the Diskus® will be self- administered by the patient under the direct supervision of the investigating physician or designee at Visits 3 and 4. The utmost care should be taken to ensure that during the treatment phase the study medication is not taken prior to coming to the site. The exact time-point of trial medication inhalation (i.e. end inhalation procedure which consists of one inhalation from the fluticasone propionate+salmeterol Diskus®) for both the morning and evening doses on visit days at the site will be captured in the MasterScope® CT spirometer.

When planning the time of the morning dose of trial medication at Visit 2, site personnel should discuss with the patient about the preferred regular time of day that the patient will be taking the morning dose of trial medication at home as this will also affect the time the patient will take the evening dose at home.

At Visit 2, the trial medication will be self-administered between 7:00 a.m. and 10:00 a.m. At subsequent clinic visits, the morning dose of trial medication will be self-administered within ±30 minutes of time of administration at Visit 2. The evening dose of trial medication will be self-administered at home by the patient between 7:00 p.m. and 10:00 p.m., twelve hours (±30 minutes) after the administration of the morning dose of trial medication.

At Visits 3 and 4 (i.e., 24-hour PFT visits), for the evening dosing, oral inhalation of one puff of medication from the Diskus® (inhaled according to the instructions provided in Appendix 10.2) will be self-administered by the patient between 7:00 p.m. and 10:00 p.m., twelve hours (±30 minutes) after administration of the morning dose of trial medication. This evening dose will be inhaled after the 11h50min PFT and prior to the 12hr30min PFT time point.

The last administration of the study medication will be taken at the clinic at Visit 4 (EOT) from the Respimat® inhaler and Diskus® inhaler that is in current use since no new medication treatment boxes will be dispensed at this visit.

Trial medication administration at home

Each morning between clinic visits and in this order, oral inhalation of two inhalations of the trial medication from the assigned Respimat®Inhaler and one puff of trial medication from the assigned Diskus® Inhaler (inhaled according to the instructions provided in Appendices 10.1 and 10.2) will be self-administered by the patient.

Patients are to be instructed that the morning and evening doses of trial medication will be self-administered within ±30 minutes of time of administration at Visit 2.

Each evening, one additional inhalation of trial medication from the Diskus® Inhaler (inhaled according to the instructions provided in Appendix 10.2) will be self-administered by the patient, twelve hours (±30 minutes) after administration of the morning dose of trial medication.

If the patient forgets to take the morning dose of trial medication within the specified time window, the patient can take the morning dose up until 12:00 p.m. (noon). After 12:00 p.m. the patient should skip the morning dose and take evening dose per protocol. The patient should then take the next morning dose at the scheduled time the following day. If the patient forgets to take the evening dose of trial medication within the specified time window, the patient can take the evening dose up until 12:00 midnight. After midnight the patient should skip the evening dose and take the next evening dose at the scheduled time the following evening.

Patients are to be instructed that on the day preceding Visits 3 and 4 that the doses of trial medication must be self-administered within ±30 minutes of time of administration at Visit 2 AND between 7:00 a.m. and 10:00 a.m. for the morning dose to avoid influence on the data collected on the site visit day. Patients should also be instructed that on the day preceding Visits 3 and 4 the evening dose of trial medication must be self-administered within ±30 minutes of time of administration at Visit 2 AND between 7:00 p.m. and 10:00 p.m. to avoid influence on the data collected on the site visit day.

Table 4.1.4.1: 1 tiotropium+olodaterol and fluticasone+salmeterol treatments

Treatment Group	Morning Dose	Evening Dose
Tiotropium+Olodaterol FDC 5µg/5µg	2 puffs – Tio+Olo 2.5µg/2.5µg inhaler plus 1 puff – **placebo** fluticasone propionate+salmeterol	1 puff – **placebo** fluticasone propionate+salmeterol
Fluticasone propionate+salmeterol FDC 250µg/50µg	2 puffs – Tio+Olo **placebo** inhaler plus 1 puff fluticasone propionate+salmeterol 250µg/50µg	1 puff fluticasone propionate+salmeterol 250µg/50µg

Respimat® and Diskus® Return

The Respimat® and Diskus® Inhalers dispensed for treatment can be used for approximately 30 days each.

All used and unused Respimat® and Diskus® Inhalers dispensed at Visit 2 and 3 must be returned to the patient treatment boxes and returned at Visit 3 and 4 respectively, after administration of trial medication at the site.

Any Respimat® Inhaler or Diskus® Inhaler that has been reported as malfunctioning by a patient or investigator will be returned to Boehringer Ingelheim for investigation. See the ISF for specific instructions and for details regarding drug accountability requirements. A detail of the procedure for the return of used inhalers is provided in Appendices 10.1 and 10.2.

4.1.5 Blinding and procedures for unblinding

4.1.5.1 Blinding

Patients, investigators and everyone involved in analyzing or with an interest in this double-blind study will remain blinded with regard to the randomized treatment assignments until after database lock.

Boehringer Ingelheim will generate the randomization scheme using validated randomization software, and prepare and code the medication in a blinded fashion. Study medication will be assigned for the patients via the IRT. Refer to Section 4.1.5.2 for rules for breaking the code for an individual or for all patients in emergency situations.

4.1.5.2 Unblinding and breaking the code

The ability to unblind will be available to the investigator via the IRT. Unblinding must only be used in emergency situations when the identity of the study drug must be known by the investigator to provide appropriate medical treatment. Each site receives a manual from the IRT provider that contains instructions on how to unblind the treatment of a patient via the IRT (via 24-hour Emergency helpline). If possible, the sponsor, i.e. Clinical Monitor Local (CML) and Trial Clinical Monitor (TCM) must be contacted prior to the site unblinding a patient's treatment. Patients unblinded to treatment will be withdrawn from the trial.

4.1.6 Packaging, labelling, and re-supply

Boehringer Ingelheim will provide all study supplies including blinded study medication, open-label Atrovent® HFA, open-label ProAir® HFA and Respimat® and Diskus® training kits. They will be packaged and labelled in accordance with the principles of Good Manufacturing Practice (GMP). Re-supply to the sites will be managed via an IRT system, which will also monitor expiry dates of supplies available at the sites.

Training Materials

- Respimat training: Training Respimat® Inhaler, placebo cartridges and disposable mouthpieces will be provided for training purposes: A training device may be used for more than one training session. The training Respimat® Inhaler can be used until 3 months after first insertion of the cartridge or until the device is empty. The date of the cartridge insertion should be entered on the medication label of the Respimat® immediately after the cartridge is inserted. A new mouthpiece should be used for each patient.

- Diskus® training: Training placebo Diskus® Inhaler kits will be provided for training purposes. The Diskus® Inhaler should not be used beyond one month after removal from the moisture-protective foil overwrap, or after all blisters have been used (when indicator reads “0”), whichever comes first. The device should be cleaned with antiseptic wipes, followed by a dry tissue after each patient use.

Open-label supplies = Auxiliary Medicinal Product (AMP)

- Atrovent® HFA for use as run-in medication will be provided by BI and purchased locally. This medication (Atrovent® HFA) will be provided for use during the LAMA washout prior to the randomization visit, on investigator’s discretion.

- ProAir® HFA MDI inhalation aerosol (100 µg per actuation) for use as rescue medication during the screening/run-in and treatment period. The rescue medication will be provided by BI and purchased locally.

Blinded study medication = Investigational Medicinal Product (IMP)

All study medication (also containing blinded placebo medication) will be contained in Respimat® or Diskus® treatment boxes identified with the trial number and a unique medication number.

The treatment boxes will have a tear-off label. This tear-off label will be attached to the drug dispensing log which will be part of the ISF. Examples of the labels are provided in the ISF.

Packaging

- The Respimat® treatment box will contain 1 Respimat® inhaler plus one drug-filled cartridge and contains sufficient medication for 30 days of treatment. The Respimat® inhaler will lock after 60 actuations have been administered and will no longer actuate any medication.

- The Diskus® treatment box will contain one Diskus® inhaler. Each Diskus® contains sufficient medication for 30 days of treatment. The Diskus® inhaler will be contained inside a foil pouch which will be heat-sealed and labelled, before being placed into the treatment box.

Labelling

Individual treatment boxes will have a medication identification label and a tear-off label. Each tear-off label should be attached to the drug accountability form which will be part of the ISF. The investigator or designee should complete the following information:

- Date of cartridge insertion, patient number and visit number should be entered at time of cartridge insertion on the inhaler booklet label.
- Investigator's name should be entered at the time of dispensing on the label of the treatment box.

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

Medication Dispensing

The assignment of Respimat® and Diskus® treatment boxes dispensed at the beginning of each treatment visit (Visit 2 and Visit 3) will be handled by an IRT system.

At randomisation (Visit 2), the site staff will phone or use the web to access the IRT and obtain medication numbers for each of the 3 Respimat® treatment kits and 3 Diskus® treatment kits to be dispensed to the patient for daily use during the 6 weeks between visits. Two of the treatment kits will be used by the patient and the third is a reserve kit.

The Respimat® and Diskus® medication and reserve kits will have unique medication numbers. One Respimat® inhaler will be primed by the site staff (see Section 4.1.4) and used to dose the patient at that site visit, and will continue to be used at home until 30 days of

treatment has been reached. The Diskus® Inhaler does not have to be primed and will be used for 30 days of treatment.

The second Respimat® kit will be primed and used by the patient to cover the remaining weeks until the next visit. The third Respimat® kit and the third Diskus® kit are reserve medication. This is to allow the patient the flexibility of not having to return to the site immediately to replace a lost or malfunctioning Respimat® or Diskus®.

NOTE: The Respimat® Inhaler and drug-filled cartridge that is not yet in use by the patient (including the reserve) should not be assembled prior to leaving the site. These devices must be assembled and primed by the patient at home when needed. The Investigator or designee should fill in the investigator's name on the medication label of all three Respimat® and Diskus® treatment boxes at time of dispensing to the patient (Visit 2 and 3 respectively).

Please note that the date of cartridge insertion should be entered (label of Respimat® inhaler only) at time of cartridge insertion only, i.e. for the first Respimat® inhaler this is entered by site staff (during Visit 2 and 3), for the second Respimat® inhaler the patient is advised to do so when assembling this device at home during the treatment period, as well as for the third (reserve) Respimat® inhaler, if necessary.

Re-Supply
Each site will receive a first supply after the first patient is registered in the IRT and will be resupplied upon demand by the IRT.

4.1.7 Storage conditions

All clinical trial supplies will be stored in a locked, secure cabinet and must be kept under the recommended storage conditions on the medication label. Clinical trial supplies may only be dispensed to trial subjects according to the protocol.

The Respimat® Inhaler and cartridges and Diskus® Inhaler should be stored as indicated on the country specific booklet page. A temperature log must be maintained at the site to make certain that the drug supplies are stored at the correct temperature as specified in storage conditions for trial medication (STORM) document. If the storage conditions are found to be outside the specified range, immediately contact the local clinical monitor.

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

Further details are provided in the STORM document and on the country-specific labels, a sample of which will be part of the ISF.

Throughout the trial, trial drug receipt and rescue drug receipt, usage and return must be documented and verified. Any discrepancies in drug supplies will be noted and explained.

4.1.8 Drug accountability

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

- Approval of the trial protocol by the IRB / ethics committee,
- Availability of a signed and dated clinical trial contract between the sponsor and the head of the investigational site,
- Approval/notification of the regulatory authority, e.g. competent authority,
- Availability of the curriculum vitae of the principal Investigator,
- Availability of a signed and dated clinical trial protocol,
- Availability of the proof of a medical license for the principal Investigator,
- Availability of Form FDA 1572

The investigator and/or pharmacist and/or investigational drug storage manager must maintain records of:

- the product's delivery to the trial site,
- the inventory at the site,
- the use by each patient,
- the return to the sponsor or alternative disposal of unused products. If applicable, the sponsor or warehouse / drug distribution centre will maintain records of the disposal,
- dates, quantities, batch / serial numbers, expiry ('use-by') dates, and the unique code numbers assigned to the investigational product and trial patients,
- adequate documentation that the patients were provided the doses specified by the CTP,
- reconciliation of all investigational products received from the sponsor.

At the time of return to the sponsor and/or appointed CRO, the investigator / pharmacist / investigational drug storage manager must verify that all unused or partially used drug supplies have been returned by the clinical trial patient and that no remaining supplies are in the Investigator's possession.

The investigator/ pharmacist will record on the drug accountability forms the following information:

For Respimat® inhaler and Diskus® inhaler

- dates (dispense and return)
- dispenser's initials
- batch/serial numbers
- expiry dates
- the unique Respimat® and Diskus® treatment box number assigned by IRT
- trial patient number

It is important to enter the date of priming on the medication label of the Respimat®
see Section 4.1.6.

Rescue medication and run-in medication

AMP accountability forms will be provided for albuterol (rescue medication) and Atrovent HFA (run-in medication-if applicable). This record will include:

- dates (dispense and return)
- dispenser's initials
- quantities
- batch/serial numbers
- expiry dates
- trial patient number

Patients will be asked to return all run-in medication (if dispensed, at Visit 2) and used /unused rescue medication and inhalers at each clinic visit. Source data documentation and full drug accountability in regard to dispensed and returned medication to investigational site and to patients is required. Only used inhalers will be replaced at each clinic visit. For further details, please refer to Section 4.2.1.

4.2 OTHER TREATMENTS, EMERGENCY PROCEDURES, RESTRICTIONS

4.2.1 Rescue Medication, emergency procedures and additional treatments

4.2.1.1 Rescue medication

Administration of rescue medication can occur at any point during the trial as deemed necessary by the patient or the investigator. Open label albuterol HFA MDI (100 µg per actuation) will be provided as rescue medication by BI; only the albuterol MDI provided by BI is allowed for rescue medication use. If the patient requires rescue medication during the pulmonary function test (PFT) days (Visits 2, 3 and 4), the PFTs will be continued if possible. The medication used, route and 24-hour clock time of administration will be recorded on the Rescue Medication eCRF page. The visit should not be re-scheduled.
In the case where the investigator decides to discontinue a patient from a PFT visit or rescue treatment is administered please contact the sponsor (e.g. the Local Clinical Monitor) prior to discontinuing the patient.

Rescue Medication on and before Pulmonary Function Test Days

All test-day rescue medication administered before the conclusion of pulmonary function testing will be recorded on a specific source data worksheet and captured in the eCRF.

4.2.1.2 Emergency procedures

There are no special emergency procedures to be followed.

4.2.1.3 Additional treatment

Medications allowed to control acute exacerbations as medically necessary during the treatment period:

- PRN albuterol HFA inhalation aerosol (MDI) provided by BI.

- Temporary additions of oral steroids are allowed during the treatment portion of the study. Pulmonary function testing visits should not occur within seven days of the last administered dose of an addition of oral steroids. Pulmonary function testing visits may be postponed up to 14 days to meet this restriction. Subsequent visits will be scheduled according to the patient's regular schedule.

- Temporary additions of theophylline preparations are allowed during the treatment portion of the study. Pulmonary function testing visits should not occur within seven days of the last dose. Pulmonary function testing visits may be postponed up to 14 days to accommodate this restriction. Subsequent visits will be scheduled according to the patient's regular schedule.

- The use of antibiotics is not restricted and may be prescribed as medically necessary for exacerbations and / or infections. If antibiotics are prescribed for a respiratory infection prior to pulmonary function testing visits, the visit will be postponed for at least two days but not more than seven days after the last dose is given. Subsequent visits will be scheduled according to the patient's regular schedule.

Oral steroids, theophylline preparations and antibiotics will not be provided by BI.

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

The following table provides an overview of permitted and restricted medication over the different study periods.

Table 4.2.2.1: 1 Permitted medications and medications restrictions

Drug Class	**Sub-class**	**Prior to study**	**Study Period**		
			Screening Period	**Treatment Period**	**Follow up Period**
Corticosteroids	Inhaled corticosteroids (not allowed for 2 weeks prior to V1)	Permitted	**NOT** permitted	**NOT** permitted	Permitted
	Oral corticosteroids (not allowed for at least 6 weeks prior to V1; permitted intermittently during the treatment phase in a case of COPD exacerbation)	Permitted	**NOT** permitted	**NOT** permitted	Permitted
	Injected Corticosteroids – local administration (for treatment of e.g. bursitis)	Permitted	Permitted	Permitted	Permitted

Table 4.2.2.1: 1 Permitted medications and medications restrictions (cont.)

Drug Class	Sub-class	Prior to study	Study Period		
			Screening Period	Treatment Period	Follow up Period
β-adrenergics	Inhaled short-acting β-adrenergics	Permitted[1]	Rescue[1]	Rescue[1]	Permitted
	Inhaled long-acting β-adrenergics (b.i.d.) (e.g. formoterol / salmeterol)	Permitted[1] (w/o 48 hrs. prior to V1)	**NOT** permitted	**NOT** permitted	Permitted
	Inhaled long-acting β-adrenergics (q.d.) (i.e. indacaterol, olodaterol)	Permitted[1] (w/o1 wk prior to V1)	**NOT** permitted (w/o 3wks. prior to V2)	**NOT** permitted	Permitted
β-adrenergics	Oral and patch beta-adrenergics	Permitted[1] (w/o 4 wks. prior to V1)	**NOT** permitted	**NOT** permitted	**NOT** permitted
	Beta blockers (If stabilized 6 wks. prior to V1)	Permitted	Permitted	Permitted	Permitted
Anti-cholinergics	Short-acting anticholinergics (inhalation aerosol, nasal spray)	Permitted[1]	Permitted[1] (w/o 8 hours prior to V2)	**NOT** permitted	Permitted
	Long-acting anticholinergics (b.i.d./q.d.) (i.e. tiotropium, aclidinium, glycopryonnium, umeclidinium, tio+olo)	Permitted (w/o 1 wk prior to V1)	**NOT** permitted (w/o 3 wks. prior to V2)	**NOT** permitted	Permitted

Table 4.2.2.1: 1 Permitted medications and medications restrictions (cont.)

Drug Class	Sub-class	Prior to study	Study Period		
			Screening Period	Treatment Period	Follow up Period
Combinations	ICS/LABA (b.i.d.) (*switch to LABA mono-product 2 weeks prior to V1, and then discontinue LABA at least 48 hrs prior to V1) (if switched to e.g. salmeterol, formoterol)	Permitted[1]	**NOT** permitted*	Study medication	Permitted
	ICS/LABA (q.d.) (*switch to LABA mono-product 2 weeks prior to V1, and then discontinue at least 1 wk. prior to V1) (if switched to e.g. indacaterol, olodaterol)	Permitted	**NOT** permitted*	**NOT** permitted	Permitted
	ICS/SABA (*switch to SABA only 2 weeks prior to V1, and then discontinue SABA at least 8 hrs prior to V1)	Permitted[1]	**NOT** permitted*	**NOT** permitted	Permitted
	short-acting anticholinergic/ SABA (*8 hrs. prior to V1)	Permitted[1]	**NOT** permitted*	**NOT** permitted	Permitted
	Long-acting anticholinergics/long-acting β-adrenergics[2] (e.g. glycopyrronium+indacaterol, umeclidinium+vilanterol)	Permitted (w/o 1 week prior to V1)	**NOT** permitted (w/o 3wks. prior to V2)	Study medication	Permitted

Table 4.2.2.1: 1 Permitted medications and medications restrictions (cont.)

Drug Class	Sub-class	Prior to study	Study Period		
			Screening Period	Treatment Period	Follow up Period
Miscellaneous	Other investigational drugs (*1 month or 6 half-lives (whichever is greater) prior to V1)	**NOT** permitted*	**NOT** permitted	**NOT** permitted	**NOT** permitted
	Cromolyn sodium / nedocromil sodium (*if prescribed for non-asthma condition)	Permitted*	Permitted*	Permitted*	Permitted*
	Antihistamines, antileukotrienes (*if prescribed for non-asthma condition)	Permitted*	Permitted*	Permitted*	Permitted*
	Methylxanthines* (*if prescribed for non-asthma condition)	Permitted[3]	Permitted[3]	Permitted[3]	Permitted[3]
	Mucolytics (not containing bronchodilators; stabilized 6 wks. prior to V1)	Permitted	Permitted	Permitted	Permitted
	Phosphodiesterase type 4 (PDE-4) inhibitor[4] (e.g. roflumilast)	**NOT** permitted	**NOT** permitted	**NOT** permitted	**NOT** permitted
	Biologic or other immunomodulators	**NOT** permitted	**NOT** permitted	**NOT** permitted	**NOT** permitted

Table 4.2.2.1: 1 Permitted medications and medications restrictions (cont.)

1.	Refer to Section 4.2.2.2 for washout period prior to PFTs.
2.	Patients may be switched to q.d. LABA and short acting anticholinergic. Refer to Section 4.2.2.2 for washout period prior to PFTs.
3.	For theophyllines: Refer to Section 4.2.2.2 for washout period prior to PFTs.
4.	Patients currently using PDE-4-inhibitors (e.g. roflumilast) should not be enrolled and roflumilast should not be withdrawn for the purpose of enrolling in this study. Patients who were using roflumilast in the past may be included if their last use was a minimum of 3 months prior to Visit 1. In the event a patient with prior use of roflumilast is enrolled, past medical records are required to support and document why and when roflumilast was stopped.

Medication restrictions for pulmonary function testing:

- Morning dose of trial medication should not be taken prior to test-day pre-dose PFT.
- At least a 2 week washout of inhaled steroids prior to PFTs at Visit 1. (Inhaled steroids are not allowed after Visit 1).
- At least an 8-hour washout of short-acting beta-adrenergic bronchodilators
- At least a 48-hour washout of long-acting beta-adrenergic bronchodilators (b.i.d.) prior to Visit 1 (not allowed between Visit 1 and 5).
- At least a 1-week washout of long-acting beta-adrenergic bronchodilators (q.d.) prior to Visit 1 and a 3-week washout prior to Visit 2.
- At least an 8-hour washout of short-acting anticholinergic bronchodilators prior to Visit 1 and 2 (not allowed during treatment periods)
- At least a 1-week washout of long-acting anticholinergic bronchodilators (b.i.d. or q.d.) prior to Visit 1 and a 3-week washout prior to Visit 2.
- At least a 4-week washout of oral and patch anticholinergics prior to Visit 1.
- At least a 24-hour washout of short-acting (b.i.d. or more frequent administration) theophylline preparations.
- At least a 48-hour washout of long-acting (q.d. administration) theophylline preparation.

4.2.2.2 Restrictions on diet and lifestyle

Restrictions prior to PFT visits:

- Medication washout restrictions should be adhered to as described in Section 4.2.2.1.

- The patient must remain in the building where the pulmonary function testing is performed and must return to the laboratory at least ten minutes prior to the start of each test. An exception is the travel to and from the overnight accommodation, which of course is allowed.

- On pulmonary function test days (including the Screening Visit), patients must refrain from strenuous activity for at least 12 hours prior to pulmonary function testing and throughout the testing period. Patients should also avoid cold temperatures, environmental smoke, dust or areas with strong odors (e.g. perfumes).

- Coffee, tea, chocolate, cola and other caffeine-containing beverages and foods, and ice-cold beverages are not allowed at least 2 hours prior to and during the pulmonary function testing at clinic visits. Decaffeinated beverages are acceptable.

- Smoking should be discouraged for the 12 hours prior to pulmonary function testing and throughout the test day and will not be permitted in the 30-minute period prior to spirometry.

  A patient visit may be re-scheduled twice due to lack of medication washout compliance.

4.2.2.3 Restriction regarding women of childbearing potential

Women of childbearing potential must use the contraception methods described in the patient information.

4.3 TREATMENT COMPLIANCE

Patients are requested to bring all remaining trial medication including empty package material with them when attending visits. Trial medication adherence should be reviewed by the investigator and reported in the eCRF.

Estimating compliance to trial medication

Respimat® Inhaler compliance: Knowing the time interval between clinic visits, it is possible to calculate the number of puffs that should have been administered by the patient. The Respimat® Inhaler contains 60 actuations (30 daily doses). The dose indicator shows approximately how much medication is left. The dose indicator scale is divided into 4 quarters. One quarter used accounts for 7 days of treatment (14 actuations). When the pointer enters the red area of the scale, there is approximately medication for 7 days (14 actuations left). Once the dose indicator has reached the end of the red scale (i.e. all 30 daily doses have been used) the Respimat® inhaler is empty.

Diskus® Inhaler compliance: There is a counter on top of the Diskus® which indicates how many doses are left. It counts down to 0.

The acceptable medication compliance should have an overall value in the range 80% to 120%. If the compliance is less than 80% the patient needs to be re-trained.

Randomised patients should not be discontinued for lack of medication compliance without prior discussion with the sponsor.

5. VARIABLES AND THEIR ASSESSMENT

5.1 TRIAL ENDPOINTS

5.1.1 Primary Endpoint(s)

The primary efficacy variable will be forced expiratory volume in one second (FEV_1), obtained during pulmonary function testing.

The primary endpoint is FEV_1 Area Under the Curve $(AUC)_{0\text{-}24\ h}$ response (change from baseline) [L] after 12 weeks of treatment.

FEV_1 $AUC_{0\text{-}24\ h}$ is calculated as the area under the FEV_1-time curve from 0-24 hours post-dose using the trapezoidal rule, divided by the duration (24 hours) and reported in Liters. FEV_1 $AUC_{0\text{-}24\ hr}$ response (change from baseline) is defined as FEV_1 $AUC_{0\text{-}24\ h}$ minus baseline FEV_1.
The same definition applies to FEV_1 $AUC_{0\text{-}12h}$.

The mean of the two pre-dose pulmonary function test measurements at Visit 2, 1 hour prior and 10 minutes prior to the administration of the first dose of the randomised treatment, is defined as the baseline FEV_1.

5.1.2 Secondary Endpoint(s)

- FEV_1 $AUC_{0\text{-}12\ h}$ response (change from baseline) [L] after 12 weeks treatment
- Trough FEV_1 response (change from baseline) [L] after 12 weeks treatment
- Peak 0-3h FEV_1 response (change from baseline) [L] after 12 weeks treatment

    - Trough FEV_1 is defined as the mean of the FEV_1 value measured at 23 hrs and at 24 hrs after trial medication administration. Trough FEV_1 response (change from baseline) is defined as trough FEV_1 minus baseline FEV_1.

    - Peak $_{0\text{-}3h}$ is defined as the maximum value measured within the first three hours post dosing.

5.2 ASSESSMENT OF EFFICACY

5.2.1 Pulmonary function testing (PFT)

MasterScope® CT spirometers will be provided to sites for the on-site spirometry measurements. The spirometers and their use, including daily calibration on test days, must meet ATS/ERS criteria [P05-12782]. Spirometry will be conducted with the patient in a seated position having abstained from medications as specified in Section 4.2.2.1, and it is preferable that the same trained individual performs the PFTs for a given patient. The best of three efforts will be defined as the highest FEV_1 and the highest FVC each obtained on any of three blows meeting the ATS criteria (with a maximum of five attempts). The highest FEV_1 and FVC will be selected regardless of whether they come from different spirometric maneuvers or from the same maneuver. The 24-hour clock time of the first maneuver for each PFT time point will be recorded.

The clock time of the start and end of inhalation procedure of trial medication will be captured by the MasterScope® CT spirometer.

At Visit 2, pulmonary function tests will be performed to determine patient eligibility and assess bronchial reversibility (for patient characterization). Further details of reversibility testing are described in Appendix 10.5. At Visit 2 the study medication will be self-administered between 07: 00 a.m. and 10:00 a.m. At Visits 3 and 4 the study medication is to be self-administered within ± 30 minutes of the time of administration at Visit 2 (please refer to Section 4.1.4.1 for time window in inhalation of trial medication).

At Visits 3 and 4 the PFT will be measured up to 24 hours after dosing of trial medication (please see specified time points in the Flow Chart). Also refer to the Flow Chart for the time windows for the PFTs.

Refer to Section 4.2.2.2 for restrictions regarding concomitant therapy prior to PFTs. Refer to Section 4.2.2.2 for restrictions on diet and life style prior to PFTs. Refer to the Flow Chart for the timing of PFTs.

5.2.2 Saint George's Respiratory Questionnaire (SGRQ)

The Saint George's Respiratory Questionnaire (SGRQ) [R96-0686] will be completed at Visit 2 and repeated after 12 weeks of treatment (Visit 4).

The SGRQ measures health status in patients with chronic airflow limitation. It comprises two parts which cover three domains (symptoms, activities and impacts) with scores ranging from 0 (no impairment to 100 (worst possible). Part 1 produces the Symptom score and Part 2 the Activity and Impacts scores. A Total score is also produced.

Part 1 (Questions 1 to 8), covers the patients' recollection of their symptoms over the past four weeks. It is not designed to be an accurate epidemiological tool; its purpose is to assess the patient's perception of their recent respiratory problems. The original version was validated using a 12-month recall period. More recently a 4-week recall version (appropriately worded) has been validated. This has slightly weaker psychometric properties than the 12-month version and produces marginally lower Symptoms score and Total score.

Part 2 (Sections 1 – 7) addresses the patients' current state (i.e. how they are these days). The Activity score just measures disturbances to patients' daily activity. The Impacts score covers a wide range of disturbances of psycho-social function. Validation studies showed that this component relates in part to respiratory symptoms, but is also correlates quite strongly with exercise performance (6-minute walking test), breathlessness in daily life (MRC breathlessness score) and disturbances of mood (anxiety and depression). The Impacts score is, therefore, the broadest component of the questionnaires, covering the whole range of disturbances that respiratory patients experience in their lives. The results will be reported in the eCRFs

Details of the SGRQ are provided in Appendix 10.4.

The baseline for SGRQ will be the measurement made prior to the first dosing at Visit 2.

5.2.3 COPD health status

The COPD Assessment Test ™ (CAT) is a short 8-item questionnaire for assessment and monitoring of COPD health status in routine practice. Its scale is 0-40 (high score = poor health). The CAT questionnaire has the advantage of a reduced-number of items and could be used to assess the effects of inhaled therapies [P11-08788]. A sample CAT is provided in Appendix 10.3).

The CAT will be performed at Visits 2 and 4.

The test will be performed according to the "HEALTHCARE PROFESSIONAL USER GUIDE; CATTM; COPD Assessment Test; Expert Guidance on frequently asked questions; Issue 3 February 2012" [R13-0957] provided in the ISF.

Site staff will check the answered CAT questionnaire for completeness. Site staff must not exercise any influence on the patient's answers.

The patient's answers will be transcribed from the CAT questionnaire into the eCRF. The CAT score is the sum of the values corresponding to the answers in the eight questions.

5.3 ASSESSMENT OF SAFETY

There is no endpoint for safety in a statistical sense in this trial. Instead, safety and tolerability will be assessed in a descriptive way based on:

- Adverse events
- Serious adverse events
- Physical examination

5.3.1 Physical examination

A complete, head-to-toe physical examination will be completed on all patients at Visits 1 and 4 (or EOT visit in case of premature withdrawal). Another Physical Examination should be performed at the follow-up visit (Visit 5) only if relevant findings are found at Visit 4. All abnormal findings at Visit 1 will be recorded in the patients' source documents and on the Baseline Conditions eCRF, if applicable. New abnormal findings or worsening of Baseline Conditions during the trial will be recorded as adverse events on the appropriate eCRF page.

The physical examination will also include measurements of systolic and diastolic blood pressure and pulse rate, which will be measured with the patient seated and after having rested for at least five minutes.

5.3.2 Laboratory parameters

Lab assessments will be performed by the central laboratory service provider.

- An absolute Eosinophil count will be performed at the screening visit (Visit 1) and randomization visit (Visit 2) to confirm stability of eosinophil counts.

- Pregnancy testing - A serum human chorionic gonadotrophin (HCG) test will be performed on all females of child-bearing potential at Visit 1. A urine dip stick pregnancy test will be performed at Visits 2, 4 and 5.

5.3.3 Electrocardiogram

A standard 12-lead electrocardiogram (ECG) will be performed on all patients at the screening visit (Visit 1). The purpose of the screening ECG is to obtain information about the patient's baseline condition that may not have been elicited in obtaining the medical history. Therefore, any significant findings from this examination not associated with a baseline condition are recorded on the Baseline Conditions eCRF page. The ECG will be evaluated by the PI and stored in the patient record.

5.3.4 Other safety parameters

Not applicable for this trial.

5.3.5 Assessment of adverse events

5.3.5.1 Definition of adverse events

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

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

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

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

- results in death,
- is life-threatening, this refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if more severe.
- requires inpatient hospitalisation or
- prolongation of existing hospitalisation,
- results in persistent or significant disability or incapacity, or
- is a congenital anomaly / birth defect,
  or
- is to be deemed serious for any other reason if it is an important medical event when based upon appropriate medical judgment which may jeopardise the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions.

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

AEs considered "Always Serious"

Cancers of new histology and exacerbations of existing cancer must be reported as a serious event regardless of the duration between discontinuation of the drug and the occurrence of the cancer.

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

The latest list of "Always Serious AEs" can be found in the EDC system.

These events should always be reported as SAEs as described above.

Adverse events of special interest (AESIs)

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

No AESIs have been defined for this trial.

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

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

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

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

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

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

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

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

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

5.3.5.2 Adverse event collection and reporting

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

- From signing the informed consent onwards through the Residual Effect Period (REP) until individual patient's end of trial:
  - all AEs (serious and non-serious).

- After the individual patient's end of trial:
  the Investigator does not need to actively monitor the patient for AEs but should only report relevant SAEs of which the Investigator may become aware of.

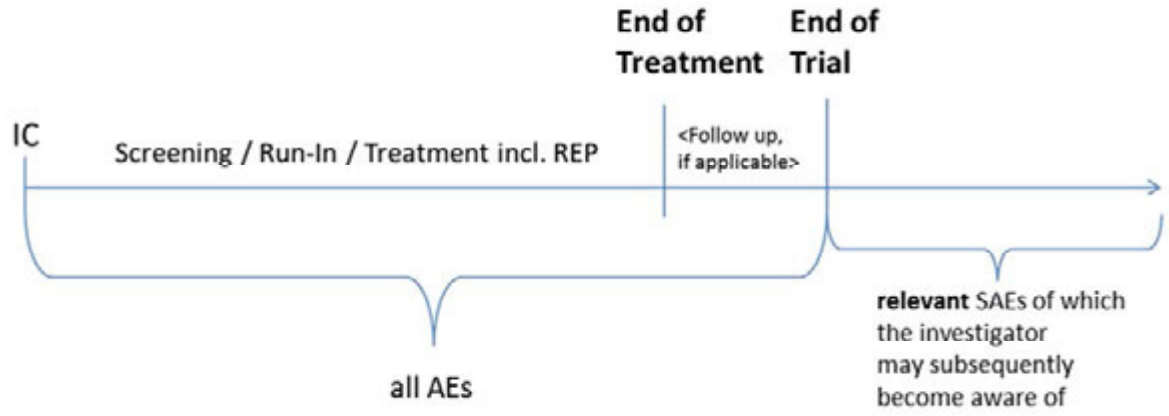

Figure 5.3.5.2: 1 All adverse events

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

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

Information required
For each AE, the Investigator should provide the information requested on the appropriate CRF pages and the BI SAE form. The Investigator should determine the causal relationship

to the trial medication and any possible interactions between the investigational drug(s) and a Non-Investigational Medicinal Product (NIMP) / Auxiliary Medicinal Product (AMP).

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

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

If such abnormalities already pre-exist prior trial inclusion they will be considered as baseline conditions.

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

Pregnancy
In rare cases pregnancy may occur in a clinical trial. Once a patient has been enrolled into this clinical trial and has taken trial medication, the Investigator must report immediately (within 24 hours) a potential drug exposure during pregnancy (DEDP) to the sponsor's unique entry point (country-specific contact details will be provided in the ISF). The Pregnancy Monitoring Form for Studies (Part A) should be used.

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

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

Exemptions to SAE reporting

Not applicable for this trial.

5.3.5.3 COPD Exacerbations

For the purpose of this study, a COPD exacerbation is defined as a complex of lower respiratory events / symptoms (increase or new onset) related to the underlying COPD, with duration of three days or more, requiring prescription of antibiotics and/or systemic steroids and/or hospitalization:

A complex of lower respiratory events is defined as at least two of the following:

- Shortness of breath
- Sputum production (volume)
- Change in sputum color
- Cough
- Wheezing
- Chest tightness

"Onset of exacerbation" will be defined by the onset of first recorded symptom. The "end of Exacerbation" will be decided by the investigator based on clinical judgment.

Exacerbations will be classified as follows:

Mild: a new prescription of maintenance bronchodilator only
Moderate: patient receiving an exacerbation-related prescription of oral corticosteroids and/ or antibiotic not requiring hospitalization.
Severe: COPD-related hospitalization

5.4 DRUG CONCENTRATION MESUREMENTS AND PHARMACOKINETICS

Not applicable for this trial.

5.5 ASSESSMENT OF BIOMARKERS

Not applicable for this trial.

5.6 OTHER ASSESSMENTS

Not applicable for this trial.

5.7 APPROPRIATENESS OF MEASUREMENTS

Measurements of efficacy parameters will be consistent with the following generally recognized standards:

Spirometry
Pulmonary function tests are a validated and well established measurement tool for lung function testing. Pulmonary function tests will be conducted at clinic visits using standardised spirometry equipment. FEV_1 is a standard measurement for the assessment of lung function.

Questionnaires

- The SGRQ is a well-established and validated questionnaire for the measurement of health status in patients with chronic airflow limitation.

- The COPD Assessment Test™ (CAT) is a short 8-item questionnaire for assessment and monitoring of COPD health status in routine practice.

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

Patients should make every attempt to complete the protocol as specified. Each visit date (with its window) is to be counted from Day 1 (Day 1 = Visit 2 / Randomization). If any visit has to be rescheduled, subsequent visits should follow the original visit date schedule. Additional visits for the purpose of re-testing or AE monitoring may be included as deemed necessary by the investigator. Investigators should encourage patient treatment compliance and adherence to other protocol specific activities. Refer to the Flow Chart for time windows for the visits. All deviations from the planned visit schedule will be documented. After this, a discussion with the Clinical Monitor should take place.

Following the screening visit (Visit 1) and the required minimum of 4 week screening period, eligible patients will be randomised into the 12-week treatment portion of the trial (Visit 2). Visit 3 will take place after approximately 6 weeks of treatment and Visit 4 will take place after approximately 12 weeks of treatment. Approximately three weeks, i.e. 21 days after completion of the end of treatment period (Visit 4), there will be one post-treatment follow-up visit (Visit 5).

Patients should make every attempt to complete the protocol as specified. Investigators should encourage patient treatment compliance and adherence to all protocol specific activities.

Rescheduling in general
A patient visit may be rescheduled twice within the permitted time window of the scheduled visit date (See Flow Chart) due to the lack of medication washout compliance or no intake of study medication the day preceding Visit 3 and 4.

Rescheduling prior to randomisation
The 4-week screening period (between Visit 1 and Visit 2) may be extended by up to 4 weeks (i.e. total up to 8 weeks or 56 days) for administrative reasons and/or to meet wash-out requirements.

If a patient experiences an upper respiratory tract infection (URTI) between Visit 1 and Visit 2, Visit 2 may be postponed until 4 weeks following recovery from the infection.

Note: Patients who experience a lower respiratory tract infection (LRTI) or symptoms of a COPD exacerbation during screening period (Visits 1-2) are not eligible for randomisation and must be withdrawn (screen failure).

If the screening is extended by more than an additional 4 weeks (but not more than an additional 8 weeks), the safety screening examinations have to be repeated prior to randomisation. The repeat screening examination will include a physical examination, measurement of vital signs (blood pressure and pulse rate), 12-lead ECG and clinical laboratory evaluation (total eosinophil count and pregnancy test). The patient should return for these evaluations within 1 week prior to the re-scheduled randomization visit (Visit 2). All adverse events and concomitant therapies will be recorded. If the screening period cannot

be completed within an extension period of 8 weeks, the patient should be considered a screen failure.

Rescheduling after randomisation
Subsequent visits after randomisation should take place at the originally scheduled dates to assure required treatment.

If rescheduling of visits after randomisation is necessary, the adherence to the correct total daily doses of the Respimat® Inhaler and/or Diskus® Inhaler must be observed. Reserve medication is dispensed at each treatment visit to avoid intermediate visits.

In case a visit needs to be re-scheduled outside the allowed time window (e.g. in order to meet PFT wash-out requirements following treatment of an acute exacerbation), the CML should be contacted.

6.2 DETAIL OF TRIAL PROCEDURES AT SELECTED VISITS

A complete overview of assessments to be performed at each visit is provided in the trial Flow Chart. Refer to Section 5 for explanations of procedures. Additional details on procedures at selected visits are provided below.

6.2.1 Screening and run-in period(s)

To keep the number of screen failures and patients with avoidable washout procedures as low as possible, patients should be very carefully selected for this trial. Therefore, investigators should make a preliminary check of major inclusion and exclusion criteria when considering patients for enrolment in the trial.

Patient numbers will be assigned in the IRT system and transferred from there to/into EDC, thereby creating the subject in EDC.
Details of any patient who is screened for the trial but is found to be ineligible must be entered in the Enrolment log and documented in the eCRF.

Eligibility will be assessed at Visits 0 and 1 and confirmed at the randomization visit (Visit 2).

Run-in Period
- Informed Consent will be obtained at Visit 0, prior to patient participation in the trial, which includes any medication washout procedures or restrictions. Upon obtaining Informed Consent, the patient will be instructed on the medication washout and other restrictions needed for the screening pulmonary function test at Visit 1.
- The patient will receive instructions on the as needed use of the albuterol MDI (as rescue medication) that will be dispensed at this visit.
- In case the patient has to wash-out of a LAMA in the run-in, at the discretion of the investigator, Atrovent HFA will be dispensed at this visit.
- A preliminary check of inclusion/exclusion criteria is recommended at Visit 0 to avoid unnecessary washout procedures in non-eligible patients.

- Any adverse events and concomitant therapies will be recorded
- The patient will receive a trial identification card.

Observations and procedures at Visit 1
Refer to the Flow Chart for procedures to be conducted at this visit:

- Demographics/Baseline conditions, Physical, COPD characteristics, lab testing, pregnancy testing, ECG, review of smoking status and concomitant medications and AE check.
- Pulmonary function testing with the MasterScope® CT spirometer will be conducted between 7:00 and 10:00 a.m. immediately prior to (-10 min) and ≥10 minutes and up to 45 minutes after the inhalation of 4 puffs of salbutamol (albuterol), (reversibility testing).
- Patients qualified to enter the 4-week (up to 12-week) screening period of the trial will be issued additional rescue medication if needed.
- Patients will receive training and instructions on:
  - the use of the Respimat® Inhaler using the training Respimat® Inhaler containing placebo
  - the use of the Diskus® Inhaler using the training Diskus® Inhaler containing placebo
  - medication restrictions and washout requirements for the screening period and subsequent visits
  - returning all issued medication to the site on all subsequent visits
- Site staff will perform "Screening" call in IRT.

Screening Period
If there is any indication during the screening period that the patient is not stable enough to complete the trial or that the patient will be non-compliant with the trial medication or restrictions, the patient should not be randomised.

A telephone contact is required approximately 1-2 days before Visit 2 to remind the patient of medication restriction requirements.

6.2.2 Treatment period(s)

The treatment period is from Visit 2 (Randomization) though the EOT (End of Treatment). Applicable eligibility criteria will be re-confirmed prior to randomization. Patients that experienced a COPD exacerbation during the screening period (as per exclusion #2) will not be eligible for randomization.

At the beginning of each visit, the investigator and site personnel should ensure that the wellbeing of the patient as well as all requirements for conduct of the visit are applicable:

- Any adverse events and changes in concomitant therapies will be recorded.
- Medication washout compliance and lifestyle restrictions will be verified.
- The 24-hour clock time of the last cigarette smoked during 12 hours prior to start of lung function measurement procedures will be recorded (and smoking status as well).
- Before dosing with trial medication site personnel should ensure that the patient knows how to inhale properly from the Respimat® Inhaler and the Diskus® Inhaler. The patient should not inhale from a placebo training device on visit days.
- At the close of each visit during treatment visit, the investigator and site personnel should ensure that the patient is provided with all instructions for the next visit.

- Patient will be instructed at each visit to bring all rescue medication to the site.

Note:
If the patient is unable to complete any of the entire test-day visits, the electronic case report form will be completed indicating the reason for stopping testing, rescue medication given and time of rescue medication. Patients who are unable to complete the test-day visit may leave the site only upon instruction from the supervising physician.

Observations and procedures:
- At Visit 2, inclusion and exclusion criteria will be reviewed again prior to randomisation. At Visit 2 only: Site staff will perform "Randomization" call in IRT.
- At Visit 2 and 3 the patient will receive instructions on use of Respimat® and Diskus® devices and will be instructed to bring all trial medication to the site in the next visit.
- Approximately 1-2 days prior to visits 2, 3 and 4, a telephone contact will be made to each patient in order to remind him/ her of the medication restrictions and to adhere to the correct time of intake of the trial medication administration the day before the site visit. Please refer to Section 4.1.4 ("trial medication administration at home"). It should be pointed out that trial medication administration on the site visit day will only be performed on site.
- Dosing of trial medication is to be performed on timing pre-determined at Visit 2 (i.e. day 1) (± 30 minutes).
- At Visit 4 only, site staff will make the "Trial Medication Termination" call to the IRT. At Visit 4, rescue medication must be returned and all patients can go back to normal medications after this visit.

6.2.3 Follow up period and trial completion

For all randomised patients termination of trial medication and trial completion must be recorded on the corresponding eCRFs.

Patients who discontinue treatment prior to the planned Flow Chart visit schedule will complete EOT visit procedures instead of the planned treatment period visit. They will also have a follow-up visit approximately 21 days after last treatment.

Following the end of the 12 weeks of treatment, patients will be followed up for an additional 21 days. They will be seen at the end of this visit (Visit 5) and adverse events and concomitant therapies will be reviewed and recorded. If the physical examination performed at Visit 4 yields abnormal values representing clinically significant changes from baseline, it will be repeated at the follow-up visit (Visit 5). Any persistently abnormal test must be fully explained by the investigator and follow-up evaluation performed if necessary. Additionally, all (S)AEs that occur within 21 days after a patient terminates trial medication must be reported according to Boehringer Ingelheim SAE procedures.

The sponsor must be consulted on all persistently abnormal tests and (S)AEs until it is agreed that follow-up is no longer necessary.

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 STATISTICAL DESIGN - MODEL

Design

This is a Phase IV, randomized, double-blind, double-dummy, multi center, active-controlled parallel group study of 12 weeks once daily treatment with orally inhaled tiotropium+olodaterol fixed dose combination delivered by the Respimat® inhaler and 12 weeks twice daily treatment with fluticasone propionate+salmeterol fixed dose combination delivered by the Diskus® in patients with Chronic Obstructive Pulmonary Disease (COPD)

Objective

To show superiority in lung function of once daily treatment with orally inhaled tiotropium (LAMA) +olodaterol (LABA) (5µg/5µg) fixed dose combination to twice daily treatment with fluticasone propionate(LABA) +salmeterol (ICS) (250µg/50µg) fixed dose combination over 12 weeks in patients with Chronic Obstructive Pulmonary Disease (COPD).

7.2 NULL AND ALTERNATIVE HYPOTHESES

The following primary hypothesis will be tested at 5% level of significance (two-sided):

H_0: Mean FEV_1 AUC $_{0\text{-}24h}$ response (change from baseline) [L] after 12 weeks of treatment for tiotropium (LAMA) +olodaterol (LABA) (5µg/5µg) = Mean FEV_1 AUC $_{0\text{-}24h}$ response (change from baseline) [L] after 12 weeks of treatment for fluticasone propionate(LABA) +salmeterol (ICS) (250µg/50µg)

H_1: Mean FEV_1 $AUC_{0\text{-}24h}$ response (change from baseline) [L] after 12 weeks of treatment for tiotropium (LAMA) +olodaterol (LABA) (5µg/5µg) $\neq$ Mean FEV_1 $AUC_{0\text{-}24h}$ response (change from baseline) [L] after 12 weeks of treatment for fluticasone propionate(LABA) +salmeterol (ICS) (250µg/50µg)

The secondary analyses will be performed using the same methodology as the primary analysis.

7.3 PLANNED ANALYSES

The efficacy analysis will be performed in all randomized patients who were documented to have received any dose of trial medication and who have both baseline and any evaluable post-baseline measurement for at least one of the efficacy endpoints. This set will be called Full Analysis Set (FAS).

After blinded review of the magnitude and potential impact of any important protocol violations, a subset of the data corresponding to those patients without any important deviations from the protocol will be created. This will be called the Per-Protocol Set (PPS). If the number of patients in PPS is less than 90% of the number of patients in FAS, the

primary analyses for the primary efficacy endpoint will also be performed on PPS. These will be supportive analyses.

All randomised patients taking any dose of the trial medication will be included in the safety evaluation (Treated Set).

The handling of randomised patients who received the wrong treatment will be specified in the TSAP"

7.3.1 Primary endpoint analyses

In the primary analysis, the two-sided hypothesis as given in Section7.2 will be tested on the adjusted means of FEV_1 AUC $_{0\text{-}24h}$ change from baseline. As PFT measurements will be collected over time, a restricted maximum likelihood (REML)-based mixed-effects model repeated measures (MMRM) model will be used. This model will include treatment, visit and treatment by visit interaction as fixed effects, and baseline as well as baseline by visit interaction as covariates. The mean of the two pre-dose pulmonary function test measurements at Visit 2, 1 hour prior and 10 minutes prior to the administration of the first dose of the randomised treatment, is defined as the baseline FEV_1.
An unstructured covariance structure will be used to model the within patient errors. The SAS procedure MIXED will be used for the restricted maximum likelihood estimation and Kenward-Roger approximation for denominator degrees of freedom. This approach is described in [R10-4391]. Adjusted mean values as well as treatment contrasts will be presented together with 95% confidence intervals. The primary treatment comparisons will be the contrasts between treatments after 12 weeks of treatment.

7.3.2 Secondary endpoint analyses

Secondary and other endpoints:

The MMRM model described for the primary analysis will be performed for the continuous secondary endpoints. Adjusted mean values as well as treatment contrasts will be presented together with the 95% confidence intervals. All calculated p-values should be considered descriptive for the analysis of the secondary endpoints. Sensitivity analyses will be defined in the TSAP, which will be signed off prior to data base lock. The TSAP will include details of sensitivity analyses designed to assess the impact of various assumptions concerning missing data.

7.3.4 Safety analyses

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary. Standard BI summary tables and listings will be produced. All adverse events with an onset between start of treatment and end of the residual effect period

(REP), a period of 21 days after the last dose of trial medication, will be assigned to the treatment period for evaluation.
All randomized patients who have taken at least one dose of study drug (i.e., the treated set) 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.

Statistical analysis and reporting of adverse events will concentrate on treatment-emergent adverse events. To this end, all adverse events occurring between start of treatment and end of the residual effect period will be considered 'treatment-emergent'. The residual effect period is defined as 21 days. Adverse events that start before first drug intake and deteriorate under treatment will also be considered as 'treatment-emergent'.

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

7.3.5 Pharmacokinetic and pharmacodynamic analyses

No pharmacokinetic analysis is planned.

7.4 INTERIM ANALYSES

No interim analysis is planned.

7.5 HANDLING OF MISSING DATA

The REML-based MMRM model described in Section 7.3.1 will handle missing data due to early drop outs or missing data in between visits which are assumed to be missing at random. Additional details on the imputation of missing data will be specified in the TSAP prior to unblinding.

If the patient requires rescue medication during the pulmonary function test (PFT) days (Visits 2, 3 and 4), the PFTs will be continued if possible. The data obtained within the required wash out period of the rescue medication (= 8 hours for albuterol) will be censored.

Missing answers for CAT and SGRQ will be handled based on related manuals [R12-1915 and R12-2870].

7.6 RANDOMISATION

Patients will be randomised in blocks to double-blind treatment. Approximately equal numbers of patients will be randomised to each treatment group. BI will arrange for the randomization and the packaging and labelling of trial medication. The randomization 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 CTR. 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 Statistical Solutions Ltd.

Assuming a standard deviation of 0.22L a total sample size of 274 completed patients, will be able to detect a treatment difference of .075 L, for FEV_1 $AUC_{0\text{-}24h}$ with 80% power, using a two-sided test at α=0.05 for superiority testing. The assumptions for sample size calculation are based on the results of 1237.5, 1237.6, and 1237.11 studies. Assuming a maximum 5% drop-out rate, in order to ensure that 274 completers, 288 patients will be randomized.

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

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

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

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

The Boehringer Ingelheim transparency and publication policy can be found on the following web page: trials.boehringer-ingelheim.com. The rights of the Investigator and of the sponsor with regard to publication of the results of this trial are described in the Investigator contract. As a rule, no trial results should be published prior to finalization of the Clinical Trial Report. The certificate of insurance cover is made available to the Investigator and the patients, and is stored in the ISF (Investigator Site File).

8.1 TRIAL APPROVAL, 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 and international 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 of the participating country. 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 patient must be given sufficient time to consider participation in the trial. The Investigator or designee 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 designee must sign (or place a seal on) 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

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

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

8.3 RECORDS

Case Report Forms (CRF) for individual patients will be provided by the sponsor. See Section 4.1.5.2 for rules about emergency code breaks. For drug accountability, refer to Section 4.1.8.

8.3.1 Source documents

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

The current medical history of the subject may not be sufficient to confirm eligibility for the trial and the Investigator may need to request previous medical histories and evidence of any diagnostic tests. In this case the Investigator must make three documented attempts to retrieve previous medical records. If this fails a verbal history from the patient, documented in their medical records, would be acceptable.

Before providing any copy of patients' source documents to the sponsor 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 to ensure patient confidentiality.

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 or year of birth (in accordance with local laws and regulations)
- Patient participation in the trial (substance, trial number, patient number, date patient was informed)
- Dates of Patient's visits, including dispensing of trial medication
- Baseline conditions (including trial indication and concomitant diseases, if applicable)
- Medication history
- Adverse events and outcome events (onset date (mandatory), and end date (if available))
- Serious adverse events (onset date (mandatory), and end date (if available))
- Concomitant therapy (start date, changes)
- Originals or copies of laboratory results and other imaging or testing results, with proper documented medical evaluation (in validated electronic format, if available)
- Completion of Patient's Participation in the trial" (end date; in case of premature discontinuation document the reason for it).
- Prior to allocation of a patient to a treatment into a clinical trial, there must be documented evidence in the source data (e.g. medical records) that the trial participant

meets all inclusion criteria and does not meet any exclusion criteria. The absence of records (either medical records, verbal documented feedback of the patient or testing conducted specific for a protocol) to support inclusion/exclusion criteria does not make the patient eligible for the clinical trial.

8.3.2 Direct access to source data and documents

The sponsor will monitor the conduct of the trial by regular on-site monitoring visits and in-house data quality review. The frequency of on-site monitoring will be determined by assessing all characteristics of the trial, including its nature, objective, methodology and the degree of any deviations of the intervention from normal clinical practice.

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

8.3.3 Storage period of records

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

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

8.4 EXPEDITED REPORTING OF ADVERSE EVENTS

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

8.5 STATEMENT OF CONFIDENTIALITY AND 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 below. Patient privacy will be ensured by using patient identification code numbers.

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.
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 as a result of the trial need to be available for inspection on request by the participating physicians, the sponsor's representatives, by the IRB / IEC and the regulatory authorities.

8.6 TRIAL MILESTONES

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

The end of the trial is defined as the date of the last visit of the last patient in the whole trial ("Last Patient Out").

The "**Last Patient Drug Discontinuation"** (LPDD) date is defined as the date on which the last patient at an individual trial site ends trial medication (as scheduled per protocol or prematurely). Individual Investigators will be notified of SUSARs occurring with the trial medication until 30 days after LPDD at their site.

Early termination of the trial is defined as the premature termination of the trial due to any reason before the end of the trial as specified in this protocol.

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

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

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10. APPENDICES

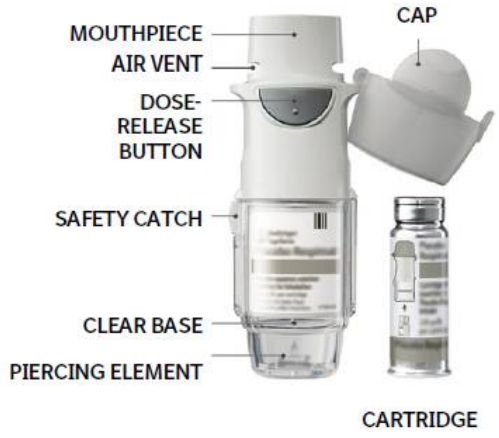
10.1 HANDLING INSTRUCTIONS FOR RESPIMAT® INHALER

How to use your RESPIMAT® inhaler

This leaflet explains how to use and care for your RESPIMAT® inhaler. Please read and carefully follow these instructions.

The RESPIMAT® inhaler releases medication slowly and gently, making it easy to inhale it into your lungs.

The RESPIMAT® inhaler enables you to inhale the medicine contained in a cartridge. You will need to use this inhaler only ONCE A DAY. Each time you use it take 2 PUFFS. In the box you will find the RESPIMAT® inhaler and the RESPIMAT® cartridge. Before the RESPIMAT® inhaler is used for the first time, the cartridge provided must be inserted.



How to store my RESPIMAT®

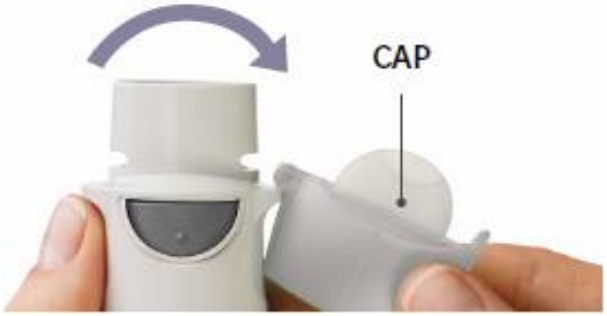
- Keep your RESPIMAT® out of the sight and reach of children.
- Do not freeze your RESPIMAT®.
- If RESPIMAT® has not been used for more than 7 days release one puff towards the ground.
- If RESPIMAT® has not been used for more than 21 days repeat steps 4 to 6 under ‘Prepare for first Use’ until a cloud is visible. Then repeat steps 4 to 6 three more times.
- Do not use your RESPIMAT® after the expiry date

When to get a new RESPIMAT®

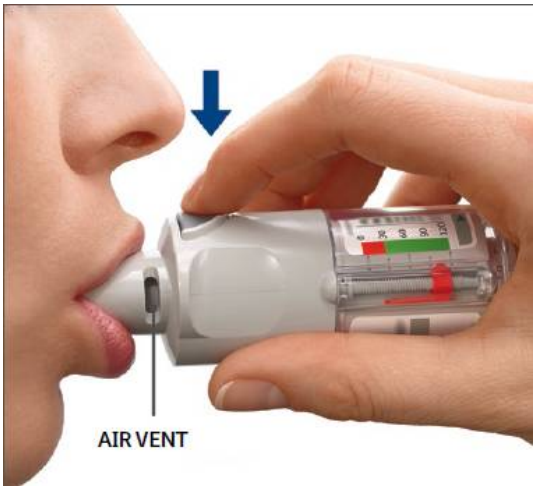
- Your RESPIMAT® inhaler contains 60 puffs if used as indicated.
- The dose indicator shows approximately how much medication is left.
- When the dose indicator enters the red area of the scale you need to get a new prescription; there are approximately 14 puffs left.
- Once the dose indicator reaches the end of the red scale, your RESPIMAT® locks automatically – no more doses can be released. At this point, the clear base cannot be turned any further.
- Three months after first use, the RESPIMAT® should be discarded even if it has not been used.

Prepare for first use

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

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

Daily use

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

Answers to Common Questions

It is difficult to insert the cartridge deep enough.

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

I cannot press the dose-release button.

Did you turn the clear base? If not, turn the clear base in a continuous movement until it clicks (half a turn).
Is the dose indicator on the RESPIMAT® pointing to zero? The RESPIMAT® inhaler is locked after 60 puffs. Prepare and use your new RESPIMAT® inhaler.

I cannot turn the clear base.

Did you turn the clear base already? If the clear base has already been turned, follow steps "OPEN" and "PRESS" under "Daily Use" to get your medicine.
Is the dose indicator on the RESPIMAT® pointing to zero? The RESPIMAT® inhaler is locked after 60 puffs. Prepare and use your new RESPIMAT® inhaler.

The dose indicator on the RESPIMAT® reaches zero too soon.

Did you use RESPIMAT® as indicated (two puffs/Once daily)? RESPIMAT® will last 30 days if used at two puffs once daily.
Did you turn the clear base before you inserted the cartridge? The dose indicator counts each turn of the clear base regardless whether a cartridge has been inserted or not.
Did you spray in the air often to check whether the RESPIMAT® is working? Once you have prepared RESPIMAT®, no test-spraying is required if used daily.
Did you insert the cartridge into a used RESPIMAT®? Always insert a new cartridge into a NEW RESPIMAT®.

My RESPIMAT® sprays automatically.

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

My RESPIMAT® doesn't spray.

Did you insert a cartridge? If not, insert a cartridge.
Did you repeat Turn, Open, Press less than three times after inserting the cartridge? Repeat Turn, Open, Press three times after inserting the cartridge as shown in the steps 4 to 6 under "Prepare for first Use".

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

How to care for your inhaler

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 the performance of your RESPIMAT® inhaler.

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

Further information

The RESPIMAT® inhaler must not be disassembled after inserting the cartridge and replacing the clear base.

Do not touch the piercing element inside the base.

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

Return of malfunctioning RESPIMAT Inhalers

Respimat® inhalers, with the used cartridge in situ, that appeared to malfunction, will be returned to Boehringer Ingelheim as soon as possible. Procedures for this return, including name, address and contact person are provided in the ISF.

10.2 THE DISKUS® INHALER

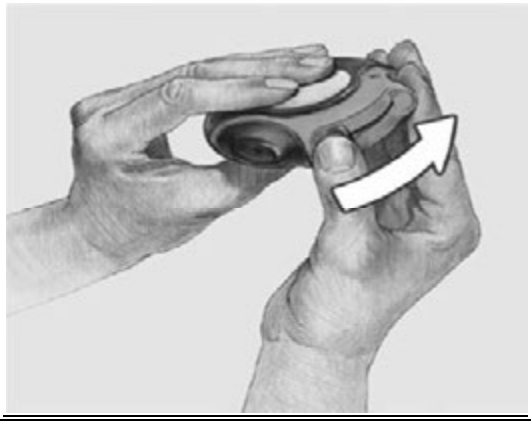
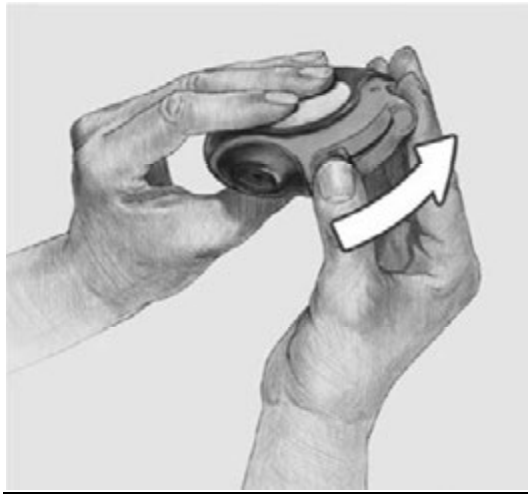
Instructions for use

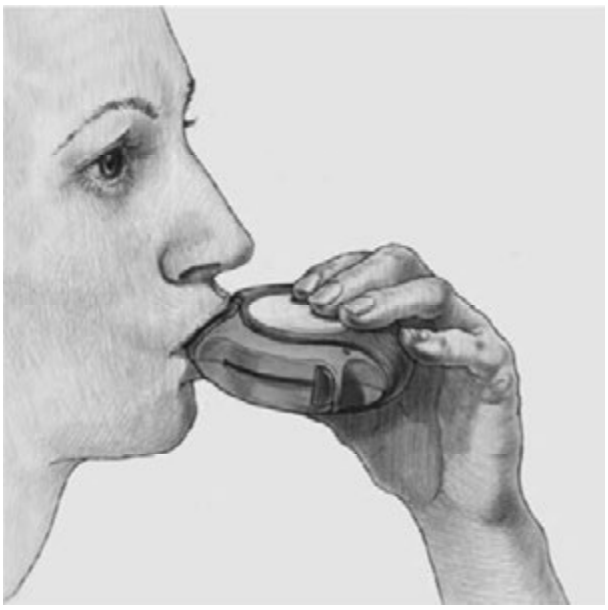
- Your doctor, nurse or pharmacist will show you how to use your inhaler. They will check how you use it from time to time. Not using the Diskus® properly or as prescribed may mean that it will not help your COPD as it should.

- The Diskus® inhaler holds blisters containing medication.

- There is a counter on top of the Diskus® which tells you how many doses are left. It counts down to 0. The numbers 5 to 0 will appear in red to warn you when there are only a few doses left. Once the counter shows 0, your inhaler is empty.

Using your inhaler

	**1** To open your Diskus®, hold the outer case in one hand and put the thumb of your other hand on the thumb grip. Push your thumb away from you as far as it will go. You will hear a click. This will open a small hole in the mouthpiece.
	**2** Hold your Diskus® with the mouthpiece towards you. You can hold it in either your right or left hand. Slide the lever away from you as far as it will go. You will hear a click. This places a dose of your medicine in the mouthpiece. Every time the lever is pulled back a blister is opened inside and the powder made ready for you to inhale. Do not play with the lever as this opens the blisters and wastes medicine.

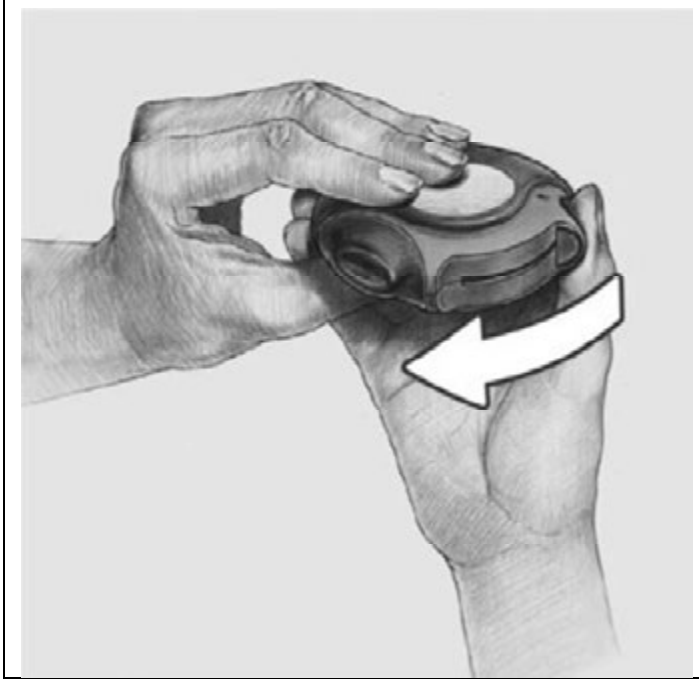


3

Hold the Diskus® away from your mouth, breathe out as far as is comfortable. Do not breathe into your Accuhaler.

4

Put the mouthpiece to your lips; breathe in steadily and deeply through the Diskus®, not through your nose. Remove the Diskus® from your mouth. Hold your breath for about 10 seconds or for as long as is comfortable. Breathe out slowly.



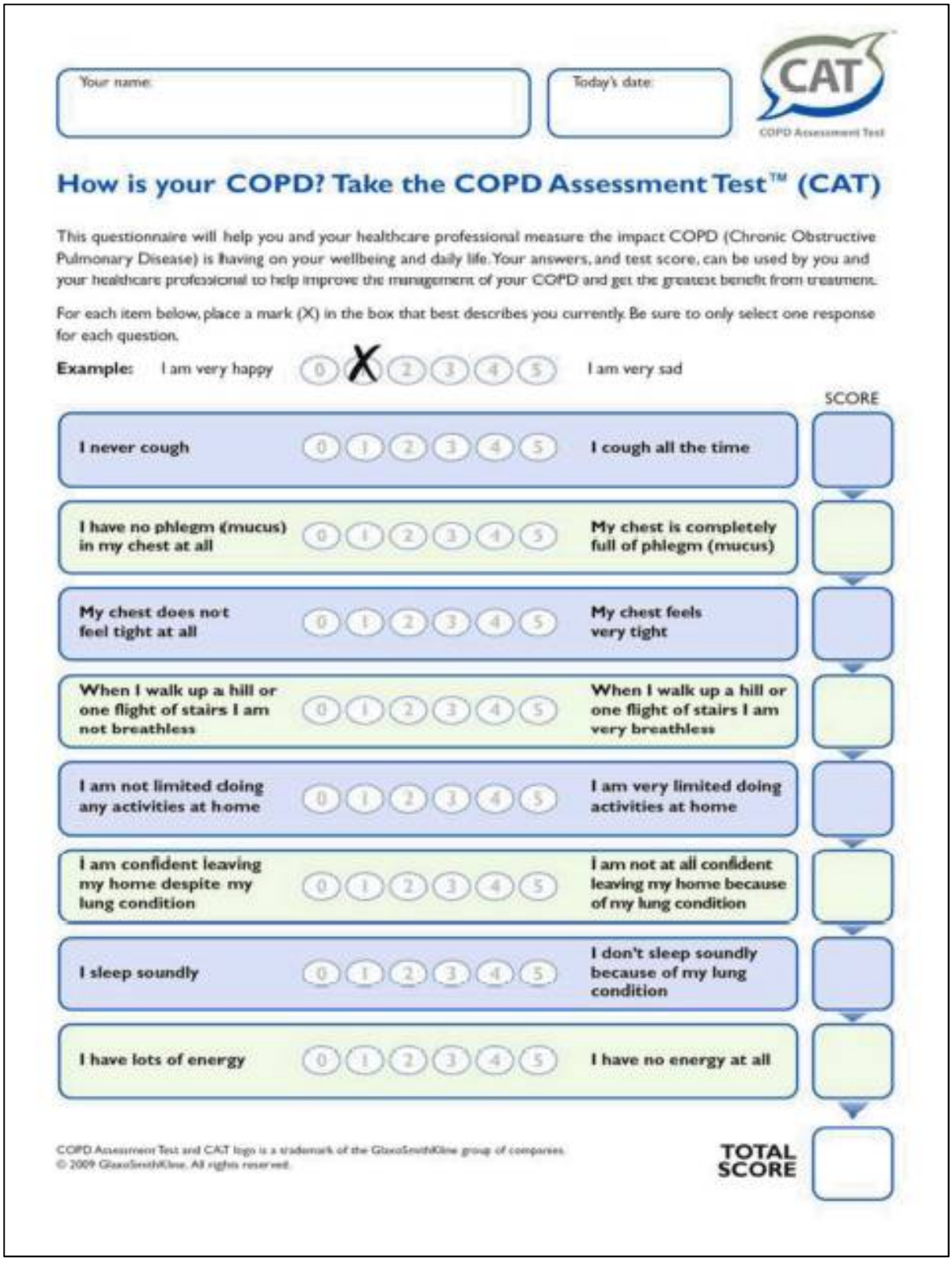
5

Afterwards rinse your mouth with water and spit it out. This may help to stop you getting thrush and being hoarse.

6

To close the Diskus®, slide the thumb grip back towards you, as far as it will go. You will hear a click. The lever will return to its original position and is reset. Your Diskus® is now ready for you to use again.

10.3 COPD ASSESSMENT TEST (CAT)



Your name:

Today's date:

CAT
COPD Assessment Test

How is your COPD? Take the COPD Assessment Test™ (CAT)

This questionnaire will help you and your healthcare professional measure the impact COPD (Chronic Obstructive Pulmonary Disease) is having on your wellbeing and daily life. Your answers, and test score, can be used by you and your healthcare professional to help improve the management of your COPD and get the greatest benefit from treatment.

For each item below, place a mark (X) in the box that best describes you currently. Be sure to only select one response for each question.

Example: I am very happy 0 X 2 3 4 5 I am very sad

		SCORE
I never cough	0 1 2 3 4 5	I cough all the time
I have no phlegm (mucus) in my chest at all	0 1 2 3 4 5	My chest is completely full of phlegm (mucus)
My chest does not feel tight at all	0 1 2 3 4 5	My chest feels very tight
When I walk up a hill or one flight of stairs I am not breathless	0 1 2 3 4 5	When I walk up a hill or one flight of stairs I am very breathless
I am not limited doing any activities at home	0 1 2 3 4 5	I am very limited doing activities at home
I am confident leaving my home despite my lung condition	0 1 2 3 4 5	I am not at all confident leaving my home because of my lung condition
I sleep soundly	0 1 2 3 4 5	I don't sleep soundly because of my lung condition
I have lots of energy	0 1 2 3 4 5	I have no energy at all
		TOTAL SCORE

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TOTAL SCORE SCORE

10.4 ST. GEORGE'S RESPIRATORY QUESTIONNAIRE (SGRQ)

What is the St George's Respiratory Questionnaire?

The SGRQ is designed to measure health impairment in patients with asthma and COPD. It is also valid for use in bronchiectasis and has been used successfully in patients with kyphoscoliosis and sarcoidosis. It is not suitable for cystic fibrosis. It is in two parts. Part I produces the Symptoms score, and Part 2 the Activity and Impacts scores. A Total score is also produced.

Part 1 (Questions 1 to 8) covers the patients' recollection of their symptoms over the past 4 weeks. It is not designed to be an accurate epidemiological tool, its purpose is to assess the patient's perception of their recent respiratory problems. The original version was validated using a 12-month recall period. More recently a four week recall version (appropriately worded) has been validated. This has slightly weaker psychometric properties than the 12-month version and produces a marginally lower Symptom score and Total score.

Part 2 (Questions 9 to 16) addresses the patients' current state (i.e. how they are these days). The Activity score just measures disturbances to patients daily physical activity. The Impacts score covers a wide range of disturbances of psycho-social function. Validation studies showed that this component relates in part to respiratory symptoms, but it also correlates quite strongly with exercise performance (6-minute walking test), breathlessness in daily life (MRC breathlessness score) and disturbances of mood (anxiety and depression). The Impacts score is, therefore, the broadest component of the questionnaires, covering the whole range of disturbances that respiratory patients experience in their lives.

How should it be administered?

The questionnaire should be completed in a quiet area free from distraction and the patient should ideally be sitting at a desk or table. Explain to the patient why they are completing the questionnaire, and how important it is for us to understand how they feel about their illness and the effect it has on their daily life. Ask the patient to complete the questionnaire as honestly as possible and stress that there are no right or wrong answers, simply the answer that the patient feels applies to them. Explain that they must answer every question and that someone will be close at hand to answer any queries.

The SGRQ is designed as a supervised self-administered questionnaire. This means that the patients should complete the questionnaire themselves but someone should be available to give advice if it is required. The patient's responses should not be influenced by the opinions of family, friends or members of staff. The questionnaire is designed to elicit the patient's opinion of his/her health, not someone else's opinion of it. If the spouse or partner has accompanied the patient they should be asked to wait in a separate area. Similarly, do not allow patients to take the SGRQ home to be completed since you cannot be sure that it will be completed without the help of family or friends.

It is very important, once the patient has finished, that you check the questionnaire to make sure a response has been given to every question and return it the patient for completion of missed items, before the patient leaves.

What should I do about queries regarding completion of the questionnaire?

If a patient asks for help with a question, do not provide an answer for them. The point of the questionnaire is to get an understanding of how the patient views his or her illness. It is appropriate to clarify a question but not to provide an answer. Questions may be read aloud if patients have difficulty with reading, but the responses must be theirs alone. It is their view of their condition we are interested in – no matter how strange the response!

The following are notes which may help you explain to patients what is required

1. In Part 1 of the questionnaire, emphasise to patients that you are interested in how much chest trouble they have had over the last 4 weeks.
2. Asthma and COPD can vary day-to day. In Part 2, we want to know about the patient's current state (these days).
3. A severe or very unpleasant attack of chest trouble (Part 1, Question 5) is any attack that could be described that way in the patient's own judgement. Not 'severe' as defined by medical staff.
4. For Question 7 emphasise that you are interested in the number of good days that they have had.
5. Question 10 regarding employment can cause patients some problems. We are interested in how a patient's chest trouble affects their current working life or how it affected life when they were working. For example, if a patient took early retirement because of their chest condition, the response would be 10a – 'My chest trouble made me stop work', if a patient's retirement was unrelated to their chest trouble, their response would be 10c 'My chest trouble does not affect my work'.
6. Questions 11 to 16 require a response to every question. It may be worth emphasising this to the patient.
7. Many patients do not engage in physical activity. It is important to determine whether this is because they do not wish to (in which case the answer would be 'False') or cannot engage in these activities because of their chest trouble (in which case the answer would be 'True').
8. Medication questions refer to medications and treatments given for a patient's chest disease and may interfere with their life if, for example, they are on oxygen support and have to carry it around with them.
9. It should be emphasised that responses to Question 15 are in terms of breathing difficulties and not any other problems. If patients do not engage in activities described in certain items, they should tick 'False'. Patients who do not engage in these activities because they are limited by their breathlessness, should tick 'True'.

EXAMPLE OF QUESTIONNAIRE

This questionnaire is designed to help us learn much more about how your breathing is troubling you and how it affects your life. We are using it to find out which aspects of your illness cause you the most problems, rather than what the doctors and nurses think your problems are.

Please read the instructions carefully and ask if you do not understand anything. Do not spend too long deciding about your answers.

Before completing the rest of the questionnaire:

Please check one box to show how you describe your current health:	Very good	Good	Fair	Poor	Very poor
	☐	☐	☐	☐	☐

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St. George's Respiratory Questionnaire
PART 1

Please describe how often your respiratory problems have affected you over the past 4 weeks.

Please check (✓) *one box for each question*:

	almost every day	several days a week	a few days a month	only with respiratory infections	not at all
1. Over the past 4 weeks, I have coughed:	☐	☐	☐	☐	☐
2. Over the past 4 weeks, I have brought up phlegm (sputum):	☐	☐	☐	☐	☐
3. Over the past 4 weeks, I have had shortness of breath:	☐	☐	☐	☐	☐
4. Over the past 4 weeks, I have had wheezing attacks:	☐	☐	☐	☐	☐

5. How many times during the past 4 weeks have you suffered from severe or very unpleasant respiratory attacks?

Please check (✓) *one*:
- more than 3 times ☐
- 3 times ☐
- 2 times ☐
- 1 time ☐
- none of the time ☐

6. How long did the worst respiratory attack last?
(Go to Question 7 if you did not have a severe attack)

Please check (✓) *one*:
- a week or more ☐
- 3 or more days ☐
- 1 or 2 days ☐
- less than a day ☐

7. Over the past 4 weeks, in a typical week, how many good days (with few respiratory problems) have you had?

Please check (✓) *one*:
- No good days ☐
- 1 or 2 good days ☐
- 3 or 4 good days ☐
- nearly every day was good ☐
- every day was good ☐

8. If you wheeze, is it worse when you get up in the morning?

Please check (✓) *one*:
No ☐
Yes ☐

St. George's Respiratory Questionnaire
PART 2

SECTION 1

How would you describe your respiratory condition?

Please check (✓) *one*:

The most important problem I have	☐
Causes me quite a lot of problems	☐
Causes me a few problems	☐
Causes no problems	☐

If you have ever held a job:

Please check (✓) *one*:

My respiratory problems made me stop working altogether	☐
My respiratory problems interfere with my job or made me change my job	☐
My respiratory problems do not affect my job	☐

SECTION 2

These are questions about what activities usually make you feel short of breath <u>these days.</u>

	For each statement please check (✓) ***the box*** that applies to you ***these days***: True	False
Sitting or lying still	☐	☐
Washing or dressing yourself	☐	☐
Walking around the house	☐	☐
Walking outside on level ground	☐	☐
Walking up a flight of stairs	☐	☐
Walking up hills	☐	☐
Playing sports or other physical activities	☐	☐

SECTION 3

These are more questions about your cough and shortness of breath <u>these days</u>.

For each statement please check (✓) ***the box*** that applies to you ***these days***:

	True	False
Coughing hurts	☐	☐
Coughing makes me tired	☐	☐
I am short of breath when I talk	☐	☐
I am short of breath when I bend over	☐	☐
My coughing or breathing disturbs my sleep	☐	☐
I get exhausted easily	☐	☐

SECTION 4

These are questions about other effects that your respiratory problems may have on you <u>these days</u>.

For each statement, please check (✓) ***the box*** that applies to you ***these days***:

	True	False
My cough or breathing is embarrassing in public	☐	☐
My respiratory problems are a nuisance to my family, friends or neighbours	☐	☐
I get afraid or panic when I cannot catch my breath	☐	☐
I feel that I am not in control of my respiratory problems	☐	☐
I do not expect my respiratory problems to get any better	☐	☐
I have become frail or an invalid because of my respiratory problems	☐	☐
Exercise is not safe for me	☐	☐
Everything seems too much of an effort	☐	☐

SECTION 5

These are questions about your respiratory treatment. If you are not receiving treatment go to section 6.

For each statement, please check (✓) ***the box*** that applies to you ***these days:***

	True	False
My treatment does not help me very much	☐	☐
I get embarrassed using my medication in public	☐	☐
I have unpleasant side effects from my medication	☐	☐
My treatment interferes with my life a lot	☐	☐

SECTION 6

These are questions about how your activities might be affected by your respiratory problems.

	For each statement, please check (✓) ***the box*** that applies to you ***because of your respiratory problems***:	
	True	False
I take a long time to get washed or dressed	☐	☐
I cannot take a bath or shower, or I take a long time to do it	☐	☐
I walk slower than other people my age, or I stop to rest	☐	☐
Jobs such as household chores take a long time, or I have to stop to rest	☐	☐
If I walk up one flight of stairs, I have to go slowly or stop	☐	☐
If I hurry or walk fast, I have to stop or slow down	☐	☐
My breathing makes it difficult to do things such as walk up hills, carry things up stairs, light gardening such as weeding, dance, bowl or play golf	☐	☐
My breathing makes it difficult to do things such as carry heavy loads, dig in the garden or shovel snow, jog or walk briskly (5 miles per hour), play tennis or swim	☐	☐
My breathing makes it difficult to do things such as very heavy manual work, ride a bike, run, swim fast, or play competitive sports	☐	☐

SECTION 7

We would like to know how your respiratory problems <u>usually</u> affect your daily life.

	For each statement, please check (✓) ***the box*** that applies to you ***because of your respiratory problems***:	
	True	False
I cannot play sports or do other physical activities	☐	☐
I cannot go out for entertainment or recreation	☐	☐
I cannot go out of the house to do the shopping	☐	☐
I cannot do household chores	☐	☐
I cannot move far from my bed or chair	☐	☐

Here is a list of other activities that your respiratory problems may prevent you from doing. (You do not have to check these, they are just to remind you of ways your shortness of breath may affect you):

Going for walks or walking the dog

Doing activities or chores at home or in the garden

Sexual intercourse

Going to a place of worship, or a place of entertainment

Going out in bad weather or into smoky rooms

Visiting family or friends or playing with children

Please write in any other important activities that your respiratory problems may stop you from doing:

. . . . . .

. . . . . .

. . . . . .

Now please check the box (one only) that you think best describes how your respiratory problems affect you:

They do not stop me from doing anything I would like to do ☐

They stop me from doing one or two things I would like to do ☐

They stop me from doing most of the things I would like to do ☐

They stop me from doing everything I would like to do ☐

Thank you for completing this questionnaire. Before you finish would you please make sure that you have answered all the questions.

10.5 ADDITIONAL INFORMATION REGARDING IN/EX CRITERIA

Reversibility testing (P05-12782)

At the screening visit (Visit 1), following the completion of three acceptable pre-bronchodilator forced expiratory manoeuvres, albuterol will be administered to each patient in order to document the degree of reversibility. Immediately after (within 10 min) pre-bronchodilator forced expiratory manoeuvres and after a gentle and incomplete expiration, a dose of 100 µg of salbutamol (albuterol) is inhaled in one breath to total lung capacity (TLC). The breath is then held for 5–10 s before the subject exhales. Four separate doses (total dose 400 µg) are delivered at approximately 30-s intervals (this dose ensures that the response is high on the salbutamol dose–response curve). Three additional, acceptable post-bronchodilator forced expiratory manoeuvre tests are recorded ≥10 minutes and up to 45 minutes later after the last dose of albuterol is inhaled.

Calculation of predicted normal values according to ECSC (R94-1408)

For height measured in inches
Males: FEV_1 predicted (L) = 4.30 x [height (inches)/39.37] - 0.029 x [age (yrs)] - 2.49
Females: FEV_1 predicted (L) = 3.95 x [height (inches)/39.37] - 0.025 x [age (yrs)] - 2.60

For height measured in meters
Males: FEV_1 predicted (L) = 4.30 x [height (m)] - 0.029 x [age (yrs)] - 2.49
Females: FEV_1 predicted (L) = 3.95 x [height (m)] - 0.025 x [age (yrs)] - 2.60

Calculation of numberof pack years

$$\text{Pack years} = \frac{\text{Number of cigarettes/day}}{20} \text{ x years of smoking}$$

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

11.1 GLOBAL AMENDMENT 1

Number of global amendment		1.0
Date of CTP revision		11 August 2017
EudraCT number		N/A
BI Trial number		1237-0063
BI Investigational Product(s)		Stiolto® Tiotropium+olodaterol
Title of protocol		A randomized, double-blind, double-dummy, active-controlled, multi-center, parallel group study to show the superiority in lung function of 12 weeks once daily treatment with orally inhaled tiotropium+olodaterol fixed dose combination delivered by the Respimat® inhaler vs. 12 weeks twice daily treatment with orally inhaled fluticasone propionate+salmeterol fixed dose combination delivered by the Diskus® in patients with Chronic Obstructive Pulmonary Disease (COPD) [ENERGITO® 2]
To be implemented only after approval of the IRB / IEC / Competent Authorities	X	
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		
Section to be changed		Section 3.3
Description of change		Exclusion criterion updated to soften contraception requirements.
Rationale for change		To be consistent with current guidance on trials with approved drugs, and to reduce discrepancies in messaging for contraception / fertility / etc. between the IC / protocol and the publically

		available drug label.
Section to be changed		Section 3.3.4.1
Description of change		Removal of the sentence: Details of all COPD exacerbations will be captured in the source notes and on AE/SAE pages.
Rationale for change		As it is not an exacerbation trial, details of exacerbation events will not be collected in this trial.
Section to be changed		Section 5.1.3 and Section 7.3
Description of change		FVC added to further endpoints FAS updated
Rationale for change		To analyse collected endpoints and to keep consistency with 1237.11. To be able to have in the full analysis dataset and therefore to analyze the patients for efficacy if they have missing PFTs but they have other efficacy endpoints collected like SGRQ or CAT.
Section to be changed		
Description of change		Revised sentences to add “or designee” and removed the following sentence: If a trial collaborator has given a supplementary explanation, the trial collaborator also signs (or places a seal on) and dates the informed consent.
Rationale for change		In the US, per FDA regulations, the PI can delegate responsibilities, including consenting of subjects to study team.
Section to be changed		Appendix 10.1
Description of change		Replace Respimat® instructions for use
Rationale for change		Respimat® instructions have been updated

11.2 GLOBAL AMENDMENT 2

Date of amendment		06 March 2018
EudraCT number **EU number**		NA
BI Trial number		1237-0063
BI Investigational Product(s)		Stiolto® Tiotropium+olodaterol
Title of protocol		A randomized, double-blind, double-dummy, active-controlled, multi-center, parallel group study to show the superiority in lung function of 12 weeks once daily treatment with orally inhaled tiotropium+olodaterol fixed dose combination delivered by the Respimat® inhaler vs. 12 weeks twice daily treatment with orally inhaled fluticasone propionate+salmeterol fixed dose combination delivered by the Diskus® in patients with Chronic Obstructive Pulmonary Disease (COPD) [ENERGITO® 2]
To be implemented only after approval of the IRB / IEC / Competent Authorities	X	
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		

Section to be changed	

		randomized at one site.
Section to be changed		Flow Chart and Guidance notes – pages 5-6
Description of change		1. Register patient in screening (IRT) changed from visit 1 to visit 0; 2. #16: remove “once daily”3. Footnote 6 – added “if needed”
Rationale for change		1. Patient numbers must be received when the patient consents, which is at visit 0; 2. Error in guidance notes; 3. clarification
Section to be changed		Section 4.1.4.1
Description of change		“if needed” added to the following sentence:). At Visits 2 - 4 detailed instructions on the use of the devices will be repeated if needed, but patients should not inhale from a training device that day.
Rationale for change		Clarification
Section to be changed		Table 4.2.2.1:1
Description of change		1.Footnote 2 - corrected q.i.d to qd; 2. LAMA/LABA combination during screening, NOT permitted (w/o 4 wks. prior to V2) changed to 3 weeks prior to V2
Rationale for change		errors
Section to be changed		Section 7.3
Description of change		Added: This set will be called Full Analysis Set (FAS).
Rationale for change		Inadvertently left out of protocol
Section to be changed		RDC updated to EDC in several places
Description of change		RDC (Remote Data Capture) is the brand name of Oracle’s EDC (electronic Data Capture System)
Rationale for change		Correctness
Section to be changed		Section 4.3
Description of change		Medication compliance updated from 80-100% to 80-120%
Rationale for change		Correction
Section to be changed		Section 4.1.4
Description of change		The Diskus Inhaler should not be used beyond one month after removal from the moisture-protective foil overwrap, or after all blisters have been used (when indicator reads “0”), whichever comes first.

Rationale for change		Clarification on timeframe to use Diskus device once opened
Section to be changed		Section 4.1.6
Description of change		The Diskus Inhaler should not be used beyond one month after removal from the moisture-protective foil overwrap, or after all blisters have been used (when indicator reads “0”), whichever comes first.
Rationale for change		Clarification on timeframe to use Diskus training device once opened
Section to be changed		Section 6.2.1
Description of change		Patients will be assigned a study patient number in the EDC system once consent is signed. This is populated from the IRT system; therefore, the site should also register the patients as screened in IRT.
Rationale for change		Corrected based in implementation of new systems

APPROVAL / SIGNATURE PAGE

Document Number: c13020187 **Technical Version Number:3.0**

Document Name: clinical-trial-protocol-version-03

Title: A randomized, double-blind, double-dummy, active-controlled, multi-center , parallel group study to show the superiority in lung function of 12 weeks once daily treatment with orally inhaled tiotropium+olodaterol fixed dose combination delivered by the Respimat® inhaler vs. 12 weeks twice daily treatment with orally inhaled fluticasone propionate+salmeterol fixed dose combination delivered by ...

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Approval-Trial Clinical Monitor		06 Mar 2018 16:03 CET
Approval-Biostatistics		06 Mar 2018 16:39 CET
Approval-Team Member Medicine		08 Mar 2018 14:54 CET
Approval-Therapeutic Area		08 Mar 2018 15:05 CET
Verification-Paper Signature Completion		08 Mar 2018 15:29 CET

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed