Clinical Trial Protocol

Doc. No.: c02247259-03

EudraCT No.:	2014-002275-28
BI Trial No.:	1237.19
BI Investigational Products:	Tiotropium + olodaterol fixed dose combination inhalation solution-RESPIMAT®
Title:	A randomised, double-blind, active-controlled parallel group study to evaluate the effect of 52 weeks of once daily treatment of orally inhaled tiotropium + olodaterol fixed dose combination compared with tiotropium on Chronic Obstructive Pulmonary Disease (COPD) exacerbation in patients with severe to very severe COPD. [DYNAGITO]
Clinical Phase:	IIIb
Trial Clinical Monitor:	[redacted] Phone: [redacted] Fax: [redacted] E-mail: [redacted]
Co-ordinating Investigator:	[redacted] Phone: [redacted]
Status:	Revised Protocol (based on global amendment 1)
Version and Date:	**Version: 2.0** **Date: 15 July 2015**

CLINICAL TRIAL PROTOCOL SYNOPSIS

Name of company: Boehringer Ingelheim		**Tabulated Trial Protocol**	
Name of finished product: Not applicable			
Name of active ingredients: - Tiotropium + olodaterol fixed dose combination inhalation solution Respimat® - Tiotropium 5 µg inhalation solution Respimat®			
Protocol date: 29 September 2014	**Trial number:** 1237.19		**Revision date:** **15 July 2015**

Title of trial:	A randomised, double-blind, active-controlled parallel group study to evaluate the effect of 52 weeks of once daily treatment of orally inhaled tiotropium + olodaterol fixed dose combination compared with tiotropium on Chronic Obstructive Pulmonary Disease (COPD) exacerbation in patients with severe to very severe COPD. [DYNAGITO]
Co-ordinating Investigator	[redacted]
Trial sites:	Multi-centre, multi-national trial
Clinical phase:	IIIb
Objective:	The overall objective is to assess the effect of once daily tiotropium + olodaterol fixed dose combination compared to 5 µg tiotropium (both delivered with the Respimat® inhaler) on moderate to severe COPD exacerbation in patients with severe to very severe COPD.
Methodology:	Randomised, double-blind, active-controlled parallel group design
No. of patients:	
total entered:	Approximately 7800 subjects
each treatment:	Approximately 3900 subjects
Diagnosis :	Severe to very severe Chronic Obstructive Pulmonary Disease (COPD)
Main criteria for inclusion:	1. Outpatients of either sex, aged ≥ 40 years with a post-bronchodilator FEV_1 < 60 % predicted and a post- bronchodilator FEV_1/FVC <70% 2. Documented history of at least 1 moderate to severe COPD exacerbation in the previous 12 months. 3. Current or ex-smokers with smoking history >10 pack years **Exclusion:** Patients with a current documented diagnosis of asthma.

Name of company: Boehringer Ingelheim		**Tabulated Trial Protocol**	
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Protocol date: 29 September 2014	**Trial number:** 1237.19		**Revision date:** **15 July 2015**

Test products:	Tiotropium + olodaterol fixed dose combination (FDC) inhalation solutionRespimat® inhaler
dose:	[5 µg tiotropium + 5 µg olodaterol] once daily
mode of admin.:	Oral inhalation
Comparator product:	Tiotropium inhalation solution– Respimat® inhaler
dose:	5 µg once daily
mode of admin.:	Oral inhalation
Duration of treatment:	52-week. In case of early drop-out, each patient will be followed up for exacerbations and vital status up to the predicted end of treatment date (52 weeks) + 21 days follow-up.
Criteria for efficacy:	Primary endpoint • Annualised rate of moderate to severe COPD exacerbation during the treatment period (within 1 day after the last drug administration date) Key secondary endpoint • Time to first moderate to severe COPD exacerbation during the treatment period (within 1 day after the last drug administration date) Secondary endpoints • Annualised rate of exacerbation leading to hospitalisation during the treatment period (within 1 day after the last drug administration date) • Time to first COPD exacerbations leading to hospitalisation during the treatment period (within 1 day after the last drug administration date) • Time to all-cause mortality (within 1 day after the last drug administration date)

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Protocol date: 29 September 2014	**Trial number:** 1237.19		**Revision date:** **15 July 2015**
Criteria for efficacy:	[redacted]		
Criteria for safety:	• Adverse events , serious adverse events and fatal adverse events		
Statistical methods:	For analysis of annualised rate of exacerbation, a negative binomial model accounting for exposure will be used. For analysis of time to event data for exacerbation, Cox's proportional hazard model will be used for hazard ratio estimations and confidence intervals, while log-rank test will be used to obtain p-values. Descriptive statistics and exploratory analyses for safety data.		

FLOW CHART

Study periods	**Screening***	**Randomised 52-week treatment period**										**Follow-up ******
Study visits (V) and phone call (☎)***	**V1**	**V2**	☎	**V3**	☎	**V4**	☎	**V5**	☎	**V6 EoT[4]**	**V6a[12]**	
Study day from Visit 2 (Days)	-1 to -7	Day1	D45 ±7	D90 ±7	D135 ±7	D180 ±7	D225 ±7	D270 ±7	D315 ±7	D360 +7	+ 1 day from V6/EoT	+21 days after V6/EoT (+7)
Informed Consent	X[1]											
Demographics	X											
Cardiovascular risk-factors	X											
Concomitant Diagnosis	X											
[redacted]	[2]											
Physical examination	X									X		X[6]
Laboratory tests	X[9]									X[9]		X[6]
Smoking status	X									X		
12-lead ECG	X											
Review of in-/exclusion criteria	X	X										
Serum pregnancy test [11]	X									X		
Urine pregnancy test		X		X		X		X				X
Screening call (IRT)	X											
Inhalation device trainings [10]	X[10a]	X[10b]		X[10c]		X[10c]		X[10c]				
Rescue medication dispensation	X[8]	X		X		X		X		X		
Medication restriction review	X[3]	X[3]										
Trial patient's card	X											
[redacted]												
Randomisation call (IRT)		X										
Administration of trial drugs in clinic		X		X		X		X				
Last administration of trial drugs in clinic										X		
Assign trial drugs (IRT)		X		X		X		X				
Dispense Patient's reminder card		X		X		X		X		X		
COPD exacerbation interview		X	X	X	X	X	X	X	X	X		X
Collect trial drugs/accountability				X		X		X		X		
Collect rescue medication/accountability				X		X		X		X		X
Compliance check				X		X		X		X		
Discontinuation assessment Vital status collection.						X[13]						X[13]
Discontinuation assessment COPD exacerbation collection			X[14]	X[14]	X[14]	X[14]	X[14]	X[14]	X[14]	X[14]		
Trial drug termination call (IRT)										X		
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X
Conclusion of patient participation												X
Trial Completion												X

STUDY PERIODS

* The visit interval (Visit 1-2) may be extended beyond 7 days for administrative reasons (1 additional week) or to allow for recovery from respiratory infections (4 weeks after recovery from the infection).
** Clinic visits: every 3 months from visit 2
*** Phone calls: between clinic visits, every 6 weeks
**** Conclusion of patient participation also needs to be completed if the patient withdraws prematurely following randomisation.

1. Informed Consent: all patients must sign an informed consent consistent with ICH-GCP guidelines prior to any study related activities which includes medication washout and restrictions. A preliminary check of in-/exclusion criteria with a particular focus on COPD exacerbation status within the previous year is recommended to avoid unnecessary study procedures in non-eligible patients.
2. FEV_1/FVC: historical data from spirometry measurements within the past 3 months either at the site or at a referral site will be used. Spirometry results for COPD severity staging need to be in the patient file on site prior to randomisation. For patients participating in the spirometry sub-study, historical data will not be used for inclusion.
3. Medication restriction review: Refer to Table 4.2.2.1: 1 (Permitted Medications and Medication Restrictions)
4. Visit 6/EoT procedures are to be completed by all patients at the time of study drug discontinuation. For patients who discontinue early, the Visit 6/EoT visit should be performed instead of the scheduled trial visit at time of discontinuation. Please complete directly Visit6/EoT eCRF pages.

[redacted]

6. Physical examination, vital signs and laboratory results: to be performed only if relevant findings at Visit 6 (or last treatment visit in case of premature discontinuation). Please refer to section 5.2.3.1 (Laboratory tests) and section 5.2.3.2 (Physical examination)
7. For prematurely discontinued patients: Vital status and COPD exacerbation status collection: Please refer to section 3.3.4.1
8. Rescue medication: to be dispensed to all patients. Please refer to section 4.2.1.1
9. Laboratory testing: fasted condition is not required
10. Inhalation device trainings: please refer to section 4.1.4.3
    10a: visit1, training session with the Respimat® inhaler training medication (placebo)
    10b: visit 2, training session with the new assigned Respimat® treatment box
    10c: visits 3, 4 and 5. Observance of the inhalation procedure from the new assigned Respimat® treatment box
11. If applicable. Serum pregnancy test at Visits 1 and 6 or EoT and urine dipstick pregnancy test at Visits 2, 3, 4, 5 and follow-up.

[redacted]

13. Vital status collection has to be collected in all patients having discontinued prematurely:
    - BEFORE Visit 4: 2 collection time points at the originally predicted visit 4 and follow-up visit
    - AFTER Visit 4: 1 collection time point at the originally predicted follow-up visit
14. COPD exacerbation status collection: has to be collected in all patients having discontinued prematurely. Collection frequency repeated every 6 weeks at the originally predicted clinic visits and telephone contacts.

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ABBREVIATIONS

AE	Adverse Event
AESI	Adverse Event of Special Interest
a.m.	Ante meridien
ATS	American Thoracic Society
AUC	Area under the curve
BAC	benzalkonium chloride
[redacted]	[redacted]
CI	Confidence Interval
CML	Local Clinical Monitor
CRA	Clinical Research Associate
CTCAE	Common Terminology Criteria for Adverse Events
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
ECG	Electrocardiogram
ECSC	European Coal and Steel Community
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EDTA	Ethylenediaminetetraacetic acid
EoT	End of Treatment
ERS	European Respiratory Society
EU	European Union
EudraCT	European Clinical Trials Database
FAS	Full Analysis Set
FDC	Fixed Dose Combination
FEV_1	Forced expiratory volume in one second
FVC	Forced vital capacity
FRC	Functional residual capacity
GCP	Good Clinical Practice
GOLD	Global Initiative for Chronic Obstructive Lung Disease
[redacted]	[redacted]
IB	Investigator's Brochure
IC	Inspiratory capacity
ICS	Inhaled corticosteroids
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
ISF	Investigator Site File
IRT	Interactive Response Technology
LABA	Long-acting β_2-agonist
LAMA	Long acting muscarinic antagonist
MAC	Mortality Adjudication Committee
MACE	Major adverse cardiovascular event
MCID	Minimal clinically important difference
MedDRA	Medical Dictionary for Drug Regulatory Activities

MDI	Metered Dose Inhaler
OPU	Operative Unit
p.o.	per os (oral)
PEFR	Peak expiratory flow rate
PFT	Pulmonary function testing
PRO	Patient-Reported Outcome
q.d.	quaque die (once a day)
RDC	Remote Data Capture
SAE	Serious Adverse Event
SPC	Summary of Product Characteristics
SGRQ	St. George's Respiratory Questionnaire
SOC	System Organ Class
SPC	Summary of Product Characteristics
TCM	Trial Clinical Monitor
TDI	Transition Dyspnea Index
TDMAP	Trial Data Management and Analysis Plan
TMF	Trial Master File
TMM	Team Member Medicine
TMW	Trial Medical Writer
TSAP	Trial Statistical Analysis Plan
US	United States
w.o	Wash-out

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

Long-acting bronchodilators, such as long-acting muscarinic antagonists (LAMAs), are the cornerstone of maintenance therapy for patients with moderate to very severe chronic obstructive pulmonary disease (COPD) whose symptoms are not adequately controlled by short-acting bronchodilators alone [P13-05794, P14-01052].

An option recommended by GOLD for patients not adequately controlled on a single long-acting bronchodilator is to combine a LAMA with a long-acting β2-agonist (LABA) [P14-01052].This has prompted the development of combining LAMA+LABA as fixed-dose combinations (FDCs) [P13-05794]. 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. Several recent studies have provided evidence in support of this increased bronchodilatory effect when LABAs are added to LAMAs.

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®: salbutamol+ipratropium bromide; [P94-1346]). The development of the novel once daily (quaque die (q.d.))long-acting β2-agonist olodaterol now offers the opportunity for a once daily fixed dose combination including the well-established long-acting muscarinic antagonist tiotropium.

Olodaterol is a highly selective and nearly full β2 agonist [P10-07776, P11-07720] that provides 24-h bronchodilation in patients with COPD [P13-11467, P13-14112, P13-11346, P13-11345] Olodaterol is also associated with symptomatic benefit [P13-11341] and enhanced exercise capacity [P13-14109]. [redacted]

The complementary modes of action of tiotropium and olodaterol have previously been demonstrated in animal models, phase II clinical trials [P10-09337, P14-12073, P10-14042, P13-02357] and during the Phase IIIa programme, which has recently be finalised. [redacted]

In the Phase III programme the additional benefits of the tiotropium + olodaterol FDC over its mono-components has been assessed on lung function, quality of Life (St. George's Respiratory Questionnaire -SGRQ), dyspnea (Transition Dyspnea Index-TDI) and exercise endurance time. Another clinically important potential benefit of the tiotropium + olodaterol FDC over the mono components has so far not thoroughly been investigated, which is the

impact on exacerbations of COPD. Exacerbation related parameters have been included into the pivotal studies as a further endpoint, to inform the planning of this dedicated exacerbation studies. While the studied showed a consistent numerical trend for a reduction in exacerbations for the tiotropium + olodaterol FDC over tiotropium, the magnitude of this effect varied considerably in magnitude, depending on the study (1237.5 vs. 1237.6), patient sub-set (treated set vs. patients with an exacerbation history) and the exacerbation related outcome (time to first exacerbation vs. annual rate), as this can be expected in a non-powered study.

1.2 DRUG PROFILE

Tiotropium

Tiotropium is an established once-daily (QD) LAMA that improves the main functional and patient-orientated outcomes of COPD [P08-12524, P10-08261, P13-04267, P11-07562, P11-03885, P13-11053]. Tiotropium has also been demonstrated to moderate disease progression, even in the early stages of COPD (e.g. patients not receiving maintenance therapy [P10-02376] or those with Global initiative for chronic Obstructive Lung Disease [P14-01052] 2 disease [P09-11278]).

Tiotropium in the dry powder inhaler HandiHaler has been approved in [redacted] countries worldwide. An alternative aqueous formulation for use in the Respimat inhaler (tiotropium 5µg q.d.) is approved in [redacted] countries worldwide including EU and Japan [redacted]. Further information about tiotropium can be found in the respective Summary of Product Characteristics (SPC) for the product.

Tiotropium + olodaterol fixed dose combination

Tiotropium + olodaterol FDC 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 (approved in the EU and [redacted] other countries worldwide), olodaterol (approved in the EU and several other countries worldwide) and Combivent® (approved in the US). One cartridge is used per inhaler, which is inserted into the device prior to first use. In pivotal clinical trials and for the intended marketed product, the clinical dose consists of two actuations once daily. The RESPIMAT inhaler uses mechanical energy to create a soft mist which is released over a period of approximately 1.5 seconds.

In the pivotal studies (1237.5/.6), tiotropium + olodaterol FDC showed statistically significant improvements in FEV_1 Area under the curve (AUC_{0-3h}) response and trough Forced expiratory volume in one second (FEV_1) response after 24 weeks compared to the mono-components and these improvements were maintained up to 52 weeks. The bronchodilatory profile of the combination was confirmed in a supportive 6-week study (1237.20), in which the mean FEV_1 improvements over 24 hours were superior to the mono-components, with improvements in forced vital capacity (FVC), inspiratory capacity (IC), functional residual capacity (FRC), morning peak expiratory flow rate (PEFR) and evening PEFR supporting the results for FEV_1.

Tiotropium + olodaterol FDC showed statistically significant improvements in health-related quality of life (SGRQ) and dyspnoea experienced during everyday activities (TDI) after 24 weeks compared to the mono-components. More patients treated with the combination had an improvement in SGRQ total score and TDI greater than the Minimal clinically important difference (MCID).

Treatment with tiotropium + olodaterol FDC resulted in reductions in both daytime and night time rescue bronchodilator use compared to the mono-components and patients treated perceived a greater improvement in their respiratory condition, as measured by a Patient´s Global Rating scale.

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 event (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.

In conclusion, the clinical trials conducted to date have shown tiotropium + olodaterol FDC to be a safe, well tolerated and efficacious combination therapy according to treatment guidelines in a moderate to very severe COPD patient population that included patients with concomitant cardiovascular diseases. 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 centred outcomes. For further information please refer the Investigators Brochure for the Tio+Olo FDC [c01735808].

2. RATIONALE, OBJECTIVES, AND BENEFIT - RISK ASSESSMENT

2.1 RATIONALE FOR PERFORMING THE TRIAL

According to the GOLD guidelines, exacerbations are important events in the course of COPD as they have major impact on the patient`s quality of life and cause an increase in symptoms and a deterioration of lung function that may take several weeks to recover from. Moreover an exacerbation will accelerate the decline of lung function and is associated with significant mortality, especially if a hospitalisation is needed. It is without doubt, that exacerbations are associated with significant socioeconomic costs [P14-01052]

The benefits of tiotropium + olodaterol (5/5 µg) FDC that have been studied in the Phase III program include improvements in lung function, quality of life, dyspnea and exercise endurance time, but the benefit on exacerbations has not formally been assessed.

2.2 TRIAL OBJECTIVES

The aim of this study is to demonstrate that once daily treatment with tiotropium 5 µg + olodaterol 5 µg fixed dose combination will reduce the number of exacerbations over tiotropium 5 µg monotherapy.

A secondary aim of the study is an assessment of a potential impact of tiotropium 5 µg + olodaterol 5 µg FDC on hospitalisation associated with exacerbations and survival, as compared to tiotropium 5 µg monotherapy. The latter will be included as secondary endpoints.

See section 5 for details concerning endpoints.

2.3 BENEFIT - RISK ASSESSMENT

The potential benefits of a treatment with tiotropium and tiotropium + olodaterol (5/5 µg) FDC from the Respimat have been described above. Tiotropium is a well-established maintenance treatment for patients with COPD across all severities.

The clinical trials conducted to date have shown tiotropium + olodaterol (5/5 µg) FDC to be a safe, well tolerated and efficacious combination therapy according to treatment guidelines in a moderate to very severe COPD patient population (including patients with concomitant cardiovascular diseases). 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 centred outcomes. Potential risks associated with administration of tiotropium include the listed (expected) adverse events for tiotropium monoproduct ([U92-0551]).

Potential risks associated with administration of the combination of tiotropium and olodaterol include the listed (expected) adverse events for tiotropium + olodaterol (5/5 µg) FDC.

Women of childbearing potential may be included in clinical trials for tiotropium + olodaterol (5/5 µg) FDC provided appropriate precautions are taken to minimize the risk of pregnancy. 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 study until the follow-up visit at 21 days after discontinuation of study medication) [R05-0370].

The trial design requires that patients will be randomized at Visit 2 (1:1) to one of the following treatments:

i. Tiotropium + olodaterol FDC (2.5 µg / 2.5 µg per actuation) inhalation solution
ii. Tiotropium (2.5 µg / per actuation) inhalation solution (control group)

There is no placebo comparator in this trial.

Patients taking commercial tiotropium with/without LABAs will take their maintenance treatment up to the day prior to the randomization visit (visit 2).

Patients receiving inhaled corticosteroids before enrolment will continue their treatment (or the inhaled corticosteroids component alone if taken as a fixed combination with bronchodilator) at the same equivalent dose and regimen during the study. The only medications that are excluded during the treatment period are anticholinergic and long-acting β-adrenergic other than the study drugs.

The proposed medication restriction scheme is considered ethically acceptable given the availability of rescue SABA and permitted use of other maintenance medications in conjunction with close clinical monitoring for exacerbation symptoms.

During the whole course of the trial Boehringer Ingelheim will provide open-label salbutamol/albuterol HFA MDI to be used as rescue medication for all patients after they have signed their informed Consent.

Safety will be monitored (as described in Section 5.2) at site visits and at each telephone contact alike. Patients will be contacted by site staff and asked for COPD exacerbation status, adverse events and change in concomitant therapy.

The study will be conducted under the guidance of a Steering Committee (SC).

An adjudicated analysis of all deaths will be also performed by an independent Mortality Adjudication Committee (MAC) in a blinded manner.

In conclusion, the proposed assessment of a potential added benefit of olodaterol to the known effects in reducing exacerbations shown with tiotropium alone is an important medical and health economic question. Therefore the potential benefits for patients outweigh potential risks and justify clinical development of tiotropium + olodaterol (5/5 µg) FDC.

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

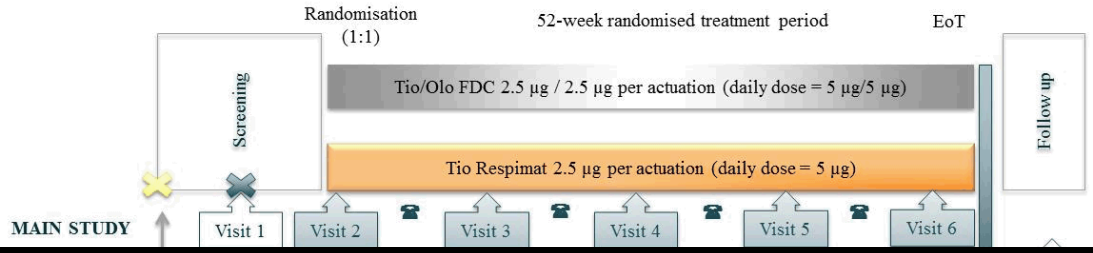
3.1 OVERALL TRIAL DESIGN AND PLAN

This is a randomised, double-blind, active-controlled parallel group, phase IIIb study to evaluate the effect of 52 weeks of once daily treatment of orally inhaled tiotropium + olodaterol (5/5 µg) fixed dose combination compared with tiotropium on Chronic Obstructive Pulmonary Disease (COPD) exacerbation in patients with severe to very severe COPD and with one or more moderate to severe COPD exacerbation during the previous 12 months.

[redacted]

The study is multinational and involves more than 50 participating countries.

The trial consists of three consecutive study periods including the screening, the treatment and follow-up periods. An overview of the trial design is shown in Figure 3.1:1.



[redacted]

Figure 3.1:1 Study Design [redacted]

Having obtained the signed informed consent, the patient will be entered in a maximum 7-day screening period to confirm the patient's eligibility. At Visit 2 after a successful review of the inclusion and exclusion criteria, the patient will be randomly allocated in equal ratio to receive once daily study treatment (Refer to section 4.1.2) and will then enter the 52-week treatment phase. The randomised treatment period consists of five 3-monthly clinic visits and in the interim a telephone contact will be scheduled every 6 weeks (Refer to Flow chart).

The planned on-treatment period will begin with the administration of the first dose of trial medication and until the completion of visit 6/EoT.

The patient's trial participation will be concluded with the follow-up visit 21 days after V6/EoT.

For visit details please refer to section 6.2.

Patients who prematurely discontinue from their treatment period will be followed for vital status and COPD exacerbation status via phone calls until their predicted normal exit date from the trial (i.e. 52 weeks after taking the first dose of randomised treatment + 21 days). Please refer to section 3.3.4.1 and section 6.2.4.

Adverse events and moderate to severe COPD exacerbation events will be documented throughout the trial, i.e. starting with informed consent and ending 21 days after last administration of trial medication.

3.1.1 Administrative structure of the trial

Sponsor: Boehringer Ingelheim, as trial sponsor, will provide funding and trial materials, including study medication. The sponsor has appointed a Trial Clinical Monitor (TCM), responsible for coordinating the activities required in order to manage the trial in accordance with applicable regulations and internal Standard Operating Procedures (SOPs), directing the clinical trial team in the preparation, conduct, and reporting of the trial, order the materials as needed for the trial, ensures appropriate training and information of local clinical monitor (CML), Clinical Research Associates (CRAs), and investigators of participating country.

Data Management and Statistical evaluation will be done by BI according to BI SOPs. For these activities, a Trial Data Manager and a Trial Statistician have been appointed.

Tasks and functions assigned in order to organise, manage, and evaluate the trial will be defined according to BI SOPs.

A list of responsible persons and relevant local information (as protocol reference if applicable) are in the investigator site file (ISF) and the trial master file (TMF) document.

Co-ordinating Investigator: the coordinating investigator is selected based on [redacted] expertise in this therapeutic area and reputation for being a leader in [redacted] field. [redacted] will review the trial protocol, any subsequent amendments to the protocol and the Clinical Trial Report (CTR). [redacted] will provide [redacted] signature on the final protocol signature page and amendments and will provide [redacted] signature on the CTR indicating that, to the best of Co-ordinator's knowledge, the final CTR accurately describes the conduct and results of the Trial.

Targeted group of Investigators: all physicians/qualified sites with access to the requested patient population and the facilities required to conduct the study assessments. The sites have to be able to perform electrocardiogram (ECG) and to conduct the procedure of blood sampling for clinical haematology and biochemistry. Patients will be treated on an outpatient basis. Recruitment is competitive. However, it is anticipated that each site will enrol an average of 10-12 patients. Beyond this commitment, sites will be able to include more patients after discussion and agreement with the TCM.

[redacted]

Mortality Adjudication Committee (MAC): an independent mortality adjudication committee will be established for the blinded adjudication of all fatal cases in the trial.

A MAC Charter, under which the principles of the study design can be carried out, will govern their activities. The charter will provide detailed definitions of each endpoint and the processes by which adjudication will occur, including how blinding will be preserved.

Centralized laboratory**:** The sample transport logistics (from site to sponsor) and blood analysis will be the responsibility of the central laboratory. The central laboratory will provide sampling, urine dip stick pregnancy test and shipment materials.

ECG: A standard 12-lead electrocardiogram will be performed on all patients at the screening visit using the site´s own equipment.

[redacted]

Pulmonary function testing: historical spirometry data from measurements within the past 3 months either at the site or at a referral site may be used for inclusion into the trial. No spirometry equipment needs to be available at the site. Should for practical reason, the pulmonary function testing (PFT) be performed at the trial site, the spirometers and their use, including daily calibration, must meet ATS/ ERS criteria (P05-12782).

IRT: an Interactive Response Technology (IRT) system will be used for randomisation in this trial and for allocation of trial medication to patients throughout the treatment period. The ability to unblind will be available to the investigator via IRT.

Patient's reminder card: all patients will be provided with a paper diary to serve as a reminder to support the structured COPD questionnaire clinic and telephone interview.

Trial documentation: all trial relevant documentation will be stored by Boehringer Ingelheim in the clinical trial master file (TMF). Trial relevant documentation for the trial sites will be filed in the Investigator Site File (ISF) at the investigator sites.

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

A randomised, double-blind trial design with parallel treatment groups is a well-established design to compare beneficial effects of once-daily tiotropium+olodaterol FDC and tiotropium on moderate to severe COPD exacerbations. Tiotropium has shown in numerous studies that it reduces the risk for a COPD exacerbation. Therefore tiotropium is the logical choice as active comparator for this trial.

End of study is defined as last patient out. This will be after the last patient has received their last dose of study drug and completed the follow-up visit 21 days thereafter.

The control group

The control group comprises the same type of COPD patients who are randomly allocated to receive tiotropium 5 µg Respimat®.

3.3 SELECTION OF TRIAL POPULATION

It is widely accepted that a COPD exacerbation increases the risk of the occurrence of future COPD exacerbations and that the frequency of exacerbations increases with progression of COPD. The trial will recruit patients with severe lung function impairment and a history occurrence of moderate to severe treated COPD exacerbations, as these patients are known to have greater likelihood of having a re-occurrence of COPD exacerbation. The eligibility criteria employed in the study will allow enriching the patient population by ensuring the recruitment of patients prone to exacerbations.

This trial will be conducted worldwide and the distribution of patients between the countries will be dependent on the access to suitable patients as well as the operational feasibility of performing the trial in the country. It is anticipated that each site will enrol an average of 10 to 12 patients.

An estimated total of 7800 patients randomised will be necessary to assess the primary endpoint “Annualised rate of moderate to severe COPD exacerbation during the treatment period”. Between Visit 1 and Visit 2, a low screen failure rate of 5% is foreseen due to the short screening period and, therefore, a lower likelihood for the enrolled patient to experience a new COPD exacerbation before the randomisation visit.

A log of all patients included 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 study entry

Outpatients with a history of COPD with severe to very severe pulmonary impairment (according to GOLD guideline) and having a documented history of at least one treated exacerbation in the previous 12 months are eligible for inclusion. All patients must fulfil all

of the inclusion criteria (Section 3.3.2) and do not present with any of the exclusion criteria (Section 3.3.3).

3.3.2 Inclusion criteria

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

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

3. All patients must have a diagnosis of COPD [P11-05865] and must meet the following spirometric criteria: stable airway obstruction with a documented post-bronchodilator FEV_1< 60% 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).

   Historical spirometry data within the past 3 months either at the site or at a referral site may be used or PFT measurement may be taken at the investigational site (See Appendix 10.5 spirometry documentation).

[redacted]

4. Patients with a documented history (please refer to section 8.3.1) of at least one moderate to severe COPD exacerbation in the previous 12 months requiring treatment with systemic corticosteroids and/or antibiotics and/or related hospitalization.

5. Investigator should also ascertain that the patient is symptomatically stable as defined by:

   - no evidence of COPD exacerbation requiring use of either antibiotics and/or steroids 4 weeks prior to visit 1,
   - no evidence of change in their usual COPD medication 4 weeks prior to visit 1.

6. Patients must be current or ex-smokers with a smoking history of more than 10 pack years. (See Appendix 10.5 calculation of number of pack years).

7. Patients must be able to perform all trial related procedures at the investigator discretion including:

   - technically acceptable and eligible pulmonary function test (if performed at site)
   - vital status follow-up in case of discontinuation until the predicted exit date (i.e.: 52 weeks from first intake of randomised treatment + 21 days).

- COPD exacerbation interview every 6 weeks in case of premature discontinuation until the predicted exit date (i.e.: 52 weeks from first intake of randomised treatment + 21 days).

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

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:

   - put the patient at risk because of participation in the study
   - influence the results of the study
   - cause concern regarding the patient's ability to participate in the study.

2. Patients with a, in the opinion of the investigator, clinically relevant abnormal baseline haematology, blood chemistry or creatinine > x2 ULN will be excluded regardless of clinical condition. (A repeat laboratory evaluation can be conducted if deemed necessary by the investigator.)

3. Patients with a current documented diagnosis of asthma. For patients with allergic rhinitis or atopy, source documentation is required to verify that the patient does not have asthma

   Patients with any of the following conditions:

4. A diagnosis of thyrotoxicosis (due to the known class side effect profile of ß2-agonists).

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

6. Life-threatening cardiac arrhythmia, as judged by the Investigator.

7. Known active tuberculosis.

8. Any malignancy unless free of disease for at least 5 years (patients with treated basal cell carcinoma or squamous cell skin cancers are allowed).

9. A history of cystic fibrosis.

10. Clinically relevant bronchiectasis, as judged by the Investigator

11. Patients with severe emphysema requiring endobronchial interventions within 6 months prior to screening

12. A history of significant alcohol or drug abuse, as judged by the Investigator.

13. 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).

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

15. Patients being treated with oral corticosteroid medication at unstable doses (i.e., less than 4 weeks on a stable dose) or at doses in excess of the equivalent of 10 mg of prednisone per day or 20 mg every other day.

16. Patients being treated with antibiotics for any reason (not limited to exacerbation infection) within 4 weeks of screening visit.

17. Patients being treated with PDE4 inhibitors within 3 months of screening visit (e.g. roflumilast) should not be enrolled and PDE4 inhibitors should not be withdrawn for the purpose of enrolling in this study.

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

19. Patients with known hypersensitivity to β-adrenergic and/or anticholinergics drugs, BAC, EDTA, or any other component of the RESPIMAT inhalation solution.

20. Pregnant or nursing women.

21. Women of childbearing potential not using a highly effective method of birth control*. Female patients will be considered to be of childbearing potential unless surgically sterilised by hysterectomy or bilateral tubal ligation, or post-menopausal for at least two years.

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

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

* *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.

3.3.4 Removal of patients from therapy or assessments

3.3.4.1 Removal of individual patients

An individual patient will be withdrawn from the trial if any of the following criteria apply:

- The patient withdraws consent, without the need to justify the decision.
- The patient is no longer able to participate for medical reasons (e.g. pregnancy, surgery, adverse events, or other diseases.
- Administrative reasons (protocol violations, persistent non-compliance).

No patient should be discontinued from the trial for a protocol violation before discussion with the clinical monitor. To be considered complete, a patient must complete all treatment visits (including telephone contacts) as specified in the flow chart.

Withdrawal from the screening phase

As long as a patient has not been assigned to a study treatment at Visit 2 (by IRT), the patient is not considered to belong to the treatment phase. Prior to the randomisation, reasons for withdrawal can be connected with the criteria described in the section 3.3.4.1 or related to eligibility criteria (please refer to section 3.3.2 and 3.3.3).The data of patients who withdraw prior to randomisation will be entered in the trial database and will be listed.

Withdrawal from the treatment phase

If the patient has prematurely stopped taking the investigational product during the treatment phase, the withdrawn patient will be followed-up for vital status and COPD exacerbation status until the end of the planned treatment period of 52 weeks + 21 days. The objective is to collect information on vital status (dead or alive) and COPD exacerbation status in the time interval between the patients' withdrawal date from the treatment period and their predicted exit date. Please refer to section 6.2.3.2.

Please note

1. A patient should not be withdrawn from the trial because he/she experiences a COPD exacerbation during the treatment period.

2. If during the treatment period, the trial medication is for any reason (e;g. hospitalisation stay) interrupted more than 14 consecutive days, a discussion with the clinical monitor is required to re-assess the patient's participation in the study.

Refer to Section 6.2.3 for procedures to be followed for patients prematurely terminating the trial.

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:

- Failure to meet expected enrolment goals overall or at a particular trial site,
- Emergence of any efficacy/safety information that could significantly affect continuation of the trial
- Violation of GCP, the CTP, or the contract by a trial site or investigator, 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 TREATMENTS TO BE ADMINISTERED

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

Patients will be randomized (1:1) to one of the following treatments:

- Tiotropium + olodaterol FDC (2.5 µg / 2.5 µg per actuation) inhalation solution
- Tiotropium (2.5 µg / per actuation) inhalation solution.

The patients inhale two puffs from the Respimat® inhaler, once a day, in the morning.

4.1.1 Identity of BI investigational product and comparator product

Substance (INN):	Tiotropium plus olodaterol fixed dose combination
Pharmaceutical form:	Inhalation solution
Unit strength:	2.5 µg / 2.5 µg per actuation
Total daily dose	5 µg / 5 µg q.d.
Route of administration:	Oral inhalation via Respimat® inhaler (A5)
Dosage regimen:	2 inhalations once daily (a.m. dosing)

Substance (INN):	Tiotropium
Pharmaceutical form:	Inhalation solution
Unit strength:	2.5 µg per actuation
Total daily dose	5 µg q.d.
Route of administration:	Oral inhalation via Respimat® inhaler (A5)
Dosage regimen:	2 inhalations once daily (a.m. dosing)

4.1.2 Method of assigning patients to treatment groups

When a patient is qualified for entry into the randomised treatment period, treatment assignment will be by means of a third-party phone/web-based randomisation on Visit 2. This will involve the use of an Interactive Response Technology (IRT) system which will implement a randomisation scheme generated using a validated randomisation software by Boehringer Ingelheim.

Refer to Section 4.1.6 for details on packaging and labelling.

Note that the Respimat® treatment box number assigned to the patient by the IRT is different from the study patient number assigned by the Remote Data capture (RDC) system upon signing informed consent.

Details on the IRT system are provided in the ISF.

4.1.3 Selection of doses in the trial

The clinical trials conducted during the Phase III programme for tiotropium + olodaterol FDC 5/5 µg 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 centred outcomes. An additional dose of tiotropium + olodaterol FDC has been studied during the Phase III programme, consisting of 2.5 µg tiotropium and 5 µg olodaterol. In the pivotal trials, a consistent difference in favour of tiotropium + olodaterol FDC 5/5 µg compared to tiotropium + olodaterol FDC 2.5/5 µg was demonstrated over the 52 week treatment period across various measures of lung function and patient-reported outcomes. Tiotropium + olodaterol FDC 5/5 µg demonstrated statistically significant and clinically relevant benefit over the individual components in all primary and secondary endpoints. On the other hand, the lung function improvement for tiotropium + olodaterol FDC 2.5/5 µg was more modest and a statistically significant benefit was not demonstrated in the pre-specified symptomatic primary endpoint, SGRQ total score. Based on these observation, the tiotropium + olodaterol FDC 5/5 µg has been submitted for regulatory approval and is therefore considered to be the most appropriate dose to be studied in this trial.

Tiotropium 5µg (2.5 µg / per actuation) inhalation solution Respimat® has been approved in more than 80 countries worldwide including Europe and Japan as an antimuscarinic bronchodilator with a once daily posology [redacted]. Therefore the marketed dose of tiotropium Respimat is deemed an adequate comparator for the study.

4.1.4 Drug assignment and administration of doses for each patient

Trial medication will be dispensed to the patient by the investigator/pharmacist. At Visit 2 eligible patients will be randomized to one of two double-blinded treatment arms (1:1 ratio) by the IRT. At subsequent clinic visits (every 3 months), the IRT will assign Respimat® treatment boxes to each patient and each Respimat® treatment box will have a unique number with 6 digits.

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

Site personnel will enter all medication numbers dispensed to each patient in the Medication Record page of the electronic case report form (eCRF).

4.1.4.1 Priming of the Respimat® inhaler

Each newly assembled Respimat® inhaler has to be primed when appropriate. The Respimat® 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.

Once assembled, the shelf-life of the Respimat® inhaler with study medication or training medication (placebo) is 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.

For detailed priming instructions please refer to the Respimat® inhaler handling instructions in Appendix 10.1

4.1.4.2 Study medication administration

For the patient's sake of convenience regarding the trial drug administration, the clinic visit must be scheduled in the morning. During the treatment phase the patient will be instructed to withhold the morning dose of the trial medication in current use prior to come to visits 3, 4 and 5 to avoid overdosing.

[redacted]

The last administration of the study medication will be taken at visit 6 (EoT) from the Respimat® inhaler that is in current use since no new Respimat® treatment box will be assigned.

Study medication administration at clinic visits

Dispensation and Respimat® inhaler assembling

Trial medication will be dispensed at visits 2, 3, 4 and 5. Patients will receive 3 new Respimat® treatment boxes + 1 Respimat® inhaler reserve. If the reserve kit is unused and intact, the IRT will not dispense a replacement reserve kit. During the clinic visit only one new Respimat® inhaler should be primed (= cartridge inserted and primed) under the oversight of the site staff. The other Respimat® inhalers should NOT be assembled prior to leaving the clinic.

Drug administration

At each clinic visit, oral inhalation of two puffs of the study medication from the new assigned Respimat® inhaler will be self-administered by the patient under the direct supervision of the investigating physician or deputy. The investigator or qualified study personnel will observe the inhalation procedure. For training session please refer to section 4.1.4.3.

[redacted]

Respimat® inhalers return

At visits 3, 4, 5 and 6 all used and unused Respimat® will be returned to the clinic by the patient. If the reserve kit is unused and intact, the IRT will not dispense a replacement reserve kit.

For rescue medication dispensation, please refer to section 4.2.1

Study medication administration at home

Each morning, oral inhalation of two puffs on the study medication from the assigned Respimat® inhaler will be self-administered by the patient. Patients should be encouraged to take their study medication at approximately the same time in the morning (morning dose window until noon). If a patient misses the daily dose he/she should take the next dose the day after. The patient must assemble and prime the Respimat® inhaler at home once the current used Respimat® inhaler is empty and the device is locked.

The patient will be asked to record any missed dose of study medication in a patient's reminder card.

4.1.4.3 Inhaler devices training

SPECIAL CONSIDERATION:

Most severe to very severe COPD patients are currently using different inhalation medications at the same time. This may cause technical challenges and affect their treatment adherence. Throughout the course of the study treatment period, the correct usage of their inhalation medications should be regularly re-instructed (ideally at each clinic visit) based on the package insert.

Respimat®
Training on the use of the Respimat® inhaler will first be provided to the site staff who will subsequently train the patients.

- At visit 1: the first patient's training session will be performed with the intention to familiarise the patient with the Respimat® inhaler training medication (placebo). Detailed written instructions for the use of the Respimat® inhaler will also be given. (See Appendix 10.1).

- At visit 2: after the randomization, the second patient's training session will be performed from the new assigned Respimat® inhaler. Instructions on how to assemble and prime the Respimat® inhaler at home should also be instructed.

- Subsequent clinic visits: observance of the inhalation procedure. The correct inhalation technique should be reinforced in case of inadequate use of Respimat® inhaler. It is also

important to remind the patient on how to assemble and prime the Respimat® inhaler at home.

Rescue medication
Before using for the first time the Salbutamol (albuterol*) HFA MDI inhalation aerosol, one actuation should be released into the air to make sure the device is working. The patient's inhaler technique should be reviewed and corrected if needed at each clinic visit.

4.1.4.4 Respimat® malfunctioning

Any Respimat® 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.

Details of the procedure for the return of malfunctioning inhalers are provided in Appendix 10.2.

4.1.5 Blinding and procedures for unblinding

4.1.5.1 Blinding

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

Boehringer Ingelheim will generate and store the randomisation schedule, and prepare and code the medication in a blinded fashion. Trial supplies will be assigned to the patients via IRT.

Refer to Section 4.1.5.2 for rules of breaking the code in emergency situations.

4.1.5.2 Procedures for emergency unblinding

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 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, rescue medication and Respimat® inhaler training kits. Expiry date will be pre-printed on the trial supplies labels.

Open-label supplies= Non Investigational Medicinal Product (NIMP)

- Training Respimat® inhaler, placebo cartridges and disposable mouthpieces for training purposes. A training device may be used for more than one training session. The training Respimat® 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.

  Respimat® inhaler and disposable mouthpieces for training purposes will be provided by IRT along with the initial supply order.

- Salbutamol (albuterol*) HFA MDI inhalation aerosol (100 µg per actuation) for use as rescue medication during screening, treatment and follow-up periods. The rescue medication will be provided by BI and purchased locally.

- Salbutamol (albuterol*) HFA MDI inhalation aerosol (100 µg per actuation) will also be used for qualifying PFT at Visit 1 (+4/*,5%(*6+-A?+(-=69

** NOTE: Albuterol sulphate is the official generic name in the US and salbutamol sulphate is the WHO recommended generic name.*

Blinded study medication= Investigational Medicinal Product (IMP)

- Packaging: the Respimat® treatment box will contain one 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.

- Labelling: individual Respimat® treatment box will have a three-part tear-off label. One part of each tear-off label should be attached to the drug accountability form which will be part of the ISF, and one part will remain on the box (an extra part is available as well). The investigator or designee should fill out the following information:
  - date of cartridge insertion should be entered at time of cartridge insertion on the cover page of the cartridge booklet
  - Investigator's name should be entered at time of dispense on the cover page of the booklet on the Respimat® treatment box.

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

#%?+-44'6
Each site will receive a first supply at or after the initiation visit and will be resupplied upon demand by IRT.

4.1.7 Storage conditions

All clinical trial supplies must be stored in a locked, secure cabinet and must be kept in their original packaging under the recommended storage conditions and may only be dispensed to trial subjects according to protocol. A temperature log must be maintained to assure that the drug supplies are stored at the correct temperature.

The Respimat® inhaler and cartridges 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. If the storage conditions are found to be outside the specified range, immediately contact the local clinical monitor.

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

4.1.8 Drug accountability

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

- approval of the study protocol by the IRB / ethics committee,
- availability of a signed and dated clinical trial contract between the sponsor and the Head of Trial Centre,
- 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 or immediately imminent signing of the clinical trial protocol, in exceptional cases, medication could already be sent to the site, before its activation via IRT.
- if applicable: availability of the proof of a medical licence for the principal investigator,
- for USA availability of the Form 1572.

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

- the product's delivery to the trial site,
- the inventory at the site,
- the use by each patient,
- the return to the sponsor or alternative disposition of used/unused trial medication.
- the adequate documentation that the patients were provided the doses specified by the CTP
- the reconciliation of all investigational products received from the sponsor

At the time of return to the sponsor, the investigator and/or pharmacist and/or investigational drug storage manager must verify that all drug supplies used/ unused or partially used 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.

<u>Respimat® inhaler:</u>

- dates (dispense and return),
- dispenser's initials,

- batch/serial numbers,
- expiry dates,
- the unique Respimat® treatment box number assigned by IRT,
- trial patient number assigned by the RDC system.

See Section 4.1.2. It is important to enter the date of priming on the medication label of the Respimat®.

Rescue medication:
One NIMP accountability form will be provided for salbutamol to the trial site. This record will include:

- dates (dispense and return)
- dispenser's initials
- quantities,
- batch/serial numbers,
- expiry date,
- the trial patient number assigned by the RDC system.

The patient will be asked to return all used/unused rescue medication 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 are required. Only used inhalers will be replaced at each clinic visit. For further details, please refer to section 4.2.1 (Rescue medication).

4.2 CONCOMITANT THERAPY, RESTRICTIONS, AND RESCUE TREATMENT

4.2.1 Rescue medication, emergency procedures, and additional treatments

4.2.1.1 Rescue medication

Patients could use the open-label salbutamol /albuterol* inhalation aerosol (HFA-MDI) for p.r.n use as needed for symptom relief. Administration of rescue medication can occur at any point during the trial as deemed necessary by the patient or the investigator.

Rescue medication will be issued to all patients at the screening visit (Visit 1) and can be dispensed at any time during the study until the follow-up Visit. It is important to provide sufficient rescue medication inhalers to cover the period between 2 clinic visits (3 months).

Rescue medication training and testing: please refer to section 4.1.4.3

Rescue medication supply: please refer to section 4.1.6

Rescue medication accountability: please refer to section 4.1.8

[redacted]

4.2.1.2 Emergency procedures

There are no special emergency procedures to be followed.

4.2.1.3 Additional treatments

In the case of COPD exacerbations, investigators are allowed to prescribe whatever COPD medication they deem appropriate for the patient.

The use of antibiotics is not restricted and may be prescribed as medically necessary for exacerbations and / or infections.

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. The COPD maintenance therapy including long-acting anticholinergic, inhaled corticosteroids and long-acting β-adrenergic drugs given either alone or in combination should be discussed at Visit 1 in order to adapt optimal treatment management in tune with the Table 4.2.2.1:1 (Permitted Medications and Medication Restrictions).

Patients receiving corticosteroids at baseline (inhaled corticosteroid component alone if taken as fixed combination with a bronchodilator) will continue treatment at the same dose or equivalent dose and regiment during their treatment period. If the patient withdraws from the treatment period, the dual ICS/LABA could be resumed.

Please refer to Section 3.3.4.1 (Removal of individual patients).

ICS mono-product adjustment is allowed during COPD exacerbation and should be linked to the reported exacerbation event.

[redacted]

Table 4.2.2.1: 1 Permitted Medications and Medication Restrictions

Drug Class	Sub-class	Prior to study	Study Period		
			Screening Period	Treatment Period	Follow up Period
Corticosteroids	**Inhaled corticosteroids (iCS)** (stabilized 4wks prior to V1)	Permitted[3]	Permitted[3]	Permitted[3]	Permitted[3]
	Oral corticosteroids [≤10 mg prednisone per day or ≤20 mg prednisone every other day (or equivalent); stabilized 4 wks prior to V1]	Permitted	Permitted	Permitted	Permitted
	Injected corticosteroids local administration (e.g. bursitis)	Permitted	Permitted	Permitted	Permitted
	Nasal corticosteroid sprays	Permitted[3]	Permitted[3]	Permitted[3]	Permitted[3]
β-adrenergics	**Inhaled short-acting β-adrenergics (SABA)**	Permitted	Rescue medication (as supplied) only [1]	Rescue medication (as supplied) only[1]	Rescue medication (as supplied) only[1]
	Inhaled long-acting β-adrenergics (bid) (LABA) (e.g. formoterol / salmeterol)	Permitted	Permitted[5]	**NOT permitted**	Permitted
	Inhaled long-acting β-adrenergics (qd) (e.g: indacaterol, vilanterol)	Permitted	Permitted[5]	**Study medication ONLY permitted**	Permitted
	Oral and patch beta-adrenergics	**NOT permitted[2]**	**NOT permitted**		Permitted
	Beta blockers (stabilized 6 wks prior to V1)	Permitted	Permitted	Permitted	Permitted
Anticholinergics	**Short-acting anticholinergics** (e.g: inhalation aerosol, nasal spray)	Permitted	Permitted[5]	**NOT permitted**	Permitted
	Long-acting anticholinergics (bid/qd) (e.g: commercial tiotropium, umeclidinium aclidinium, glycopyrronium)	Permitted	Permitted[5]	**Study medication ONLY permitted**	Permitted

Table 4.2.2.1: 1 Permitted Medications and Medication Restrictions (cont'd)

Drug Class	Sub-class	Prior to study	Study Period		
			Screening Period	Treatment Period	Follow up Period
Combinations	**iCS/LABA (bid/qd)** Switch to iCS mono-product at the same dose or equivalent dose and regiment during their treatment period. (e.g.fluticasone/vilanterol)	Permitted	Permitted[5+6]	**NOT permitted**	Permitted
	iCS/SABA Switch to iCS mono-product at the same dose or equivalent dose and regiment during their treatment period.	Permitted	Permitted[5+6]	**NOT permitted**	Permitted
	Inhaled long-acting anticholinergics/ LABA (e.g.glycopyrronium+indacaterol, umeclidinium+vilanterol)	Permitted	Permitted[5+6]	**NOT permitted**	Permitted
	Short-acting anticholinergic/ SABA	Permitted	Permitted[5]	**NOT permitted**	Permitted
Antibiotics	For respiratory infections The use of antibiotics is not restricted and may be prescribed as medically necessary for COPD exacerbation episodes and / or infections.	**NOT permitted[2]**	Permitted (except antibiotics for prevention of exacerbation of COPD)		
	Any other infections	**NOT permitted[2]**	Permitted	Permitted	Permitted
Miscellaneous	**Other investigational drugs** (*see exclusion criterion #18)	**NOT permitted[2]**	**NOT permitted**		
	Cromolyn sodium / nedocromil sodium[3]	Permitted	Permitted	Permitted	Permitted
	Antihistamines (including nasal route), antileukotrienes[3]	Permitted	Permitted	Permitted	Permitted
	Methylxanthines[3]	Permitted	Permitted	Permitted	Permitted
	Mucolytics not containing bronchodilators (stabilized 4 weeks prior to V1)	Permitted	Permitted	Permitted	Permitted
	Mucolytics containing bronchodilators	**NOT permitted[2]**	**NOT permitted**		
	PDE-4 inhibitor (e.g: Roflumilast)	**NOT permitted[4]**	**NOT permitted**		

1. Use rescue medication delivered at Visit 1 (or Visit 0 for patients involved in the sub-study)
2. Not permitted within 4 weeks prior to screening visit (w.o. 4 wks prior to V1)
3. Permitted if prescribed for non-asthma condition
4. 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.
5. Treatment(s) should be discontinued at the latest the day before Visit 2 without wash-out requirement.
6. Last dose of ICS/LABA combination product at the latest the day before Visit 2 and first dose of mono-ICS the day of Visit 2.

4.2.2.2 Restrictions on diet and life style

Not applicable to this trial.

4.3 TREATMENT COMPLIANCE

Each patient will be trained in the correct use of the Respimat® inhaler using the training Respimat® inhaler with inserted placebo cartridge. Please refer to section 4.1.4.3.

Patients will be asked to return inhalation aerosols and devices (used and unused) to the study site. The trial medication adherence should be reviewed by the investigator and reported in the eCRF.

Estimating Compliance to trial medication

Knowing the time interval between clinic visits should provide the estimate of the number of puffs that should have been administered by the patient three or four Respimat® inhalers used during that period of time.

The Respimat® inhaler contains 60 actuations (30 daily doses). The dose indicator shows approximately how much medication is left. When the pointer enters the red area of the scale, there is, approximately, medication for 7 days (14 actuations) left.

The dose indicator scale is divided into 4 quarters. One-quarter used accounts for 7 days of treatment (14 actuations).

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. Over a period of 3 months that is to say between 2 clinic visits, patient should return 3 Respimat® inhalers empty (the dose indicator has reached the end of the red scale). The acceptable medication compliance should have an overall value

in the range from 80% to 100%. If the compliance is less than 80% the patient needs to be re-trained. Please refer to section 4.1.4.3.

Randomised patients should not be discontinued for a lack of compliance without prior discussion with the local clinical monitor.

Figure 4.3:1 Respimat® inhaler dose indicator

5. VARIABLES AND THEIR ASSESSMENT

5.1 EFFICACY

In this study, it is important to note that lung function measurements are not used as criteria for treatment effectiveness. The primary efficacy endpoint is based on the annual rate of moderate/severe COPD exacerbations during a fixed-treatment period of 52 weeks.

5.1.1 Endpoints of efficacy

Primary endpoint

- Annualised rate of moderate to severe COPD exacerbation during the treatment period (within 1 day* after the last drug administration date).

Key secondary endpoint

- Time to first moderate to severe COPD exacerbation during the treatment period (within 1 day* after the last drug administration date).

Secondary endpoints

- Annualised rate of exacerbation leading to hospitalisation during the treatment period (within 1 day* after the last drug administration date).
- Time to first COPD exacerbations leading to hospitalisation during the treatment period (within 1 day* after the last drug administration date).
- Time to all-cause mortality (within 1 day* after the last drug administration date).

[redacted]

5.1.2 Assessment of efficacy

5.1.2.1 Definition of moderate and severe 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 a prescription of antibiotics and / or systemic steroids and/or hospitalisation.
A complex of lower respiratory events / symptoms is defined as at least two of the following:

- Shortness of breath
- Sputum production (volume)
- Change in sputum colour
- 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 hospitalisation.
Severe: COPD-related hospitalisation including emergency room visit*

To consider hospitalisation associated with COPD exacerbation, the information collected should include the start date of all COPD-related hospitalisations as well as the discharge date from the hospital or equivalent

*Visit in emergency is defined as: an unscheduled emergency room visit resulting in prescription of oral corticosteroids and/ or antibiotic.

Only the investigator-diagnosed COPD exacerbation fitting the above criteria of moderate to severe COPD exacerbation will be used for the analysis of the annualized moderate to severe exacerbation rate as the primary endpoint.

5.1.2.2 Assessment of moderate and severe COPD exacerbations

Information regarding exacerbations will be collected by the physicians during the visits and will be recorded in the eCRF. During all telephone calls and clinic visits, the same questions regarding exacerbation will be addressed for collecting exacerbation-related details and then recorded in the eCRF.

At every clinical visit, the investigator will be asked to review (not to collect) the patient's reminder card and all telephone calls since the last clinical visit to ensure that all exacerbations have been recorded and that the exacerbations meet the definition of study exacerbation.

The investigator (or deputy) will record the COPD exacerbation information the length of time the patient is treated with the trial medication but also for patients who will discontinue early.

For all patients (completed/discontinued) the COPD exacerbation collection time of interest will be the planned 52-week + 21 days starting from visit 2.

If patients are hospitalised, the study site will be responsible for collecting and reviewing pertinent medical records so that an informed judgment can be made as to the primary cause for admission.

Patient's reminder card

The patient's reminder card will be used to note changes in symptoms, missed dose medication or utilisation of health care services between visits and serve as a reminder for the patients. The patient reminder cards will not be collected by the site and remains the exclusive property of the patient. The patient will complete reminder cards entries daily from Visit 2 until the follow-up visit.

In case of withdrawal from the treatment phase, discontinued patients are encouraged to complete their reminder cards in order to be able to answer questions on their COPD exacerbation status.

[redacted]

5.1.2.3 Assessment all-cause mortality

Death from any cause includes cardiovascular death, non-cardiovascular-death and undetermined cause of death, as classified by adjudication. For all patients (completed/discontinued) vital status collection time of interest will be the planned 52-week + 21 days starting from visit 2.

Further details on death classification will be specified in the mortality adjudication charter.

5.2 SAFETY

5.2.1 Endpoints of safety

Adverse events, serious adverse events and fatal adverse events

5.2.2 Assessment of adverse events

5.2.2.1 Definitions of adverse events

Adverse event

An adverse event (AE) is defined as any untoward medical occurrence, including an exacerbation of a pre-existing condition, in a patient in a clinical investigation who received a pharmaceutical product. The event does not necessarily have to have a causal relationship with this treatment.

Serious adverse event

A serious adverse event (SAE) is defined as any AE which results in death, is immediately life-threatening, results in persistent or significant disability / incapacity, requires or prolongs patient hospitalisation, 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 judgement which may jeopardise the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions.

Cancers of new histology or exacerbations of existing cancer are considered serious adverse events.

Vital status and COPD exacerbation status from patients who prematurely discontinue treatment will be collected.

ADDITIONAL INFORMATION FOR JAPAN:

The following events will be handled as "deemed serious for any other reason". An AE which possibly leads to disability will be reported as an SAE. Every new occurrence of cancer will be reported as a SAE regardless of the duration between discontinuation of the drug and the occurrence of the cancer.

Intensity of adverse event

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

Mild: Awareness of sign(s) or symptom(s) which 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 adverse event

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. Assessment of causal relationship should be recorded in the case report forms.

ADDITIONAL INFORMATION FOR JAPAN:

The reason for the decision on causal relationship needs to be provided in the eCRF.

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

If a SAE is reported from a still blinded trial, the causal relationship must be provided by the investigator for all potential trial drugs, i.e. the BI trial drug and for all other trial drugs (i.e. any active comparator).

The Investigator (or designee) will enter these events (even if they meet the criteria of an SAE) in the corresponding pages in the eCRF within 24 hours of awareness, as well as providing any defined supporting documentation This will be provided by the Sponsor to the AC, as defined in the charter.

Worsening of the underlying disease or other pre-existing conditions

Worsening of the underlying disease or of other pre-existing conditions will be recorded as an (S)AE in the eCRF.

Changes in vital signs, physical examination, and laboratory test results

Changes in vital signs, physical examination and laboratory test results will be recorded as an (S)AE in the eCRF , if they are judged clinically relevant by the investigator.

Protocol-specified adverse events of special interest (AESIs)

There are no protocol-specified adverse events of special interest (AESIs) in this trial.

5.2.2.2 Adverse event and serious adverse event reporting

All adverse events, serious and non-serious, occurring during the course of the clinical trial (i.e., from signing the informed consent onwards through the follow-up period until 21 days after the last administration of trial medication) will be collected, documented and reported to the sponsor by the investigator on the appropriate eCRFs / SAE reporting forms. Reporting will be done according to the specific definitions and instructions detailed in the 'Adverse Event Reporting' section of the Investigator Site File.

For each adverse event, the investigator will provide:

- Onset date
- End date
- Intensity
- Treatment required
- Outcome
- Seriousness*
- Action taken with the investigational drug.
- Causal relationship: SAEs and non-serious AEs must include a causal relationship assessment of the investigational drug made by the investigator as defined in section 5.2.2.1.

The investigator must report the following events via telephone/fax using the SAE form immediately (within 24 hours or the next business day, whichever is shorter) to the sponsor: SAEs and non-serious AEs relevant to the reported SAE.

With receipt of any further information to these events, a follow-up SAE report has to be provided. SAEs and non-serious AEs must include a causal relationship assessment made by the investigator.

Always serious adverse events

BI has set up a list of AEs which are defined to be always serious. The list of these adverse events can be found via the RDC-system. In order to support the investigator with the identification of these "always serious adverse events", if a non serious AE is identified to be serious per BI definition, a query will be raised. The investigator must verify the description and seriousness* of the event. If the event description is correct, the item "serious" needs to be ticked and an SAE has to be reported in expedited fashion following the same procedure as above.

With receipt of any further information to these events, a follow-up SAE report has to be provided.

ADDITIONAL INFORMATION FOR JAPAN: this information must be also reported immediately to the head of the trial site.

The SAE form is to be forwarded to the defined unique entry point identified for the BI OPU (country-specific contact details will be provided in the Investigator Site File). This immediate report is required irrespective of whether the investigational product has been

administered or not and irrespective of causal relationship. It also applies if new information to existing SAEs or protocol-specified adverse events becomes available.

AE and SAE reporting including the Follow-up period

The investigator also has the responsibility to report all serious and non-serious AEs occurring within the 21 days (+ 7 days of agreed time window) residual effect period. Any AEs reported to the sponsor during this period must be documented in the safety database.

All events with an onset after the first dose of trial medication up to a period of 21 days (+ 7 days) after the last dose of trial medication will be assigned to the treatment period for evaluation.

AE and SAE reporting after the follow-up period

The Investigator does not need to actively monitor patients for AEs once the clinical trial has ended. However, if the Investigator becomes aware of an SAE that occurred after the patient has completed the clinical trial (including the follow-up period), the Investigator should report it to the sponsor if the Investigator considers it relevant to BI investigational product.

Pregnancy

In rare cases, pregnancy might occur in clinical trials. Once a female subject has been enrolled into the clinical trial, after having taken study medication, the investigator must report immediately any drug exposure during pregnancy to the sponsor. Drug exposure during pregnancy has to be reported immediately (within 24 hours or next business day whichever is shorter) to the defined unique entry point for SAE forms of the respective BI OPU (country-specific contact details will be provided in the Investigator Site File). The study medication must be interrupted without delay (i.e.; as soon as pregnancy is known). The outcome of the pregnancy associated with the drug exposure during pregnancy must be followed up. In the absence of an (S)AE, only the Pregnancy Monitoring Form for Clinical Trials and not the SAE form is to be completed.

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

5.2.2.3 Vital status collection

The vital status collection will only concern patients having prematurely withdrawn BEFORE their predicted trial exit date. For the period of interest and frequency of survival information, please refer to section 3.3.4.1. The vital status information does not require a patient visit. If no information can be collected after at least 3 attempted (documented) phone calls and at least one registered letter, the patient will be regarded as lost to follow-up.

5.2.3 Assessment of other safety parameters

The safety endpoints will also evaluate vital signs, routine laboratory evaluations and physical examination.

5.2.3.1 Laboratory tests

Clinical laboratory testing will be conducted on all patients at Visits 1 and 6/EoT. The fasted condition is not required. The laboratory tests at Visit 1 will be considered as the baseline measurements and the results of the Visit 1 tests have to be assessed by the investigator or designee prior to randomisation, to ensure no exclusion criteria are met.

Follow-up clinical laboratory testing must be performed at the follow-up visit if there are any clinically significant findings at the last study treatment visit (for completed patient = visit 6).

It is the responsibility of the investigator to evaluate changes in laboratory value and reporting of adverse event should be followed according to the definition outlines in section 5.2.2.2.

Hematology

- Hemoglobin,
- Hematocrit
- Erythrocyte count
- Total and differential leucocyte count eosinophil count and
- Platelet count.

Serum chemistry

- Alkaline phosphatase (ALP)
- LDH
- Gamma-glutamyltranspeptidase (GGT)
- Alanin aminotransferase (ALT) or SGOT
- Aspartate aminotransferase (AST) or SGPT
- Glucose
- Calcium
- Inorganic phosphorus
- Uric acid
- Urea nitrogen
- Creatinine
- Protein (total)
- Potassium
- Sodium
- Chloride
- Total bilirubin
- Creatinine phosphokinase.

Pregnancy Testing

A serum human chorionic gonadotrophin (HCG) test will be performed on all females of child-bearing potential at Visits 1 and 6 (or last study treatment visit in case of premature withdrawal). A urine dip stick pregnancy test will be performed at clinic visit (please refer to the flow chart).

5.2.3.2 Physical examination

A complete, head-to-toe physical examination will be completed on all patients at Visits 1 and 6 (or last study treatment visit in case of premature withdrawal).

All abnormal findings at Visit 1 will be recorded in the patients' source documents and on the Medical History eCRF, if applicable. New abnormal findings or worsening of baseline conditions/medical history detected at Visit 6 will be re-assessed at follow-up visit and recorded as adverse events on the appropriate eCRF page.

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5.2.3.3 Electrocardiograms

A 12-lead ECG will be recorded at Visit 1 to evaluate the patient's eligibility. All abnormal findings at Visit 1 will be recorded in the patients' source documents and on the Medical History eCRF, if applicable.

5.3 OTHER

Other endpoints are defined in section 5.1.1

5.4 APPROPRIATENESS OF MEASUREMENTS

The occurrence of COPD exacerbations will be investigated at every clinic visits. The exacerbation-related information will be reviewed and collected by the investigator during the clinic visits and recorded in the eCRF. Only the investigator-diagnosed COPD exacerbations that fit the criteria of moderate to severe COPD exacerbation definition section 5.1.2 will be used for the analysis of the exacerbation rate as primary endpoint.

[redacted]

Concomitant Therapies

All concomitant therapies taken within the 3 months preceding Visit 1 and throughout the study will be recorded in the subjects' source documents and entered on the Concomitant Therapy eCRF, if applicable.

Cardiovascular risk-factor

Information on the cardiovascular (CV) risk-factors will be collected on all patients at the screening visit (Visit 1). The reported terms will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology.

Pulmonary Function Testing

IF HISTORICAL DATA IS NOT AVAILABLE: the qualifying pulmonary function tests are to be conducted at the investigational site. Subsequently, patients must have completed spirometry at or within 3 months of the screening visit that meet the post-bronchodilator criterion listed in Section 3.3.2 for inclusion into the trial. Measurements of FEV_1 and FVC will be performed using calibrated electronic spirometers at the investigational site or a referral site. Spirometers and their use, including daily calibration, must meet American Thoracic Society (ATS)/ European Respiratory Society (ERS) criteria (P05-12782). Spirometry will be conducted with the patient in a seated position. The test will be conducted in triplicate. The highest FEV_1 and FVC from an acceptable maneuver will be recorded regardless of whether they come from different spirometric maneuvers or from the same maneuver (preferably with a maximum of five attempts).

5.5 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

Not applicable to this trial.

5.6 BIOMARKER

Not applicable to this trial.

5.7 PHARMACODYNAMICS

Not applicable to this trial.

5.8 PHARMACOKINETIC - PHARMACODYNAMIC RELATIONSHIP

Not applicable to this trial.

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

All patients are to adhere to the visit schedule as specified in the Flow Chart. Some flexibility is allowed in scheduling the visits according to visit time windows as specified in the Flow Chart. If any visit has to be rescheduled, subsequent visits should follow the original visit date schedule (calculated from Visit 2). The trial medication kits contain sufficient medication to allow for these time windows. All deviations from the planned visit schedule will be documented.

[redacted]

The screening period should be restricted as much as possible to avoid any exacerbation episode during this period. For a patient in stable condition screening procedures should be completed within 7 days (between visit 1 and visit 2). The qualifying PFT and safety laboratory report must be available to confirm the eligibility at least on the day of randomization (Visit 2).

However, the screening period (between Visit 1 and Visit 2) may be extended by an additional 1 week for administrative reasons.

In case of respiratory tract infections or exacerbation during the screening period: visit 2 can be postponed 4 weeks following the recovery from the infection or exacerbation (based on the last dose of systemic corticosteroids and/or antibiotics). The complete procedures and observations of Visit 1 are to be repeated to ensure the complete review of the In/Ex criteria at Visit 2.

Rescheduling visits after Visit 2

If rescheduling of clinic visits after the randomisation is necessary, the total daily dose of the study medication needs to be maintained and the use of the reserve trial medication is recommended to continue the treatment without any interruption.

Any rescheduling of visits should be discussed with your monitor.

[redacted]

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

A preliminary check of in-/exclusion criteria with a particular focus on COPD exacerbation within the previous year is recommended to avoid unnecessary study procedures in non-eligible patients.

A complete overview of assessments to be performed at each visit is provided in the trial Flow Chart.

6.2.1 Screening period

Informed consent will be obtained prior to patient participation in the trial, which includes any medication washout procedures or restrictions. The study requirements, including the procedure for the follow-up of prematurely withdrawn patients must be fully explained to the patient and written informed consent obtained prior to initiating any study-related evaluation.

Patients will be assigned a study patient number by the Remote Data capture (RDC) system once consent is signed. The site should also register the patient as a screened patient in IRT.

Eligibility will be assessed at the initial screening visit and confirmed at the randomisation visit (Visit 2). Patients who fail to complete all of the testing procedures will not be re-enrolled at a later date.

[redacted]

Screening Visit 1

Procedures and observations

Informed Consent	To be obtained prior to patient participation in the trial.
Demographics	Sex, race, date of birth, height, weight, trial indication with the duration of COPD will be recorded.
Cardiovascular risk-factor	Assessment
Physical examination	A complete head-to-toe physical examination including measurements of systolic and diastolic blood pressure and pulse rate. Refer to section 5.2.3.2 (Sub-study)Vital signs must be taken immediately prior to the qualifying PFT
Concomitant diagnosis	Information for current conditions and conditions for which therapy is given. Any new clinically relevant findings (for instance after the ECG assessment or physical examination) should be reported (excluding trial indication).

[redacted]

Qualifying * FEV_1 and FVC	*Based on historical data. A standard spirometry testing can be performed if no historical spirometry measurements within the last 3 months are available at site. [redacted]
Haematology, serum chemistry laboratory tests	To be submitted to the central laboratory. *(Fasted condition is not required).*
Pregnancy test	Serum pregnancy test is to be conducted in all female patients of child bearing potential.
Smoking status	To be recorded
12-lead ECG	Performed locally.
Medication restriction	Medication restriction outlined in Section 4.2.2 will be reviewed with the patient.
In-/exclusion criteria	To be reviewed
Screening call (IRT)	Please refer to the IRT manual
Inhalation device trainings	Training sessions on: the use of rescue medication (salbutamol/albuterol) the use of the Respimat® inhaler training medication (placebo) Please refer to section 4.1.4.3 Inhaler devices training
Rescue medication	Rescue medication will be issued to all patients. Please refer to section 4.2.1. Provide sufficient rescue medication inhalers to cover the period between 2 clinic visits. The patient should be instructed to return all used/unused rescue medication inhalers at each clinic visit.
Trial patient's card	A trial identification card should be given.
Adverse events	To be checked
Concomitant medication	Medication used by the patient for the previous 3 months will be recorded in the source document on the Concomitant Therapies eCRF, if applicable.
Appointment	The qualifying PFT and safety laboratory report must be available to confirm the eligibility at least on the day of randomization (V2). [redacted]

6.2.2 Treatment periods

Patients who were already randomised in the study are not allowed to re-enter in case of premature discontinuation.

[redacted]

6.2.2.1 Randomisation Visit 2 (Day 1)

Procedures and observations

[redacted]

Pregnancy test	Urine pregnancy test is to be conducted in all female patients of child bearing potential prior to randomization.
Medication restriction review	Medication restriction outlined in Section 4.2.2 will be reviewed with the patient.

[redacted]

COPD exacerbation interview	Please refer to the section 5.1.2.2
Review of in-/exclusion criteria	Conclusion of screening including the review of laboratory results to determine eligibility.
Randomisation call	Please refer to the IRT manual
Assignment of trial drugs	Allocate the appropriate medication kit using IRT.
Dispense trial drug	Three new Respimat® treatment boxes + 1 Respimat® inhaler reserve are assigned. Enter the date of priming on the medication label of the Respimat®. Record medication kit numbers in the eCRF.

[redacted]

Trial drug: training and first intake	The patient's training session occurs after the randomization. The patient will self-administer the trial drug (from the new assigned Respimat® inhaler) under the oversight of the site staff. Give instructions on how to assemble and prime the Respimat® inhaler at home.

[redacted]

Rescue medication	Provide sufficient rescue medication inhalers to cover the period between 2 clinic visits.
Patient's reminder card	Patients will have the reminder card explained and will be provided with a copy. Refer to 5.1.2.2. Patients will be instructed to bring the reminder card to the study site on the next scheduled visit (not to be collected by the site).
Adverse events	All adverse events experienced since the previous visit will be reviewed and documented.
Concomitant medication	Any changes in concomitant medications since the last visit will be reviewed and documented
Appointments	Patients will be instructed to bring all issued trial medication (used/unused) and the rescue medication (used/unused) to the study site on the next scheduled clinic visit (Visit 3). G.)%=-'% • a phone appointment 6 weeks later • [redacted] • next clinic visit 3 months after the Visit 2

6.2.2.2 Clinic visits (Visits 3, 4 and 5)

Procedures and observations

[redacted]

Pregnancy test	Urine pregnancy test
COPD exacerbation interview	• Patient's reminder card (filled in by the patient) should be reviewed with the investigator. • Telephone call(s) information since the last clinic visit should be reviewed. Please refer to the section 5.1.2.2
Patient's reminder card	Patients will be provided with a new card.

[redacted]

Assignment of trial drugs	Allocate the appropriate medication kits using IRT.
Dispense trial drug	Three new Respimat® treatment boxes + 1 Respimat® inhaler reserve are assigned. Enter the date of priming on the medication label of the Respimat®. Record medication kit numbers in the eCRF.
Administration of trial drug	The patient will self-administer the trial drug (from the new assigned Respimat® inhaler) under the oversight of the site staff.

[redacted]

Inhalation observance	Observance of the inhalation procedure. Give instructions on how to assemble and prime the Respimat® inhaler at home.
Rescue medication	Provide sufficient rescue medication inhalers to cover the period between 2 clinic visits.
Collect trial drugs	All trial medications are to be collected. Compliance to be checked. Please refer to section 4.3 Treatment compliance.
Adverse events	All adverse events experienced since the previous visit will be reviewed and documented.

Concomitant medication	Any changes in concomitant medications since the last visit will be reviewed and documented
Appointments	Patients will be instructed to bring all issued trial medication (used/unused) and the rescue medication (used/unused) to the study site on the next scheduled clinic visit. Schedule: • J 4),0% &44,/0(5%0(K;%%<+&(%* • [redacted] • L%C(.'/0/. 2/+/(8 5,0()+ '&(%@

6.2.2.3 Telephone contacts between clinic visits

Study sites will follow up patients and collect information by telephone interviews every 6-week (± 7 days). A patient's reminder card will be provided to assist their memory recall in terms of respiratory symptoms, COPD exacerbations, hospitalisation or interim health care visits, concomitant therapy.

At each telephone contact, the investigator or deputy will review with the patient any related COPD exacerbation information (new occurrence of exacerbation, respiratory symptoms, COPD exacerbation-related hospitalisation etc…) and will record it in the eCRF. If patients are hospitalised, the study site will be responsible for collecting and reviewing pertinent medical records so that an informed judgment can be made as to the primary cause for admission.

Relevant sources of information may include hospital records, telephone or written correspondence with primary physicians, discharge summaries, and death certificates.

Emphasis will be placed on the first diagnosis listed in the discharge summary in determining the primary cause for the hospital admission. In case of hospitalisation, patients will be encouraged to inform the study site prior to their regularly scheduled telephone interviews.

Details of all exacerbations will be captured in the source notes.

[redacted]

6.2.3 End of treatment

6.2.3.1 Visit 6/EoT

At the conclusion of the 52-week treatment period, the following information will be collected for all patients (these visit procedures also apply for a patient who is discontinuing trial medication before the end of the trial).

Procedures and observations

Physical examination	Physical examination including measurements of systolic and diastolic blood pressure and pulse rate.
Haematology, serum chemistry laboratory tests	To be submitted to the central laboratory. *(Fasted condition is not required).*
Smoking status	To be reported.
[redacted]	
COPD exacerbation interview	• Patient's reminder card (filled in by the patient) should be reviewed with the investigator • Telephone call(s) information since the last clinic visit should be reviewed. Please refer to the section 5.1.2.2
Patient's reminder card	Patients will be provided with a new card.
[redacted]	
Last trial drug administration	The last administration of the study medication from the Respimat® inhaler that is in current use since no new Respimat® treatment box will be assigned.
[redacted]	
Collect trial drug	All trial medications are to be collected. Compliance to be checked. Please refer to section 4.3 (Treatment compliance).
Rescue medication	Rescue medication will be issued to all patients to cover the period until the follow-up Visit.
Adverse events	All adverse events experienced since the previous visit will be reviewed and documented.

Concomitant medication	Any changes in concomitant medications since the last visit will be reviewed and documented
Appointment	Patients will be instructed to bring all issued rescue medication (used/unused) at the follow-up visit. G.)%=-'%Ⱦ,",; ?-4 2/+/(MN=&6+&>(%6*/+/(K@
Trial drug termination call	Please refer to the IRT manual

[redacted]

[redacted]

6.2.3.2 Premature discontinuation

The Visit 6/EoT visit should be performed instead of the scheduled trial visit at time of premature discontinuation (Please refer to section 6.2.3.1). Afterwards, the initiation of the survival and exacerbation information collection will be initiated.

The need for follow-up information (vital status and COPD exacerbation) should have been explained to patients prior to their participation in the trial and will be part of the written informed consent.

COPD exacerbation status collection

The collection of the COPD exacerbation status will be repeated every 6 weeks at the originally predicted clinic visits and telephone contacts until the predicted Visit 6.

Exacerbation contact information will be reported on the “COPD exacerbation check” eCRF. Exacerbation-related details will likewise recorded as an (S)AE and recorded in the COPD event eCRF, if applicable. In order to be able to provide COPD information, patients are strongly encouraged to use and complete the patient’s reminder card until the completion of the collection period.

Starting from the premise that COPD exacerbation and vital status collection should be timely aligned with the originally planned clinic visits and telephone contact. If the patient is not reachable during this period a second attempt is to be planned later (reason documented i.e: hospitalization, holiday, family events….).

Vital status collection

Depending on the time of the patient's withdrawal, the survival status collection will be scheduled as following:

- BEFORE Visit 4: 2 collection time points at the originally predicted visit 4 (26 weeks from Visit 2) and follow-up visit (52 weeks + 21 days from Visit 2)
- AFTER Visit 4: 1 collection time point at the originally predicted follow-up visit (52 weeks + 21 days from Visit 2).

The time interval of interest will be defined from the date of the Termination of Trial Medication (TTM) until their predicted follow-up visit.

If death occurs, the investigator will review the circumstances, including the relevant medical records to ascertain the most likely primary cause. Vital status information will be collected in accordance with national ethical and regulatory guidelines.

6.2.4 Follow-up visit

At the completion of the Visit 6 the follow-up visit should be performed in any case as described in the flow chart.

A patient who is withdrawn from therapy should complete the follow-up visit 21 days later last treatment study visit (including the EOT assessments). Please refer to section 6.2.3.2.

Physical examination	To be re-assessed ONLY in case of relevant findings at Visit 6 or at the last study treatment visit (in case of premature discontinuation)
Laboratory tests	To be re-assessed ONLY in case of relevant findings at Visit 6 or at the last study treatment visit (in case of premature discontinuation)
Pregnancy test	Urine pregnancy test
COPD exacerbation interview	• Patient's reminder card (filled in by the patient) should be reviewed with the investigator • Telephone call(s) information since the last clinic visit should be reviewed. Please refer to the section 5.1.2.2
Rescue medication	To be collected
Adverse events	All adverse events experienced since the previous visit will be reviewed and documented.
Trial Completion	

6.2.5 Trial completion

For completed patient

The "Trial completion" definition takes into consideration the trial drug termination date (i.e., visit 6) completed 21 days later by the follow-up visit.

Trial completion page has to be filled-in when the patient has terminated the follow-up visit.

For discontinued patient

The "Trial completion" definition takes into consideration the premature trial drug termination date (i.e., prior to visit 6) completed 21 days later by the follow-up visit.

Trial completion page has to be filled-in when the patient has terminated the follow-up visit. Please refer to section 6.2.3.2.

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 STATISTICAL DESIGN - MODEL

This is a randomised, double-blind, active-controlled parallel group, phase IIIb study. The primary objective of this study is to evaluate the effect of once daily treatment of tiotropium 5 µg + olodaterol 5 µg FDC delivered by the Respimat® inhaler on COPD exacerbation as compared with 5 µg tiotropium delivered by the Respimat® inhaler in patients with severe to very severe COPD. Each patient will stay in the trial for 52 weeks and will be followed up for COPD exacerbation if dropped out earlier. Vital status will be collected over the entire study period (52 weeks + 21 days follow-up).

7.2 NULL AND ALTERNATIVE HYPOTHESES

The effect of tiotropium + olodaterol FDC on COPD exacerbation will be assessed by testing the rate ratio for annual rate of moderate/severe COPD exacerbation and hazard ratio for moderate/severe COPD exacerbation between T+O FDC and Tio 5 in the following hypothesis testing hierarchy:

9. H_{10}: the annualised rate of moderate to severe COPD exacerbation is equal between T+O 5/5 and Tio 5

   vs.

   H_{11}: the annualised rate of moderate to severe COPD exacerbation is different between T+O 5/5 and Tio 5.

10. H_{20}: the survival distribution for the onset of the first moderate to severe COPD exacerbation is equal for T+O 5/5 and Tio 5

    vs.

    H_{21}: the survival distribution for the onset of the first moderate to severe COPD exacerbation is different for T+O 5/5 and Tio 5

This hypothesis testing strategy ensures that the overall type I error is protected at two-sided 0.01 level.

7.3 PLANNED ANALYSES

7.3.1 Primary analyses

The primary analysis includes all randomised patients who are documented to have received any dose of study medication, i.e., the primary analysis is performed using the treated set.

The primary endpoint, i.e., annualised rate of moderate to severe COPD exacerbation will be analysed using a negative binomial model including the fixed, categorical effect of treatment

as well as the logarithm of the treatment exposure as an offset. In all analyses of annualised rate of event, the length of the event will be subtracted from the extent of exposure or the length of the observation period because one cannot expect to have another event during an event. Moderate to severe COPD exacerbations occurring within 1 day (i.e.: 24 hours) after the last drug administration date are included in the primary analysis.

[redacted]

7.3.2 Secondary analyses

For the key secondary endpoint, i.e., time to the onset of the first moderate to severe COPD exacerbation, as well as other time to event endpoints (see Section 5.1.1), a Cox's proportional hazard model will be used to estimate the hazard ratio and the corresponding 99% confidence intervals, while log-rank test will be used to obtain the p-value for testing the survival curves. For other annualised rate of event endpoints (see Section 5.1.1), the same negative binomial model as specified for the primary endpoint will be used.

[redacted]

For all efficacy analyses including time to all-cause mortality the treated set (on-treatment + 1 day) will be used. [redacted]

[redacted]

7.3.3 Safety analyses

All treated patients will be included in the safety analysis. In general, safety analyses will be descriptive in nature and will be based on BI standards. No hypothesis testing is planned prospectively.

Adverse events will be coded using the current version of the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary. Standard BI summary tables and listings will be produced to compare the incidence of adverse events across treatment groups. All adverse events with an onset after the first dose of trial medication and up to 21 days after the last dose of trial medication will be assigned to the on-treatment period. Other adverse events

will be assigned either to the screening period, post-treatment period or the post-study period as appropriate.

Changes from baseline in vital signs and laboratory value will be summarised by treatment group and compared descriptively.

7.3.4 Interim analyses

No interim analysis is planned for this trial.

[redacted]

7.3.6 Pharmacokinetic analyses

No pharmacokinetic analyses are planned for this trial.

7.3.7 Pharmacodynamic analyses

No pharmacodynamic analyses are planned for this trial.

7.3.8 Pharmacogenomic analyses

No pharmacogenomic analyses are planned for this trial.

7.4 HANDLING OF MISSING DATA

Since patients are followed up for exacerbations and vital status and the CAT questionnaire is an exploratory endpoint, missing data will not be imputed. Missing safety data will not be imputed with the exception of missing AE dates which will be imputed according to BI standards.

[redacted]

Randomly missing data (not due to worsening of disease or use of rescue medication) after inhalation for which there are data from that visit both before and after inhalations will be linearly interpolated. Randomly missing data with no subsequent non-missing values for that visit will be imputed using the last observation carried forward (LOCF) techniques prior to calculating AUC.

7.5 RANDOMISATION

Patients will be randomised in equal ratio to one of the two treatment groups in this trial and blocked randomisation will be used. Boehringer Ingelheim will generate the randomisation scheme and will prepare and code the medications to maintain the double-blind.

In order to maintain flexibility for drug supply, each individual medication kit will have a separate identification number. Assignment of medications at the clinic visits will be accomplished through the use of IRT. Each patient will be assigned a single randomisation number indicating the randomised treatment the patient will be on throughout the trial. BI will provide the randomisation and medication kit number lists to the IRT and the sites will access the IRT to obtain the randomisation number and medication kit numbers to be dispensed to the patient.

7.6 DETERMINATION OF SAMPLE SIZE

Based on a recent publication on the SPARK study (Wedzicha, et al, Lancet, 2013) and data from a previous BI study [redacted], the rate ratio and hazard ratio of moderate to severe COPD exacerbation between T+O FDCs and Tio 5 are assumed to be 0.88.

Assuming an annualised rate of moderate to severe COPD exacerbation for Tio 5 to be 0.85, a 12-month fixed study duration, two-sided type I error rate of 0.01 and 90% power, the sample size depends on the dispersion parameter for the negative binomial distribution. Table 7.6: 1 gives the sample size estimations for a range of the dispersion parameters. In addition, assuming a 15% loss of information in patient-years, the estimated power corresponding to the sample size is also provided in the last column in Table 7.6: 1 below.

Table 7.6: 1 Sample size estimations for annualised rate of moderate to severe COPD exacerbation under different dispersion parameters with 2-sided type I error rate of 0.01, 90% power, annual rate of 0.85 in Tio 5 and rate ratio = 0.88

Annual Rate in Tio 5 (r_1)	**Annual Rate in T+O FDC (r_2)**	**r_2/r_1**	**Dispersion Parameter**	**N per arm**	**Average exposure (months)**	**Total exposure adjusted for 15% loss of information (patient – years)**	**Power (after adjusting 15% loss of information in patient-years)**
0.85	0.748	0.88	0.625 (SPARK)	3427	12	2913	85.8%
0.85	0.748	0.88	0.7	3563	12	3029	86.0%
0.85	0.748	0.88	0.8	3745	12	3184	86.2%
0.85	0.748	0.88	0.9	3927	12	3338	86.4%

The above calculation is based on the formulas in Zhu and Lakkis [P14-09564] and was calculated using the validated software package R. A sample size of 3900 patients per arm will give a power between 90% to 94% under different dispersion parameters to detect a rate ratio of 0.88 between T+O FDC and Tio 5 in the annualised rate of moderate to severe COPD exacerbation assuming the annual rate in Tio 5 is 0.85 and two-sided type I error rate of 0.01. After adjusting for a 15% loss of information in patient-years and the same assumptions as above, a sample size of 3900 patients per arm will give a power between 86.1% to 90.6%

Assuming the proportion of patients who had at least one moderate to severe COPD exacerbation within 1 year in the Tio 5 arm is 0.65, a hazard ratio between T+O FDC and Tio 5 of 0.88, a two-sided type I error rate of 0.01 and power of 90%, the estimated sample size for time to the first moderate/severe COPD exacerbation is 2915 patients per arm (using nQuery Advisor 7.0). A sample size of 3900 patients per arm will give a power of 97% using the same assumptions.

A sample size of 3900 patients per arm or 7800 patients in total is selected for this trial because it provides acceptable power to detect a 12% reduction in annualised rate of moderate to severe COPD exacerbation of T+O FDC as compared with Tio 5 using a two-sided type I error rate of 0.01, under a reasonable range of dispersion parameters of the negative binomial distribution and assuming the annual rate in Tio 5 is 0.85. This sample size also gives sufficient power to detect a 12% reduction in the hazard rate of moderate to severe COPD exacerbation of T+O FDC as compared to Tio 5 at a two-sided type I error rate of 0.01 and assuming the proportion of patients who had at least one moderate/severe COPD exacerbation after 1 year in the Tio 5 arm is 0.65.

[redacted]

8. INFORMED CONSENT, DATA PROTECTION, TRIAL RECORDS

The trial will be carried out in compliance with the protocol, the principles laid down in the Declaration of Helsinki, in accordance with the ICH Harmonised Tripartite Guideline for Good Clinical Practice (GCP) and relevant BI Standard Operating Procedures (SOPs). Standard medical care (prophylactic, diagnostic and therapeutic procedures) remains in the responsibility of the treating physician of the patient.

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

The rights of the investigator and of the sponsor with regard to publication of the results of this trial are described in the investigator contract. As a general rule, no trial results should be published prior to finalisation of the Clinical Trial Report.

ADDITIONAL INFORMATION FOR JAPAN:

For Japan and the Japanese GCP regulations (Ministry of Health and Welfare Ordinance No.28, March 27, 1997).

The rights of the investigator/trial site and of the sponsor with regard to publication of the results of this trial are described in the investigator/trial site's contract.

Insurance Cover: The terms and conditions of the insurance cover are made available to the investigator and the patients via documentation in the ISF (Investigator Site File).

8.1 STUDY APPROVAL, PATIENT INFORMATION, AND INFORMED CONSENT

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

Prior to 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.

Informed consent procedure and Vital Status information collection

In order to successfully maintain the safety objectives of this trial, it is necessary that each patient's COPD exacerbation follow-up and vital status be maintained until the predicted

patient's exit date (i.e. 52 weeks (+ 1 week) +21 days after taking the first dose of randomized treatment). For this reason the informed consent *includes a COPD exacerbation collection and vital status statements*. All patients will agree to be followed for COPD exacerbation and vital status as a part of the informed consent procedure. Hence, patients who withdraw prematurely from study treatment will still be periodically contacted (approximately every 6 months contact) to determine survival status and every 6 weeks to collect COPD exacerbation status.

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

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

The investigator must give a full explanation to trial patients by using the patient information form, which is prepared avoiding the use of technical terms and expressions. The patient is given sufficient time to consider participation in the trial. The investigator 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 must sign (or place a seal on) and date the informed consent form.

If a trial collaborator has given a supplementary explanation, the trial collaborator also signs (or places a seal on) and dates the informed consent.

8.2 DATA QUALITY ASSURANCE

The trial will be conducted according to the principles of Good Clinical Practice (GCP) and the company standard operating procedures (SOPs). The following steps will be taken to ensure accurate, consistent, complete, and reliable data:

- Investigator meetings
- Training sessions including training material and training records
- Centralised evaluations (central laboratory)
- On-site monitoring and extent of source data verification
- Risk Based Monitoring strategy
- A quality assurance audit/inspection of this trial may be conducted by the sponsor or sponsor's designees or by IRBs/IECs or by regulatory authorities. The quality assurance auditor will have access to all medical records, the investigator's trial-related files and correspondence, and the informed consent documentation of this clinical trial.
- Coding (mention the dictionaries and thesauruses used, e.g. MedDRA)
- Data management procedures: "The data management procedures to ensure the quality of the data are described in detail in the trial data management and analysis plan (TDMAP) available in the TMF."
- Mortality adjudication committee (refer to Section 3.1)

- Steps to maintain the blind (refer to Section 4.1.5.1)

[redacted]

8.3 RECORDS

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

8.3.1 Source documents

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

Data entered in the *eCRFs* that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the trial; also current medical records must be available.

The patient's reminder card will not be collected by the site.

For eCRFs all data must be derived from source documents.

8.3.2 Direct access to source data and documents

The investigator / institution will permit trial-related monitoring, audits, IRB / IEC review and regulatory inspection, providing direct access to all related source data / documents. eCRFs and all source documents, including progress notes and copies of laboratory and medical test results must be available at all times for review by the sponsor's clinical trial monitor, auditor and inspection by health authorities (e.g. FDA). The Clinical Research Associate (CRA) / on site monitor and auditor may review all eCRFs, and written informed consents. An adaptive approach to clinical trial monitoring that directs monitoring focus and activities to the evolving areas of greatest risk which have the most potential to impact subject safety and data quality will be utilised. The accuracy of the data will be verified by reviewing the documents described in Section 8.3.1.

8.3.3 Storage of records

ADDITIONAL INFORMATION FOR JAPAN:

Trial site(s):

The trial site(s) must retain the source documents and essential documents for a period defined by the Japanese GCP regulation and in the trial site's contract with the sponsor.

Sponsor:

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

8.4 LISTEDNESS AND EXPEDITED REPORTING OF ADVERSE EVENTS

8.4.1 Listedness

To fulfil the regulatory requirements for expedited safety reporting, the sponsor evaluates whether a particular adverse event is "listed", i.e. is a known side effect of the drug or not. Therefore a unique reference document for the evaluation of listedness needs to be provided. For the 5 µg tiotropium inhalation solution this is the current version of the Investigator's Brochure [U92-0551]. For the Fixed Dose Combination of tiotropium and olodaterol this is the current version of the Investigator's Brochure [c01735808]. For the non-investigational medicinal product salbutamol/albuterol, the reference document is the US-PI (Proair HFA). The current versions of these reference documents are to be provided in the ISF. No AEs are classified as listed for matching placebo (for training purposes only), study design, or invasive procedures.

8.4.2 Expedited reporting to health authorities and IECs/IRBs

Expedited reporting of serious adverse events, e.g. suspected unexpected serious adverse reactions (SUSARs) to health authorities and IECs/IRBs, will be done according to local regulatory requirements. Further details regarding this reporting procedure are provided in the Investigator Site File.

8.5 STATEMENT OF CONFIDENTIALITY

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

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 for EU>, *i.e. the CA*.

8.6 COMPLETION OF TRIAL

ADDITIONAL INFORMATION FOR JAPAN:

When the trial is completed, the principal investigator should inform the head of the trial site of the completion in writing, and the head of the trial site should promptly inform the IRB and sponsor of the completion in writing.

ADDITIONAL INFORMATION FOR EU MEMBER STATES

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

8.7 PROTOCOL VIOLATIONS

ADDITIONAL INFORMATION FOR JAPAN:

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

8.8 COMPENSATION AVAILABLE TO THE PATIENT IN THE EVENT OF TRIAL RELATED INJURY

ADDITIONAL INFORMATION FOR JAPAN

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

9. REFERENCES

9.1 PUBLISHED REFERENCES

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10. APPENDICES

10.1 THE RESPIMAT INHALER

Instructions for Use

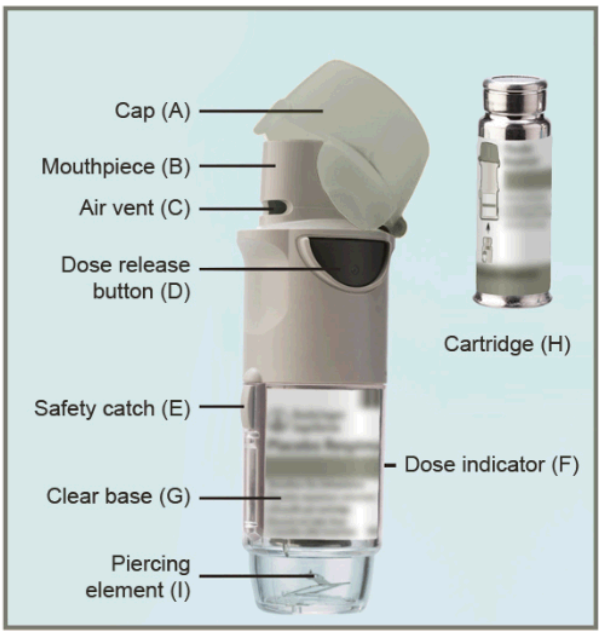
Respimat® inhaler

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.



RESPIMAT® inhaler and the RESPIMAT® cartridge

Inserting the cartridge and preparation for use

The following steps 1-6 are necessary before first use:

 1	**1** With the grey cap (A) closed, press the safety catch (E) and pull off the clear base (G).
 2a	**2** Take the cartridge (H) out of the box. Push the **narrow** end of the cartridge into the inhaler until it **clicks** into place (2a). The cartridge should be pushed **firmly** against a firm surface to ensure that it has gone all the way in (2b). **The cartridge will not be flush with the inhaler; you will still see the silver ring on the lower end of the cartridge.**
 2b	Do not remove the cartridge once it has been inserted into the inhaler.
 3	**3** Replace the clear base (G). Do not remove the clear base again.

To prepare the RESPIMAT® inhaler for first-time use

 4	**4** Hold RESPIMAT® inhaler upright, with the grey cap (A) closed. Turn the clear base (G) in the direction of the red arrows on the label until it **clicks** (half a turn).
 5	**5** Open the grey cap (A) until it snaps fully open.
 6	**6** Point the RESPIMAT® inhaler towards the ground. Press the dose release button (D). Close the grey cap (A). **Repeat steps 4, 5 and 6 until a cloud is visible.** **Then repeat steps 4, 5 and 6 three more times to ensure the inhaler is prepared for use.** **Your RESPIMAT® inhaler is now ready to use.** These steps will not affect the number of doses available. After preparation your RESPIMAT® inhaler will be able to deliver 60 puffs (30 medicinal doses).

Daily use of your RESPIMAT® inhaler

You will need to use this inhaler only ONCE A DAY.
Each time you use it take TWO PUFFS.

 I	**I** Hold the RESPIMAT® inhaler upright, with the grey cap (A) closed, to avoid accidental release of dose. Turn the base (G) in the direction of the red arrows on the label until it clicks (half a turn).
 II	**II** Open the grey cap (A) until it snaps fully open. Breathe out slowly and fully, and then close your lips around the end of the mouthpiece without covering the air vents (C). Point your RESPIMAT® inhaler to the back of your throat. While taking in a slow, deep breath through your mouth, press the dose release button (D) and continue to breathe in slowly for as long as you can. Hold your breath for 10 seconds or for as long as comfortable. **III** **Repeat steps I and II so that you get the full dose.** **You will need to use this inhaler only ONCE A DAY.** **Close the grey cap until you use your RESPIMAT® inhaler again.** If the RESPIMAT® inhaler has not been used for more than 3 days release one puff towards the ground. If the RESPIMAT® inhaler has not been used for more than 21 days repeat steps 4 to 6 until a cloud is visible. Then repeat steps 4 to 6 three more times.

When to get a new RESPIMAT® inhaler

	The RESPIMAT® inhaler contains 60 puffs (30 medicinal doses). The dose indicator shows approximately how much medication is left. When the pointer enters the red area of the scale, there is, approximately, medication for 7 days (14 puffs) left. Once the dose indicator has reached the end of the red scale (i.e. all 30 doses have been used), the RESPIMAT® inhaler is empty and locks automatically. At this point, the base cannot be turned any further.

What if...

What if...	Reason	What to do
I can't turn the base easily.	a) The RESPIMAT® inhaler is already prepared and ready to use. b) The RESPIMAT® inhaler is locked after 60 puffs (30 doses).	a) The RESPIMAT® inhaler can be used as it is. b) Prepare and use your new RESPIMAT® inhaler.
I can't press the dose release button.	The clear base has not been turned.	Turn the clear base until it **clicks**. (half a turn)
The clear base springs back after I have turned it.	The clear base was not turned far enough.	Prepare the RESPIMAT® inhaler for use by turning the clear base until it **clicks**. (half a turn)
I can turn the clear base past the point where it clicks.	Either the dose release button has been pressed, or the clear base has been turned too far.	With the grey cap closed, turn the base until it **clicks**. (half a turn)

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.

Keep out of the reach and sight of children.

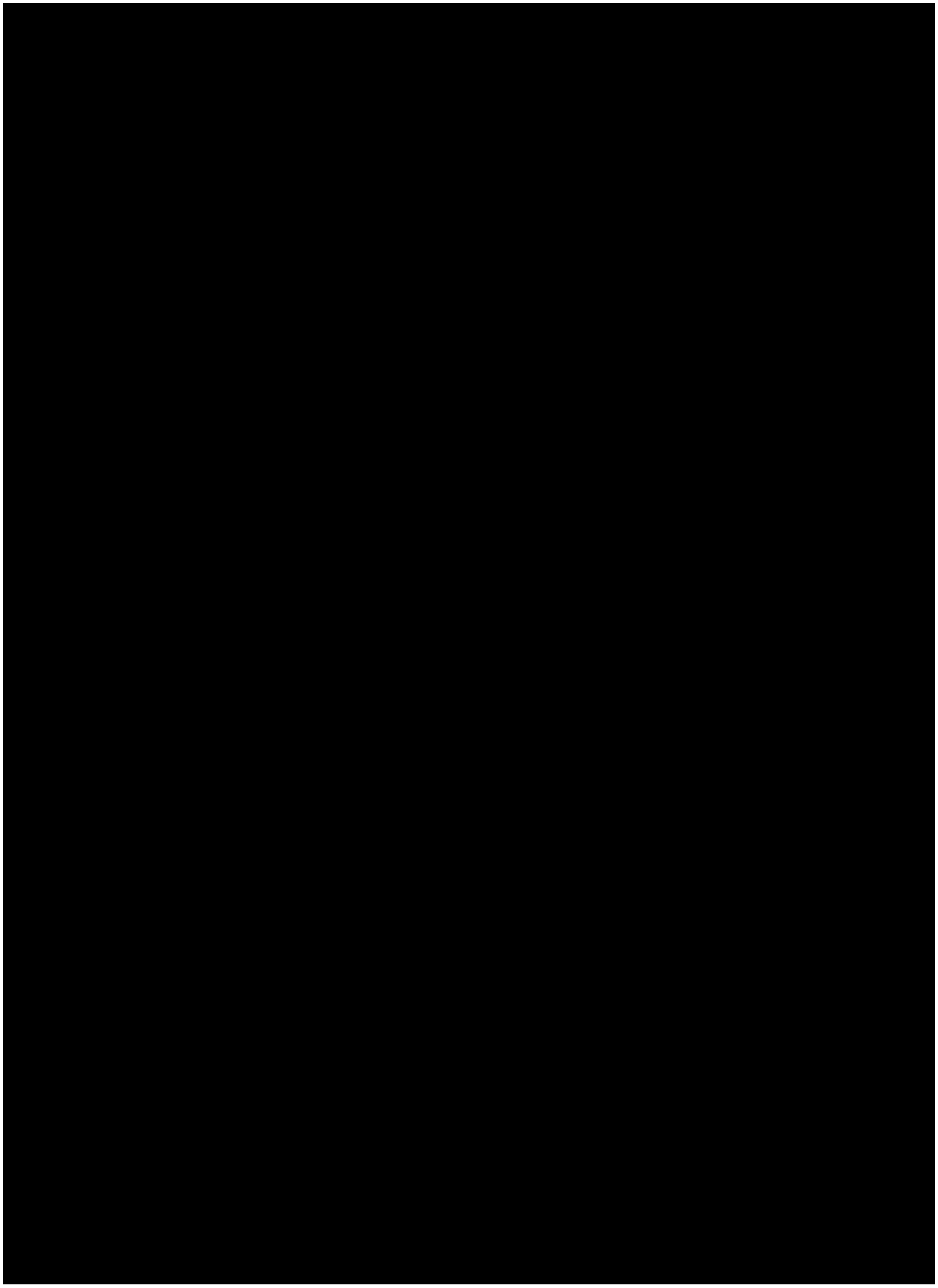
Do not freeze.

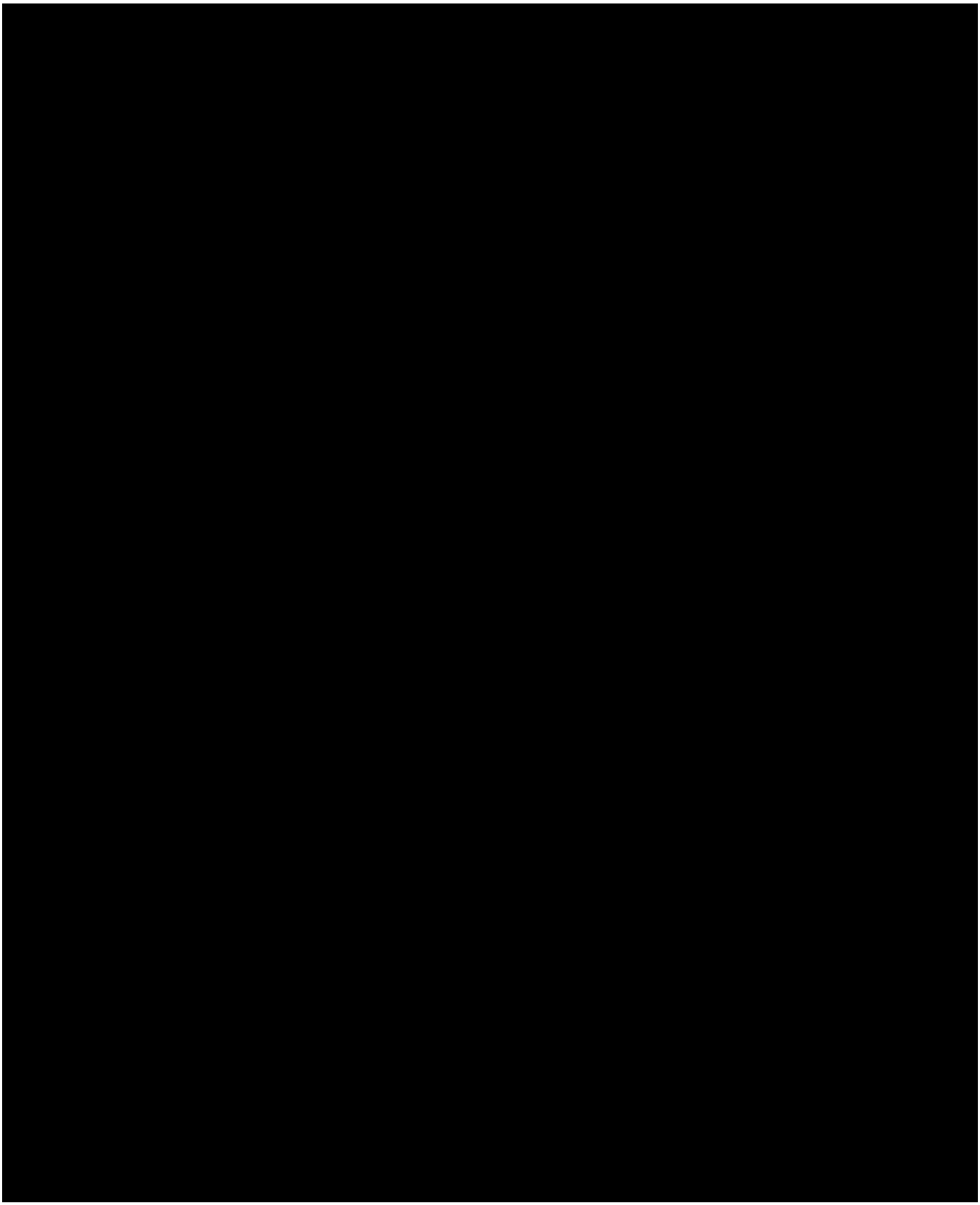
Boehringer Ingelheim Pharma GmbH & Co. KG
D - 55216 Ingelheim, Germany

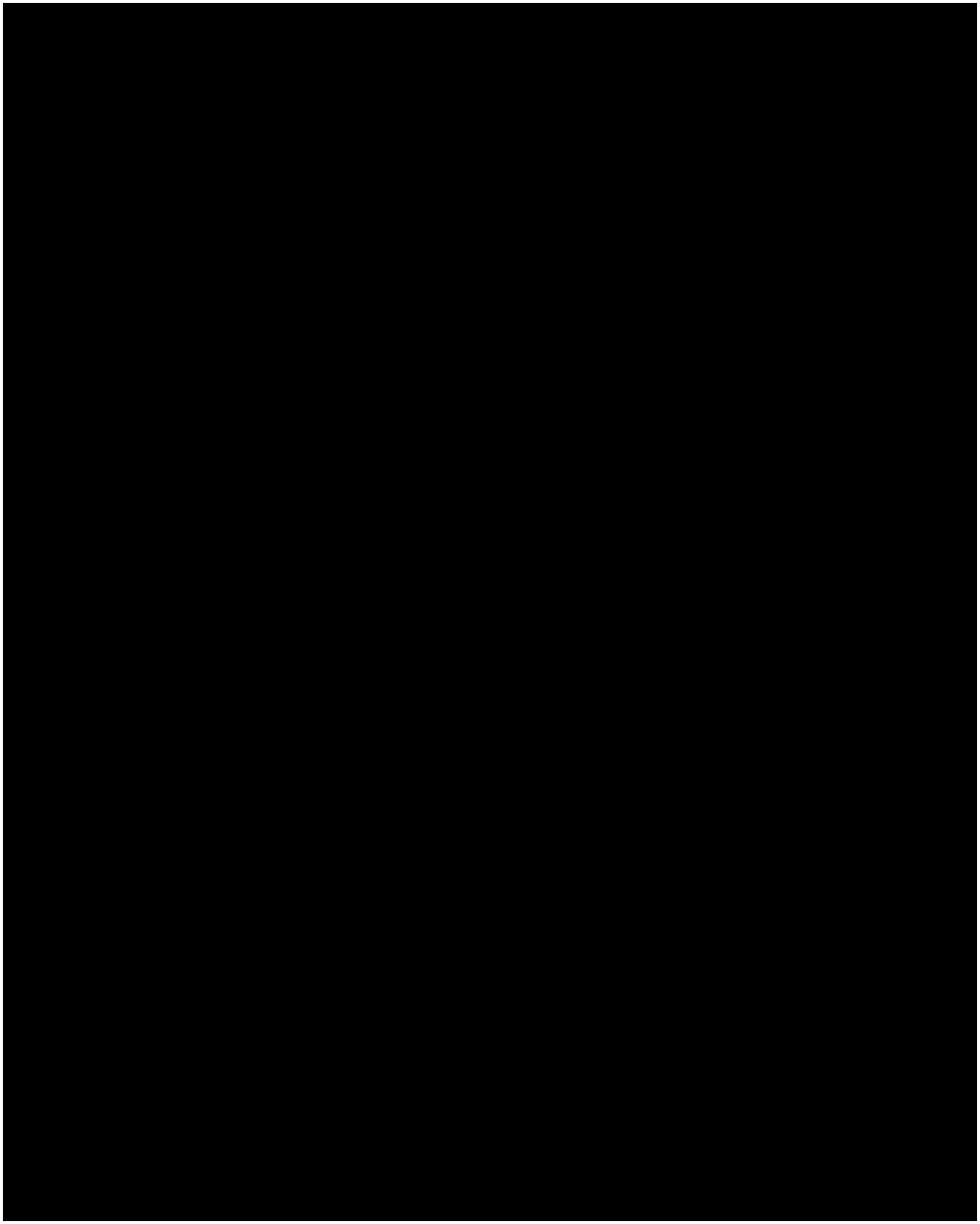
CE 0123 **HI-Master-Version-06-tiotropium+olodaterol-combination-Respimat-20140516**

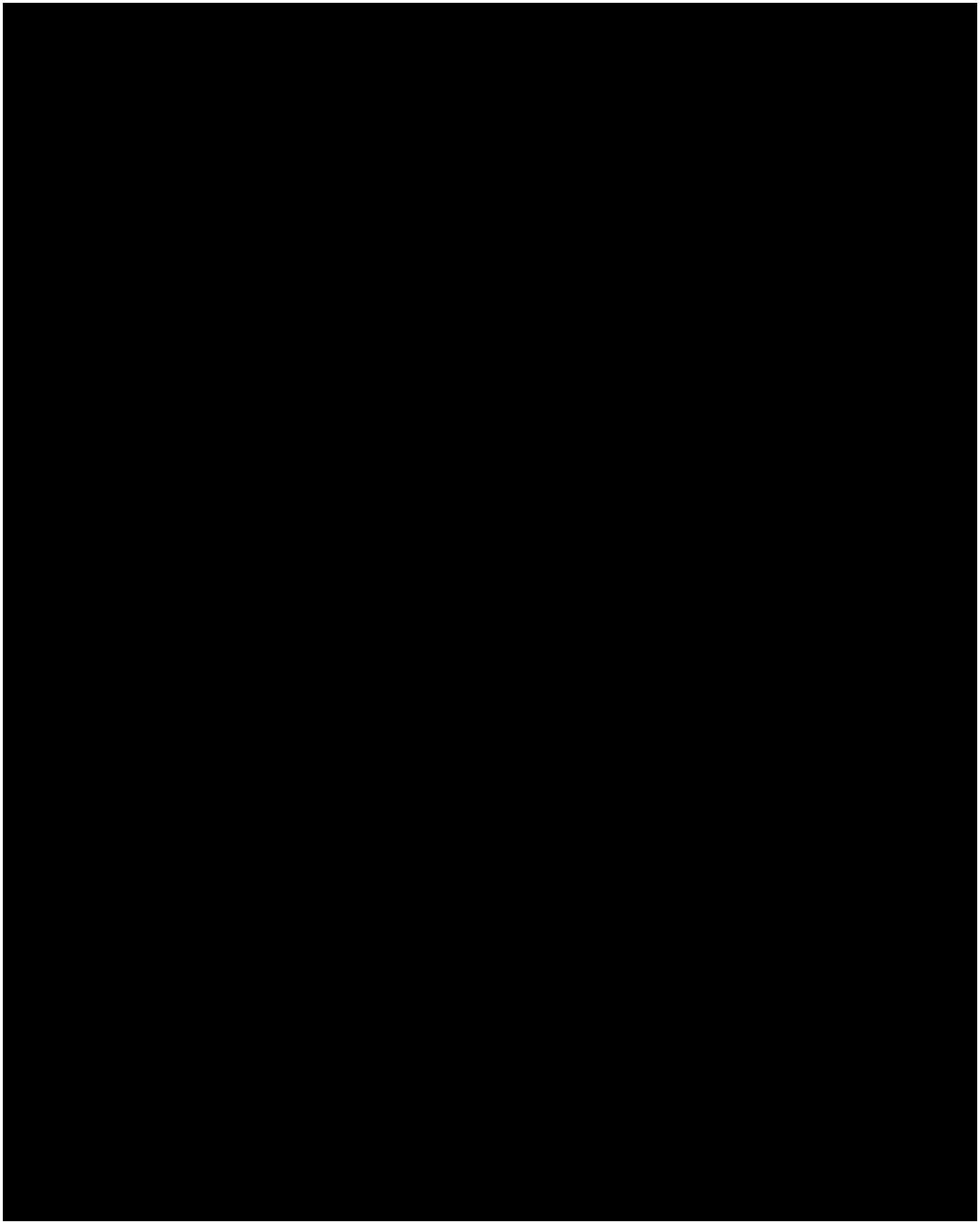
10.2 RETURN OF INHALERS/CARTRIDGES

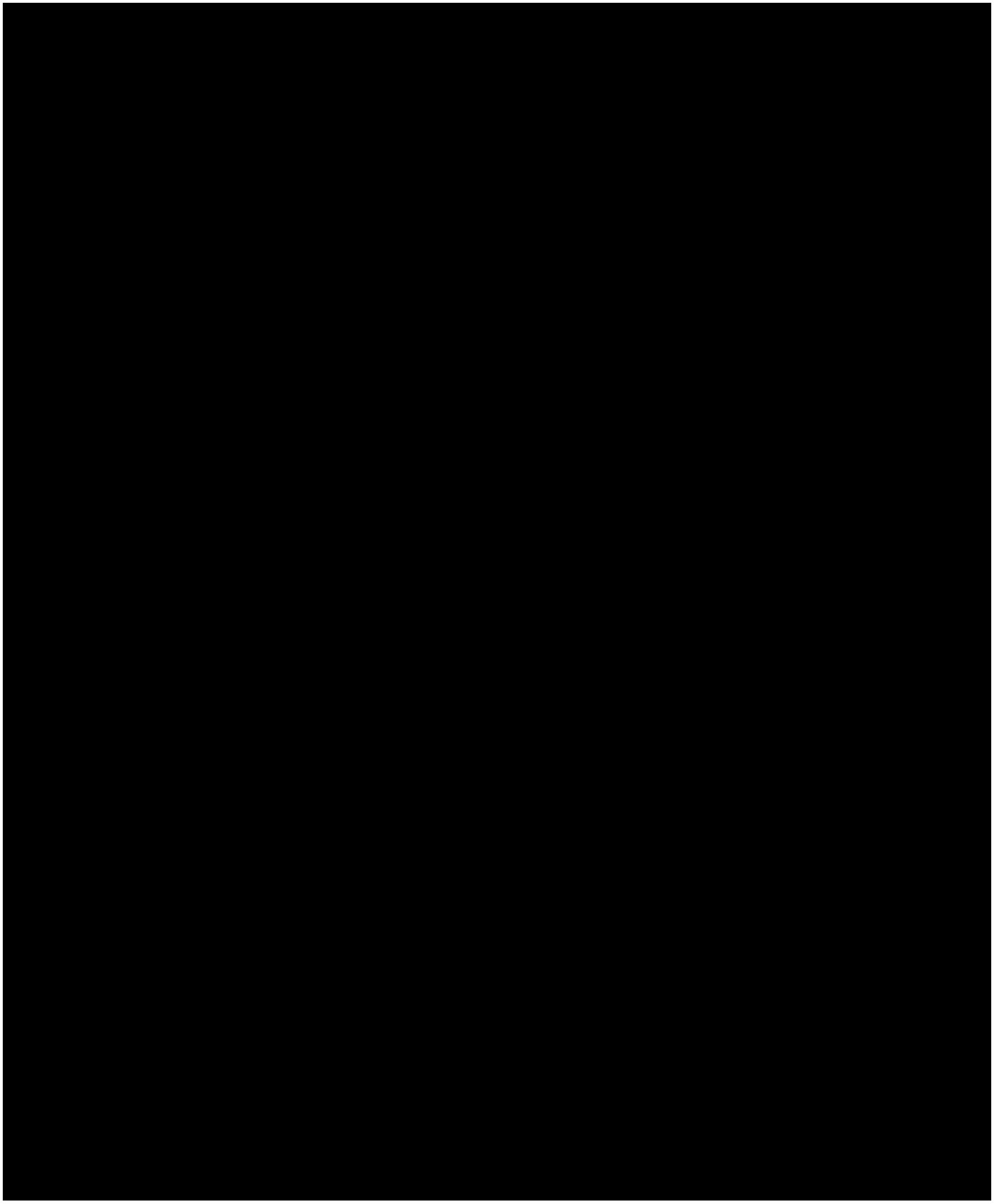
Return of Malfunctioning RESPIMAT Inhalers
Respimat® inhalers, with the used cartridge in situ, that appeared to malfunction, will be returned to Boehringer Ingelheim as soon as possible. **Procedures for this return, including** name, address and contact person are provided in the ISF.

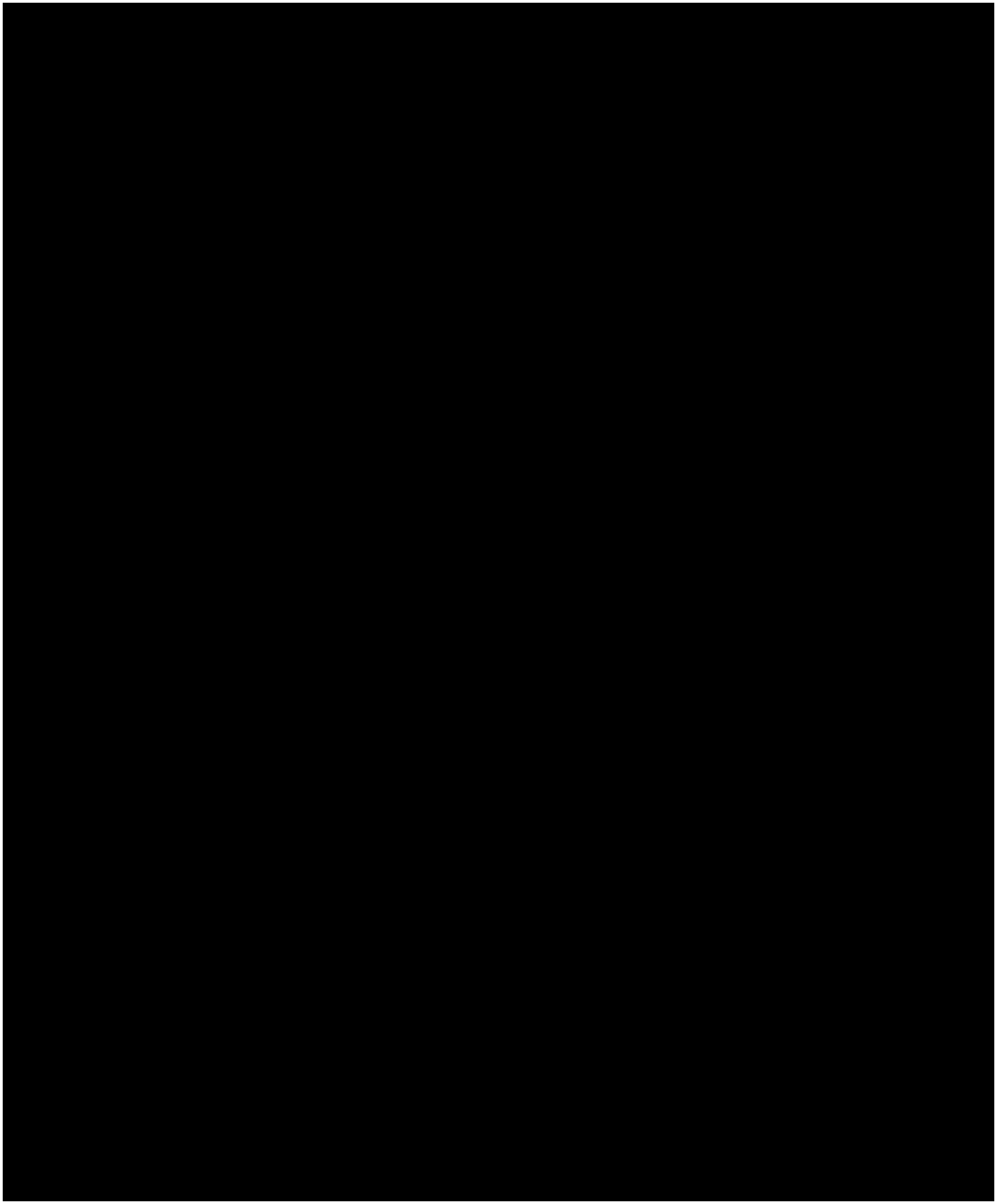


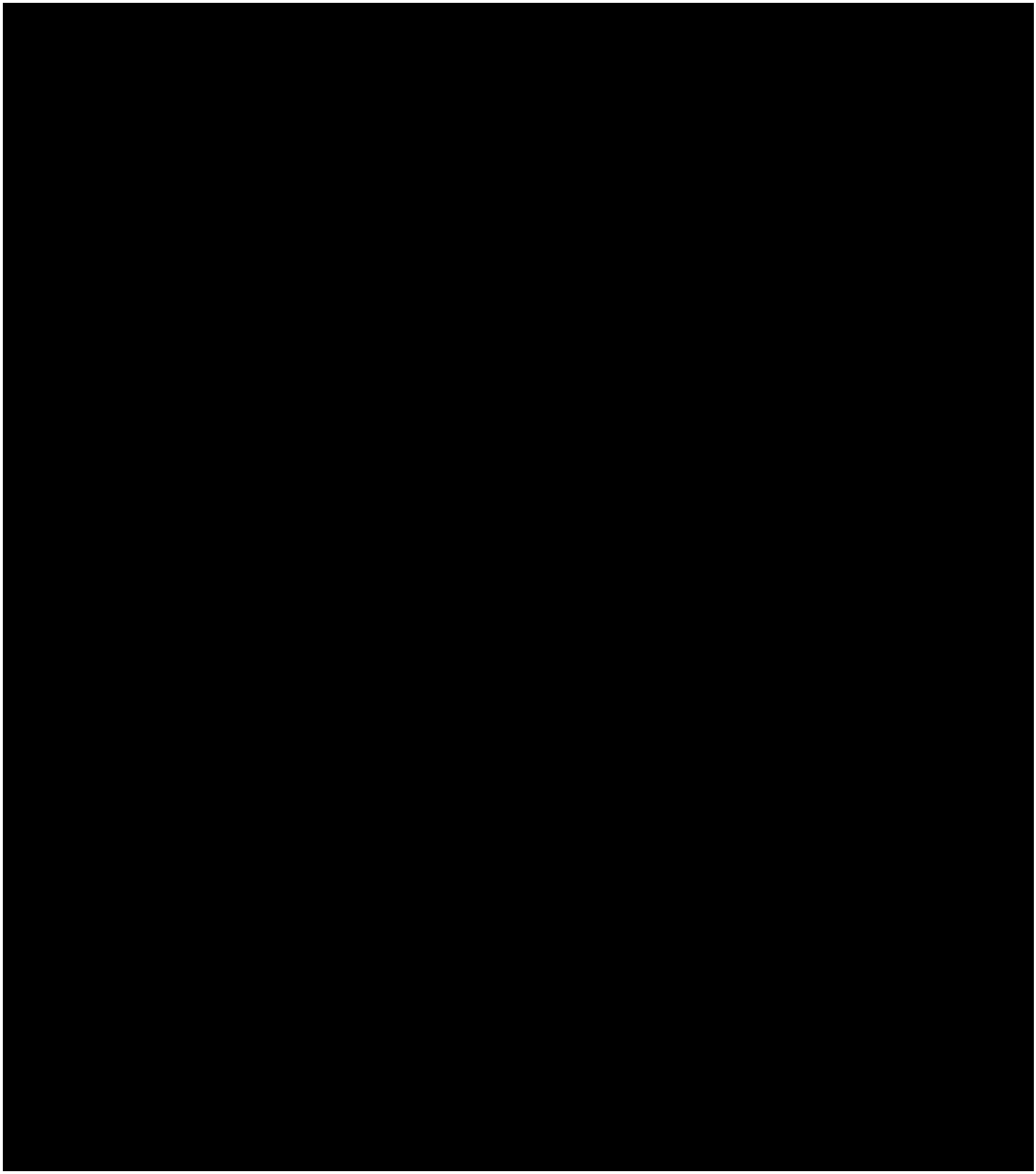












10.5 ADDITIONAL INFORMATION REGARDING IN/EX CRITERIA

Calculation of predicted normal values according to ECSC

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

Post-bronchodilator FEV1< 60% of predicted normal (ECSC) and post-bronchodilator FEV_1/FVC <70% of predicted normal (ECSC): documentation

Patients may not be randomised to the study without the availability of spirometry data at the actual study site.

Historical data

To be performed within the past 3 months either at the site or at a referral site will be used.
A referral letter and signed copies of the measurement printouts must be provided to the trial site for source data verification. However, any referral documentation does not result in the need to open "satellite sites".

In case several qualifying spirometry measurements are available, the most recent one should be referred to as long as it was not performed during an exacerbation.

OR

PFT measurement at investigational site:

Patient must be able to perform a post-dose pulmonary function test after the administration of 400 µg salbutamol/albuterol (preferred) for qualification.

OR: testing with either 200 µg salbutamol/albuterol or a combination of salbutamol/albuterol with ipratropium bromide (2 to 4 actuations) is acceptable.

The spirometers and their use, including daily calibration, must meet American Thoracic Society (ATS)/ European Respiratory Society (ERS) criteria.

[redacted]

[redacted]

Calculation of number of pack years

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

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

This is a revised protocol.

Number of global amendment		1.0
Date of CTP revision		15 July 2015
EudraCT number		2014-002275-28
BI Trial number		1237.19
BI Investigational Products		- Tiotropium + olodaterol fixed dose combination inhalation solution Respimat® - Tiotropium 5 µg inhalation solution Respimat®
Title of protocol		A randomised, double-blind, active-controlled parallel group study to evaluate the effect of 52 weeks of once daily treatment of orally inhaled tiotropium + olodaterol fixed dose combination compared with tiotropium on Chronic Obstructive Pulmonary Disease (COPD) exacerbation in patients with severe to very severe COPD. [DYNAGITO]
To be implemented only after approval of the IRB/IEC/Competent Authorities		☒
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		☐
Can be implemented without IRB/IEC/ Competent Authority approval as changes involve logistical or administrative aspects only		☐
Section to be changed	1 2 3 4 5 6 7 8 9	Synopsis, flowcharts (including footnotes) Abbreviations Section 3.1 Overall trial design and plan Section 3.1.1 Administrative structure of the trial Section 3.3 Selection of trial population Section 3.3.2 Inclusion criteria Section 3.3.3 Exclusion criteria Section 4.1.4.2 Study medication administration Section 4.1.6 Packaging, labelling and re-supply

Number of global amendment		1.0
	10	Section 4.2.1.1 Rescue medication
	11	Section 4.2.2.1 Restrictions regarding concomitant medication
	12	Table 4.2.2.1 Permitted medications and medications restrictions (including footnotes)
	13	Section 4.2.2.2 Restrictions on diet and life style
	14	Section 5.1.1 Endpoints of efficacy
	15	Section 5.1.2.2 Assessment of moderate to severe COPD exacerbation
	16	Section 5.1.3.1 Laboratory test
	17	Section 5.1.3.2 Physical examination
	18	Section 5.4 Appropriateness of measurements
	19	Section 6.1 Visit schedule
	20	Section 6.2 Details of trial procedures at selected visits
	21	Section 6.2.1 Screening period
	22	Section 6.2 Treatment periods
	23	Section 6.2.2.1 randomisation Visit 2
	24	Section 6.2.2.2 Clinic visits (Visits 3, 4 and 5)
	25	Section 6.2.2.3 telephone contacts between clinic visits
	26	Section 6.2.2.2 Visit 6/EoT
	27	Section 6.2.3.2 Premature discontinuation
	28	Section 6.2.4 Follow-up visit
	29	Section 7.3.5 Other analyses
	30	Section 7.4 Handling of missing data
	31	Section 7.6 Determination of sample size
	32	Section 8.2 Data Quality assurance
	33	10.5 Additional information regarding in/ex criteria
Description of change		**Administrative changes, corrections and added clarifications** Main flow chart *(Time points for Vital status and COPD exacerbation collection time points re-specified, [redacted]) [redacted], pregnancy test re-specified. The IRT trial completion call was removed.* Abbreviations- update Section 3.3 Selection of trial population *(enrolment average per site increased 10-12 patients)* Section 3.3.3 Exclusion criteria *(Ex #2: urinalysis removed. Possibility to repeat the lab test)* *(Ex # 15-16: medication restrictions and wash-out revised for oral CS, antibiotics)* Table 4.2.2.1 Permitted medications and medications restrictions (including footnotes)

Number of global amendment		1.0
		Clarification on use of respiratory medicine including information related to antibiotics use not limited to COPD exacerbation) Section 4.2.2.2 Restrictions on diet and life style Section 5.1.2.2 Assessment of moderate to severe COPD exacerbation *(The patient's reminded card will collect the missed dose medication)* Section 5.1.3.1 Laboratory test Section 5.1.3.2 Physical examination Section 5.4 Appropriateness of measurements *(The CAT questionnaire should be collected before the SGRQ)* Section 6.1 Visit schedule *(The screening period between V1 and V2 can be expanded by an additional 1 week)* Section 6.2.2.2 Visit 6/EoT *(Clarification on procedures carried out for completed patients and prematurely discontinued patients)* Section 6.2.3.2 Premature discontinuation *Clarification on timing of procedures* Section 6.2.4 Follow-up visit *(Urine pregnancy testing added to be consistent with the section 5.2.3.1 laboratory tests)*

[redacted]

Number of global amendment		1.0

[redacted]

APPROVAL / SIGNATURE PAGE

Document Number: c02247259 **Technical Version Number:3.0**

Document Name: clinical-trial-protocol

Title: A randomised, double-blind, active-controlled parallel group study to evaluate the effect of 52 weeks of once daily treatment of orally inhaled tiotropium + olodaterol fixed dose combination compared with tiotropium on Chronic Obstructive Pulmonary Disease (COPD) exacerbation in patients with severe to very severe COPD. [DYNAGITO]

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Author-Clinical Monitor	[redacted]	16 Jul 2015 16:03 CEST
Verification-Paper Signature Completion	[redacted]	16 Jul 2015 16:09 CEST
Approval-Therapeutic Area [redacted]	[redacted]	16 Jul 2015 16:48 CEST
Approval-Team Member Medical Affairs	[redacted]	16 Jul 2015 17:12 CEST
Approval-Biostatistics	[redacted]	16 Jul 2015 17:49 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed