

Clinical Trial Protocol

Document Number:		c03560350-04
EudraCT No.: EU Trial No:	2015-002641-66	
BI Trial No.:	1237.36	
BI Investigational Product(s):	Tiotropium + olodaterol fixed dose combination inhalation solution - Respimat®	
Title:	An exploratory, randomised, double-blind, double-dummy, active-controlled, two period cross-over study to investigate the effect of 6 weeks treatment of orally inhaled tiotropium + olodaterol fixed dose combination (FDC) delivered by the Respimat® Inhaler with fluticasone propionate + salmeterol FDC delivered by the Accuhaler® Inhaler, on left ventricular function and arterial stiffness in patients with Chronic Obstructive Pulmonary Disease (COPD)	
Lay Title:	Cardiovascular function in COPD patients	
Clinical Phase:	IV	
Trial Clinical Monitor:	Phone: _____, Fax: _____	
Coordinating Investigator:	Phone: _____, Fax: _____	
Status:	Final Protocol (Revised Protocol based on global amendment 3)	
Version and Date:	Version: 4.0	Date: 30 November 2017
Page 1 of 99		
<p style="text-align: center;">Proprietary confidential information.</p> <p>© 2017 Boehringer Ingelheim International GmbH or one or more of its affiliated companies. All rights reserved. This document may not - in full or in part - be passed on, reproduced, published or otherwise used without prior written permission.</p>		

CLINICAL TRIAL PROTOCOL SYNOPSIS

Name of company:		Boehringer Ingelheim	
Name of finished product:		Spiolto [®] Respimat [®] inhalation solution	
Name of active ingredient:		Tiotropium + olodaterol fixed dose combination inhalation solution - Respimat [®]	
Protocol date: 25 Oct 2016	Trial number: 1237.36		Revision date: 30 Nov 2017
Title of trial:	An exploratory, randomised, double-blind, double-dummy, active-controlled, two period cross-over study to investigate the effect of 6 weeks treatment of orally inhaled tiotropium + olodaterol fixed dose combination (FDC) delivered by the Respimat [®] Inhaler with fluticasone propionate + salmeterol FDC delivered by the Accuhaler [®] Inhaler, on left ventricular function and arterial stiffness in patients with Chronic Obstructive Pulmonary Disease (COPD)		
Coordinating Investigator	<div> <div></div> <div>Phone:</div> <div></div> <div>, Fax:</div> <div></div> </div>		
Trial site(s):	Multi-centre trial (approximately 10 centres in Germany)		
Clinical phase:	IV		
Objective(s):	<p>The primary objective of the study is to explore the effect of treatment with tiotropium + olodaterol FDC compared to fluticasone propionate + salmeterol FDC on reversal of left ventricular diastolic dysfunction assessed with cardiac magnetic resonance (CMR) imaging.</p> <p>A secondary objective is to explore the effect of tiotropium + olodaterol FDC compared to fluticasone propionate + salmeterol FDC on measures of arterial stiffness assessed by CMR and central blood pressure assessed by pulse wave analysis (PWA), and on reduction of lung hyperinflation assessed with body plethysmography (pleth) and post dose spirometry.</p>		
Methodology:	Exploratory, randomised, double-blind, double-dummy, active-controlled, cross-over design comparing two treatments after 6 weeks of treatment.		

Name of company:		Boehringer Ingelheim	
Name of finished product:		Spiolto [®] Respimat [®] inhalation solution	
Name of active ingredient:		Tiotropium + olodaterol fixed dose combination inhalation solution - Respimat [®]	
Protocol date: 25 Oct 2016	Trial number: 1237.36		Revision date: 30 Nov 2017
No. of patients:	Approximately 74		
total entered:	Approximately 74		
each treatment:	Approximately 74		
Diagnosis :	Chronic Obstructive Pulmonary Disease (COPD)		
Main criteria for inclusion:	Outpatients of either sex, aged ≥ 40 years and ≤ 75 years with smoking history > 10 pack years, post bronchodilator FEV ₁ $< 70\%$ predicted, post-bronchodilator FEV ₁ /FVC $< 70\%$, FRC _{pleth} $> 120\%$ predicted normal, with post-bronchodilator reversibility which improves by greater than or equal to 7,5 percentage points, clinically free of cardiovascular (CV) disease.		
Test product(s):	Tiotropium + olodaterol FDC inhalation solution - Respimat [®]		
dose:	[5 µg tiotropium + 5 µg olodaterol] (2.5 µg / 2.5 µg per actuation)		
mode of administration:	Oral inhalation (2 inhalations in the morning)		
Comparator products:	Fluticasone propionate + salmeterol FDC dry powder for inhalation - Accuhaler [®]		
dose:	[1000 µg fluticasone propionate + 100 µg salmeterol] (500 µg / 50 µg per actuation)		
mode of administration:	Oral inhalation (2 x 1 inhalation daily) bid		

Name of company:		Boehringer Ingelheim	
Name of finished product:		Spiolto [®] Respimat [®] inhalation solution	
Name of active ingredient:		Tiotropium + olodaterol fixed dose combination inhalation solution - Respimat [®]	
Protocol date: 25 Oct 2016	Trial number: 1237.36		Revision date: 30 Nov 2017
Duration of treatment:		2 x 6-week treatment periods (total treatment duration of 12 weeks)	
Endpoints		<p>Primary endpoint is change from baseline in left ventricular end diastolic volume index (LVEDVI) after 6 weeks of treatment.</p> <p>Secondary endpoints, all calculated as change from baseline, include: Aortic distensibility, pulmonary artery pulsatility. Central systolic, pulse and augmentation index. FRC_{pleth} % predicted after 6 weeks of treatment. 1,5 hour post dose FEV₁, after 6 weeks of treatment. 1,5 hour post dose FVC, after 6 weeks of treatment.</p>	
Safety criteria:		Heart rate and blood pressure in conjunction with lung function testing as applicable, adverse events and physical examination.	
Statistical methods:		<p>Restricted Maximum Likelihood (REML) estimation based Mixed-effects Model for Repeated Measures (MMRM) analysis will be used to obtain adjusted means for the treatment effects.</p> <p>This model will include treatment and period as fixed effects, patient as a random effect and baseline as a covariate. (Unstructured covariance structure will be used for within patient variation).</p> <p>Descriptive statistics for the safety analyses/assessment.</p>	

FLOW CHART

	Screening period Run-in Period		Treatment phase			Discontinuation ³	Follow-up
			Period 1 and 2				
Visit	0	1	2	3 ¹	4 ¹		5
Week of treatment (cumulative)	-	-3 to -1	0	6	12 EoT		V4 + 3 EoO
Day of treatment	-	-21 to -7	1	43	85		106
Day of treatment (cumulative) Time window (days)*	-	-21 to -7	1	43 ±3	85 ±3		V4 + 21 +7
Informed consent, patient information	X ²						
Register patient in screening (IRT)	X						
Demographics		X					
Medical history/Baseline Conditions		X					
COPD/patient characteristics		X					
Smoking status		X	X	X	X	X	
In-/Exclusion criteria		X	X				
Physical examination		X		X	X	X	X ⁴
Laboratory tests		X					
Pregnancy test ⁵		X	X	X	X	X	X
12 lead-ECG ⁶		X					
Training in use of Respimat [®] and Accuhaler [®]		X	X ⁷	X ⁷			
Randomisation (IRT)			X				
Medication washout check		X	X	X	X		
Dispense and explain use of rescue medication	X ⁸	X	X	X			
Collect rescue medication		X	X	X	X	X	
Dispense trial medication (IRT)			X	X			
Administer trial medication at clinic			X	X	X		
Collect trial medication				X ⁹	X ⁹	X	
Drug and/or rescue med. accountability check		X	X	X	X		
mMRC ¹⁰		X					
Cardiac Magnetic Resonance (CMR) ¹¹			X ^{11a}	X ^{11b}	X ^{11b}		
Body Plethysmography (FRC, RVol, TLC, IC)		X ¹²	X ¹³	X ¹³	X ¹³		
Spirometry (FEV ₁ , FVC)		X ¹²	X ¹³	X ¹³	X ¹³	X	
Vital signs (seated) ¹⁴		X	X	X	X	X	
Blood pressure and PWA ¹⁵		X	X	X	X		
Adverse events		X	X	X	X	X	X
Concomitant therapy		X	X	X	X	X	X
Medication washout		X	X	X	X		
Rescue Medication Use ¹⁶		X	X	X	X	X	
Trial Medication Adherence ¹⁶				X	X	X	
Telephone contacts ¹⁷		X	X	X	X		
Trial medication termination (IRT)					X	X	
Completion of patient participation							X

- * Site should make every effort to attain 6 weeks treatment exactly when scheduling the visit days with the patient at the beginning of the trial.
- 1 Treatment phase: Procedures during visits 3 and 4 will be identical.
- 2 Informed Consent: All patients must sign an informed consent consistent with ICH-GCP guidelines prior to participation in the trial, which includes medical washout and restrictions.
- 3 Premature discontinuation procedures and observations: To be completed by all patients who took at least one dose of trial medication including those who discontinue early (see [Section 6.2.3](#)).
- 4 End of observation (EoO) examinations: To be performed in the event of any clinically relevant findings at Visit 4.
- 5 Pregnancy testing: Women of child-bearing potential: serum pregnancy test at Visit 1; urine pregnancy test at Visits 2, 3, 4 and 5.
- 6 ECG: 12-lead ECG recording at screening (Visit 1) for inclusion in the study.
- 7 Device training: The patient will be instructed in the use of the Respimat® inhaler and Accuhaler® inhaler, but the patient **should not** inhale from the placebo/demonstrational inhaler at these visits.
- 8 Rescue medication: To be supplied to all patients at Visit 0.
- 9 Trial Medication collection: Last dose of trial medication for the respective treatment period will be the morning dose, taken in the clinic on visit day (Visit 3 – day 43 and Visit 4 – day 85). All medication is collected after this dosing.
- 10 mMRC ; Refer to [Appendix 10.4](#) and [10.5](#), respectively.
- 11 Cardiovascular MR:
11a - baseline evaluation - in a week prior to randomisation (Visit 2) but at the latest 3 days prior to the Visit 2 to allow for the assessment of ejection fraction level for inclusion.
11b - end of treatment evaluation - in a week prior to end of treatment period visits or on the visit day (Visit 3 and 4) after the visit procedures have been completed and within the time frame 1-8 hours post morning study medication dose.
Washouts planned for baseline Visit 2 should be reached also for baseline CMR evaluation conducted in a week prior to visit 2. For CMRs prior to Visits 3 and 4 rescue medication washout needed as for respective clinic visits.
- 12 Reduction of hyperinflation and reversibility testing: Pre- and post-bronchodilator (400 µg salbutamol (albuterol)) spirometry and body plethysmography at Visit 1. [note: hyperinflation at rest defined as $FRC_{pleth} > 120\%$ predicted, with post-bronchodilator reversibility greater than or equal to 7.5 percentage points at Visit 1 is an inclusion criterion]. Refer to [Appendix 10.3](#).
- 13 Body plethysmography followed by spirometry measurements:
Visit 2 - Pre-dose measurement: 1 hour prior to inhalation of morning dose of study medication at Visit 2.
Visits 3 and 4 - Post-dose measurement: 1.5 hour post morning dose of trial medication at Visits 3 and 4.
- 14 Vital Signs: immediately prior to body plethysmography.
- 15 Blood pressure measurement and pulse wave analysis: should be performed during vital signs assessment prior to body plethysmography.
- 16 Medication Use: From medication counter for IMP and rescue medication.
- 17 Telephone contacts: Site staff will telephone the patient prior to patient's scheduled CMR examination and 1-2 days prior to clinic visits to remind them of medication washout and any other requirements.

TABLE OF CONTENTS

TITLE PAGE	1
CLINICAL TRIAL PROTOCOL SYNOPSIS	2
FLOW CHART	5
TABLE OF CONTENTS	7
ABBREVIATIONS	10
1. INTRODUCTION.....	13
1.1 MEDICAL BACKGROUND.....	13
1.2 DRUG PROFILE	15
2. RATIONALE, OBJECTIVES, AND BENEFIT - RISK ASSESSMENT	17
2.1 RATIONALE FOR PERFORMING THE TRIAL	17
2.2 TRIAL OBJECTIVES.....	17
2.3 BENEFIT - RISK ASSESSMENT.....	17
3. DESCRIPTION OF DESIGN AND TRIAL POPULATION	20
3.1 OVERALL TRIAL DESIGN AND PLAN	20
3.1.1 Administrative structure of the trial	21
3.2 DISCUSSION OF TRIAL DESIGN, INCLUDING THE CHOICE OF CONTROL GROUP(S)	22
3.3 SELECTION OF TRIAL POPULATION	23
3.3.1 Main diagnosis for trial entry	24
3.3.2 Inclusion criteria	24
3.3.3 Exclusion criteria	25
3.3.4 Removal of patients from therapy or assessments.....	27
3.3.4.1 Removal of individual patients	27
3.3.4.2 Discontinuation of the trial by the sponsor	28
4. TREATMENTS.....	29
4.1 INVESTIGATIONAL TREATMENTS	29
4.1.1 Identity of the Investigational Medicinal Products.....	29
4.1.2 Selection of doses in the trial.....	31
4.1.3 Method of assigning patients to treatment groups.....	31
4.1.4 Drug assignment and administration of doses for each patient.....	31
4.1.4.1 Dispensing of trial medication	31
4.1.4.2 Study medication administration	32
4.1.4.3 Inhaler devices training.....	34
4.1.4.4 RespiMat [®] malfunctioning	35
4.1.5 Blinding and procedures for unblinding.....	35
4.1.5.1 Blinding.....	35
4.1.5.2 Unblinding and breaking the code	35
4.1.6 Packaging, labelling, and re-supply.....	35
4.1.7 Storage conditions	37

4.1.8	Drug accountability.....	37
4.2	OTHER TREATMENTS, EMERGENCY PROCEDURES, RESTRICTIONS	39
4.2.1	Other treatments and emergency procedures	39
4.2.2	Restrictions	40
4.2.2.1	Restrictions regarding concomitant treatment	40
4.2.2.2	Restrictions for pulmonary function testing and CMR assessment	45
4.2.2.3	Restrictions on diet and life style	45
4.3	TREATMENT COMPLIANCE	45
5.	VARIABLES AND THEIR ASSESSMENT	47
5.1	TRIAL ENDPOINTS.....	47
5.1.1	Primary Endpoint(s).....	47
5.1.2	Secondary Endpoint(s)	47
5.2	ASSESSMENT OF EFFICACY	48
5.3	ASSESSMENT OF SAFETY	50
5.3.1	Physical examination	50
5.3.2	Vital Signs	50
5.3.3	Safety laboratory parameters	50
5.3.4	Electrocardiogram	51
5.3.5	Other safety parameters.....	51
5.3.6	Assessment of adverse events	51
5.3.6.1	Definitions of AEs	51
5.3.6.2	Adverse event collection and reporting	54
5.3.6.3	COPD Exacerbations	55
5.4	DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS	56
5.4.1	Assessment of Pharmacokinetics	56
5.5	ASSESSMENT OF BIOMARKER(S)	56
5.6	OTHER ASSESSMENTS.....	56
5.7	APPROPRIATENESS OF MEASUREMENTS	57
6.	INVESTIGATIONAL PLAN.....	58
6.1	VISIT SCHEDULE.....	58
6.2	DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS	59
6.2.1	Screening and run-in period(s)	59
6.2.2	Treatment period(s)	61
6.2.3	Follow Up Period and Trial Completion.....	66
7.	STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE	68
7.1	STATISTICAL DESIGN - MODEL	68
7.2	NULL AND ALTERNATIVE HYPOTHESES	68
7.3	PLANNED ANALYSES	68
7.3.1	Primary endpoint analyses.....	69
7.3.2	Secondary endpoint analyses	69
	69

7.3.4	Safety analyses.....	69
7.3.5	Pharmacokinetic analyses	70
7.4	INTERIM ANALYSES	70
7.5	HANDLING OF MISSING DATA	70
7.6	RANDOMISATION	70
7.7	DETERMINATION OF SAMPLE SIZE	70
8.	INFORMED CONSENT, TRIAL RECORDS, DATA PROTECTION, PUBLICATION POLICY	72
8.1	TRIAL APPROVAL, PATIENT INFORMATION, INFORMED CONSENT	72
8.2	DATA QUALITY ASSURANCE	73
8.3	RECORDS	73
8.3.1	Source documents	73
8.3.2	Direct access to source data and documents.....	74
8.3.3	Storage period of records	74
8.4	EXPEDITED REPORTING OF ADVERSE EVENTS	74
8.5	STATEMENT OF CONFIDENTIALITY AND PATIENT PRIVACY	74
8.6	TRIAL MILESTONES.....	75
9.	REFERENCES.....	76
9.1	PUBLISHED REFERENCES.....	76
9.2	UNPUBLISHED REFERENCES.....	79
10.	APPENDICES	80
10.1	THE RESPIMAT® INHALER	80
10.2	THE ACCUHALER® INHALER.....	85
10.3	ADDITIONAL INFORMATION REGARDING IN/EX CRITERIA	87
10.4	MODIFIED MEDICAL RESEARCH COUNCIL DYSPNEA SCALE	88
10.6	NEW YORK HEART ASSOCIATION (NYHA) FUNCTIONAL CLASSIFICATION	90
11.	DESCRIPTION OF GLOBAL AMENDMENT(S)	91

ABBREVIATIONS

AE	Adverse Event
AESI	Adverse Event of Special Interest
AI	Augmentation Index
AMP	Auxiliary Medicinal Product
ATS	American Thoracic Society
AUC	Area under the Curve
BAC	Benzalkonium chloride
BI	Boehringer Ingelheim
bid	bis in die (twice daily dosing)
BMI	Body Mass Index
BSA	body surface area
CABG	Coronary Artery Bypass Graft
CI	Confidence Interval
CML	Local Clinical Monitor
CMR	Cardiac Magnetic Resonance
COPD	Chronic Obstructive Pulmonary Disease
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Contract Research Organisation
CT	Computer tomography
CTMF	Clinical trial master file
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
CV	Cardiovascular
DEDP	drug exposure during pregnancy
DPI	Dry Powder Inhaler
ECG	Electrocardiography
eCRF	Electronic Case Report Form
ECSC	European Coal and Steel Community
ED	end diastolic
EDTA	Disodium edentate
EF	ejection fraction
EFL	Expiratory flow limitation
EoO	End of Observation
EoT	End of Treatment
ERS	European Respiratory Society
ERV	Expiratory reserve volume
EU	European Union
EudraCT	European Clinical Trials Database
FAS	Full Analysis Set
FC	Flow Chart
FDC	Fixed Dose Combination
FEV ₁	Forced Expiratory Volume in 1 st second
FRC	Functional Residual Capacity

FVC	Forced Vital Capacity
GCP	Good Clinical Practice
GOLD	Global Initiative for Chronic Obstructive Lung Disease
HCG	human chorionic gonadotropin
HFA	hydrofluoroalkane
IB	Investigator's Brochure
IC	Inspiratory capacity
ICS	Inhaled corticosteroids
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISF	Investigator Site File
IVC	inspiratory vital capacity
LABA	Long-acting β_2 -agonist
LAMA	Long-acting muscarinic antagonists
LBBB	Left bundle branch block
LDH	Lactate Dehydrogenase
LPDD	Last Patient Drug Discontinuation
LV	Left Ventricle
LVEDVI	Left Ventricular End Diastolic Volume Index
LVH	Left ventricular hypertrophy
MACE	Major adverse cardiovascular event
MCID	Minimal clinically important difference
MD	Medical Degree
MDI	Metered Dose Inhaler
MedDRA	Medical Dictionary for Drug Regulatory Activities
MMI	Myocardial mass index
mMRC	Modified Medical Research Council Dyspnoea Scale
MMRM	Mixed-effects Model for Repeated Measures
MST	Medical Sub Team
NIMP	Non Investigational Medicinal Product
NYHA	New York Heart Association
PD	Pharmacodynamics
PA	pulmonary artery
PDE-4	Phosphodiesterase Type 4
Pleth	Body Plethysmography
PFT	Pulmonary function testing
PRN	pro re nata (as needed)
PWA	Pulse Wave Analysis
qd	quaque die (once a day)
REML	Restricted Maximum Likelihood
REP	Residual effect period, after the last dose of medication with measureable drug levels or pharmacodynamic effects still likely to be present
RV	right ventricular
RVol	Residual Volume

SAE	Serious Adverse Event
SGOT	Serum glutamic-oxaloacetic transaminase
SGPT	Serum glutamic-pyruvic transaminase
SGRQ	St. George's Respiratory Questionnaire
SOP	Standard operating procedures
SmPC	Summary of Product Characteristics
STORM	storage conditions for trial medication
SUSAR	Suspected Unexpected Serious Adverse Reaction
SVI	Stroke volume index
TCM	Trial Clinical Monitor
TDI	Transitional dyspnoea index
TLC	Total Lung Capacity
TMF	Trial Master File
TSAP	Trial Statistical Analysis Plan
UK	United Kingdom
US	United States

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

European Respiratory Society (ERS), American Thoracic Society (ATS) and Global Initiative for Chronic Obstructive Lung Disease (GOLD) treatment guidelines all place bronchodilators as the foundation of pharmacologic management of COPD. In patients with moderate to very severe pulmonary impairment (i.e., GOLD Stage 2 to 4) whose symptoms are not adequately controlled with as-needed short-acting bronchodilators, adding regular treatment with one or more long-acting inhaled bronchodilators is recommended (long-acting β_2 -agonists (LABAs); long-acting muscarinic antagonists, (LAMAs)).

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 β_2 -adrenergic pathways, with the expectation of an increase in the degree of bronchodilation for equivalent or lesser side effects. When beta-agonists and muscarinic antagonists with similar or equivalent posologies are combined, the opportunity exists for offering a simpler and more convenient administration regimen with the development of fixed combinations within the same inhaler device. The recently completed clinical development program for tiotropium +olodaterol fixed dose combination (FDC) was based on the hypothesis that the combination of the LAMA, tiotropium, and the LABA, olodaterol, inhaled once daily, is superior in improving airflow over 24 hours compared with tiotropium monotherapy once daily and olodaterol monotherapy once daily.

Cardiovascular disease in COPD

COPD is a chronic inflammatory disease of the lungs known to have systemic features, among which is an increased risk of CV disease. Large population studies have confirmed the importance of COPD as an independent risk factor for ischemic heart disease and sudden cardiac death [[R12-4840](#), [R16-3513](#) and [R16-3514](#)]. Besides traditional risk factors, as smoking, leading to inflammation and dysfunctionality in the lungs there is increasing evidence of systemic inflammation and further more physiologic stresses and abnormalities of the vascular wall that accelerate cardiovascular pathology in COPD.

Bronchial obstruction and hypoxia play important role in inducing hemodynamic stress that contribute to cardiovascular morbidity and mortality. It is evident that developing an obstructive lung pattern early in life is associated with an underfilling in the left heart and low cardiac output [[R16-3515](#), [R16-3516](#) and [R16-3517](#)]. Reversing of functional impairment of lungs with bronchodilation would reduce lung hyperinflation and would have an effect on hemodynamic stress on the heart and abnormalities of arterial wall that could be assessed and used as a control in provision of treatment and in prognosis of COPD especially with respect to cardiovascular comorbidity typical for COPD.

COPD and lung hyperinflation

Expiratory flow limitation (EFL) is the pathophysiological hallmark of COPD and is caused by parenchymal destruction (emphysema) and airway dysfunction which is a consequence of small airway inflammation, airway remodelling, mucus impaction and possibly increased cholinergic airway muscle tone. Emphysema results in reduced elastic recoil which together with increased airway resistance leads to a reset of relaxation volume of respiratory system to a higher level than in age-matched healthy individuals. This is so called “static” lung hyperinflation. In laboratory gas trapping is defined as Residual Volume (RVol) or Residual Volume/Total Lung Capacity (RVol/TLC) above the upper limits of normal and hyperexpansion as FRC or TLC above the upper limits of normal or IC/TLC below the lower limit of normal. Isolated hyperexpansion is associated with greater percent emphysema, lower Body Mass Index (BMI) and a higher blood haemoglobin concentration [[R16-3518](#)] and hyperinflation as measured with RVol or RVol/TLC is associated with greater LV mass [[R15-2161](#)]. Decreasing of hyperinflation in the lungs would have an effect on cardiac and arterial dysfunction that could be measured comparing two alternative treatments and used to explore further the separate effects of diastolic dysfunction vs reduced left ventricle (LV) preload due to pulmonary causes [[R16-3519](#)].

Arterial stiffness and diastolic dysfunction as important predictors of CV events

Arterial stiffness is increasingly recognised as a surrogate end point for CV disease. As measured by the carotid-femoral pulse wave velocity as a “gold standard” it is a strong predictor of future CV events especially in persons with higher baseline CV risk. Increased large artery stiffness results in greater central aortic systolic pressures, increased left ventricular afterload and reduced diastolic coronary artery filling. Even in the present absence of evidence that pharmacological treatment of COPD has direct beneficial effect lowering the pulse wave velocity there are other measures indirectly connected to arterial stiffness of central arteries (central pressure, pulse pressure, augmentation index) that allow us to explore further the measures of the effect of arterial stiffness particularly on the left heart failure with preserved ejection fraction [[R16-3528](#)].

Diagnostic modalities in assessing cardiac function and arterial stiffness in COPD

Assessment of early changes of cardiac function in COPD is challenging and validated gold standard is missing. Due to hyperinflation echocardiography has been proven to have limitations and is replaced more and more with cardiac magnetic resonance (CMR) established as a gold standard for the measurements of volumes, mass and ejection fraction of both left and right ventricles and particularly left atrium [[R16-3556](#), [R16-3557](#)]. It also allows the assessment of pulmonary artery pulsatility and aortic distensibility that are local measures of arterial stiffness [[R16-3558](#)].

1.2 DRUG PROFILE

Tiotropium + olodaterol combination

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

In the pivotal studies (1237.5/.6) [[c01735218/c01735249](#)] tiotropium + olodaterol FDC showed statistically significant improvements in Forced Expiratory Volume in first second (FEV₁) Area under the curve (AUC_{0-3h}) response and trough FEV₁ response after 24 weeks compared to the mono-components and these improvements were maintained up to 52 weeks. Tiotropium + olodaterol FDC showed statistically significant improvements in health-related quality of life [St. George's Respiratory Questionnaire (SGRQ)] and dyspnea experienced during everyday activities [Transitional Dyspnea Index (TDI)] after 24 weeks compared to the mono-components. More patients treated with the combination had an improvement in SGRQ total score and TDI focal score greater than the Minimal clinically important difference (MCID). Treatment with tiotropium + olodaterol FDC also resulted in reductions in both daytime and night time rescue bronchodilator use compared to the mono-components. Supportive evidence characterizing the bronchodilating profile of tiotropium + olodaterol FDC over 24- hour dosing interval, with similar 24-hour FEV₁- time profiles and an increased bronchodilatory activity compared to twice daily fluticasone propionate + salmeterol FDC, was provided from a 6-week cross-over trial (1237.11) [[P16-01440](#)].

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

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

Fluticasone propionate + salmeterol combination

Fluticasone propionate and salmeterol are the constituents in the FDC product Seretide[®] (Viani[®], Atmadisc[®]). Seretide[®] Accuhaler[®] (50 µg salmeterol and 500 µg fluticasone propionate in a dry powder inhaler- DPI) given twice daily is approved in the EU for the symptomatic treatment of patients with severe COPD and a history of repeated exacerbations, who have significant symptoms despite regular bronchodilator. More information can be found in the SmPC for Seretide[®], included in the ISF.

The FDC of fluticasone and salmeterol is registered for the maintenance treatment of patients with severe to very severe COPD and frequent exacerbations in many countries. Despite this

labeled indication, the real world use of LABA/Inhaled corticosteroids (ICS) combinations is different and comparable doses to those in the trial are being used from maintenance initiation onwards in many EU countries, including Germany. Therefore we believe that it is justified to use the comparator product as specified in the trial protocol.

2. RATIONALE, OBJECTIVES, AND BENEFIT - RISK ASSESSMENT

2.1 RATIONALE FOR PERFORMING THE TRIAL

Diastolic dysfunction of the heart carries a substantial risk of heart failure and reduced survival, even when it is asymptomatic. Diastolic dysfunction is defined as functional abnormalities that exist during ventricular relaxation and filling and carries a mortality rate that is similar to that seen in systolic failure. In the last 20 years, the survival of patients with systolic heart failure has improved, whereas the prognosis of diastolic heart failure has not changed.

The hypothesis in our trial is that in absence of any clinically evident cardiovascular disease COPD patients would have sub-clinical cardiac dysfunction and arterial wall stiffness that would be related to the severity of airways obstruction and air trapping and would change under influence of treatment.

Evidence that pharmacological treatment of COPD has consistent beneficial and plausible effects on cardiac function and pulmonary vasculature that may contribute to favourable effects of inhaled therapies is already published. The trial was of short duration (7-14 days of treatment), using a combination of LABA/ICS against placebo [[R16-3512](#)].

In this study we want to go explore further if cardiac function improves even more if two bronchodilators (a long-acting β_2 -agonist and long-acting muscarinic antagonist) are used, and if these are better compared to LABA/ICS combination, and also in longer treatment duration [[P16-08905](#)].

2.2 TRIAL OBJECTIVES

The primary objective of the study is to explore the effect of treatment with tiotropium + olodaterol FDC compared to fluticasone propionate + salmeterol FDC on reversal of left ventricular diastolic dysfunction assessed by cardiac magnetic resonance (CMR) imaging.

A secondary objective is to explore the effect of tiotropium + olodaterol FDC compared to fluticasone propionate + salmeterol FDC on:

- measures of arterial stiffness assessed by CMR and
- central blood pressure assessed by PWA and
- reduction of lung hyperinflation assessed with body plethysmography and
- post dose spirometry.

2.3 BENEFIT - RISK ASSESSMENT

The clinical trials conducted to date have shown tiotropium + olodaterol 5 μ g / 5 μ g 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 tiotropium + olodaterol 5 µg / 5 µg compared to the individual components translated into benefits that were meaningful to the patient, with improvements in several patient centered outcomes. As such, tiotropium + olodaterol 5 µg / 5 µg will be a valuable additional therapeutic option for patients with COPD, offering increased treatment benefit compared to the monotherapies with a comparable safety profile.

Based on the overall assessment of benefit to risk, the application for marketing authorization for tiotropium + olodaterol FDC was submitted in the EU and the US in May 2014 and then subsequently in several other countries. At the time of the final protocol for 1237.36, marketing authorization has been granted in almost all EU countries, United States (US), Japan and several other countries.

The trial design requires that all eligible patients complete a 3 or 4 week screening period in which LABAs, LAMAs and inhaled corticosteroids (ICS) are withdrawn prior to randomisation. Boehringer Ingelheim (BI) will provide open-label salbutamol (albuterol) and ipratropium metered dose inhalers as needed (PRN) rescue medication for all patients who have signed Informed Consent. At the investigator's discretion, ipratropium metered dose inhaler (MDI) may be provided to patients who are primarily required to wash out LAMA during the washout period prior to baseline CMR and Visit 2. In spite of provision of salbutamol and/or ipratropium there is approximately 1% risk that patients may withdraw in the screening period because of intolerance to their prescribed medication withdrawal.

All patients will receive active treatment with either tiotropium + olodaterol FDC (5 µg / 5 µg) or fluticasone propionate + salmeterol FDC (1000 µg / 100 µg) inhalation solution (control group) during the treatment periods. There is no separate placebo arm in this trial and placebo is used for the double-dummy treatment design.

The potential benefits for patients outweigh potential risks and justify inclusion of tiotropium + olodaterol FDC Respimat® as intervention in the study.

The FDC of fluticasone and salmeterol is registered in many countries for the maintenance treatment of patients with COPD, with a FEV₁ < 60% predicted normal (pre-bronchodilator) and a history of repeated exacerbations, who have significant symptoms with regular bronchodilatory therapy. Despite this labeled indication, the real world use of LABA/ICS combinations is different and comparable doses to those in the trial are being used from maintenance initiation onwards in many EU countries, including Germany. The use of LABA/ICS in COPD patients with post-bronchodilator FEV₁ less than 70% predicted normal as a comparator product in our trial was also decided because this was effective therapy for COPD, leading to change in cardiac function, in already published short term study [[R16-3512](#)].

Therefore, both treatment regimens are considered options for long-term therapy of COPD and comparison of both regimens regarding the effects of lung deflation on cardiovascular

function is of importance for the treatment of COPD patients and development of CV comorbidities in patients with COPD.

The proposed medication restriction scheme is considered ethically acceptable given the availability of ipratropium MDI (primarily during the washout period) and/or salbutamol (albuterol) as rescue medication.

According to the prescribing information for Spiolto®, as a precautionary measure, it is preferable to avoid the use of Spiolto® during pregnancy. Women of childbearing potential may be included in clinical trials for tiotropium + olodaterol (5 µg / 5 µg) FDC provided appropriate precautions are taken to minimize the risk of pregnancy. These precautions include pregnancy testing and use of highly effective methods 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 subjects participation in the study requires standard medical procedures known to patients with respiratory diseases. The examinations include common procedures like physical examination, 12-lead ECG, spirometry and body plethysmography. Other procedures include common medical practices such as disease-specific questionnaires and routine blood sampling for safety assessment. All these procedures are known to have an acceptable safety risk. An amount of 50 ml of blood will be drawn during study (once for safety assessment and three times for determination of
and no safety-related risk to the patient is expected from this blood withdrawal.

Safety will be monitored (as described in [Section 5.3](#)) at site visits and withdrawal criteria will be provided for investigators' consideration (as listed in [Section 3.3.4.1](#)).

Cardiac Magnet Resonance imaging (CMR) will be conducted in all subjects. CMR uses strong magnetic fields and radio waves to generate cross-sectional images of the body. In this study, CMR will be used to acquire morphological and functional information of the heart, aorta and pulmonary artery. In contrast to Computer tomography (CT), CMR does not use ionizing radiation (X-rays) and there are no known harmful effects associated with temporary exposure to the strong magnetic field of CMR scanners in patients without metal foreign bodies. Potential safety concerns are related to implanted medical devices (i.e. heart pacemaker and metal implants like vascular clips, metal silver in patient's eye), which may dislodge and can malfunction or heat up during the exams. Dyes from tattoos and tattooed eyeliner can cause skin or eye irritation, and medication patches can cause skin burn due to heating effects. Some subjects might suffer from claustrophobia during the examination. Subjects in the CMR scanner will be exposed to some noise, which will be minimized by ear protection but can still cause some discomfort. No contrast or stress agent will be used during the examinations. Potential risks associated with CMR will be avoided by implementing standards CMR procedure under appropriate supervision [[R16-3555](#)].

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

This is an exploratory, randomised, double-blind, double-dummy, active-controlled, two-period complete cross-over study to investigate the effect of 6 weeks treatment of orally inhaled tiotropium + olodaterol FDC (5 µg / 5 µg) (delivered by the Respimat® Inhaler) compared with fluticasone propionate + salmeterol (1000 µg / 100 µg) (delivered by the Accuhaler® Inhaler) on left ventricular function and arterial stiffness in patients with COPD.

The trial consists of a run-in period, two 6-week treatment periods with no washout in between the treatments and a follow-up period.

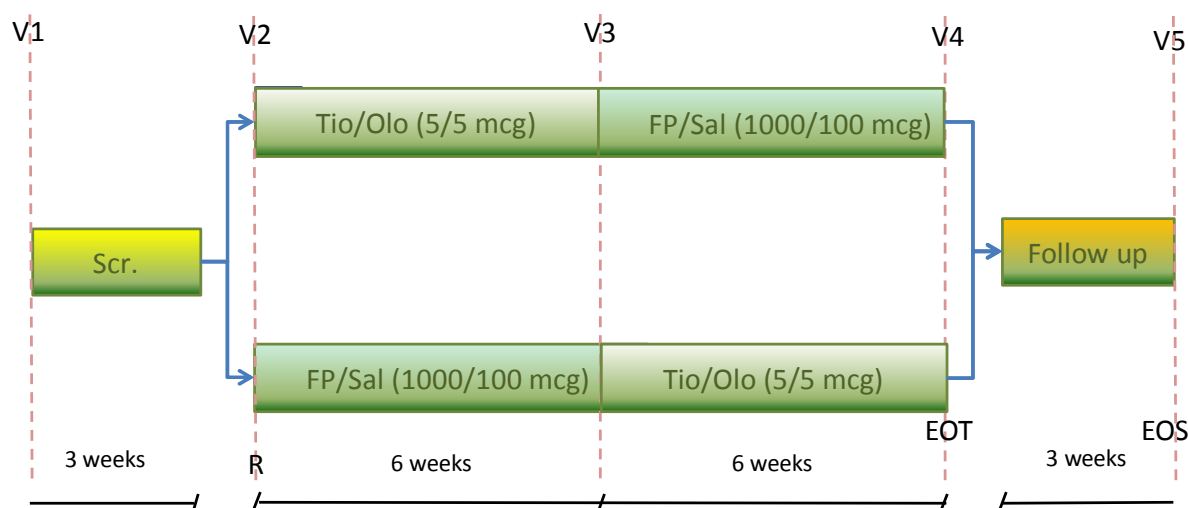


Figure 3.1:1. Overview of the trial design

After signing Informed Consent and completing an initial screening visit (Visit 1), patients will enter a 3 to 4-week run-in period to reach their baseline level of diastolic heart function prior to changes under treatment. In a week prior to randomisation, patients will conduct an assessment of heart (left ventricular) function with CMR examination.

Patients who meet all the inclusion criteria and none of the exclusion criteria will be randomised at Visit 2 into the first of 2 x 6-week double-blind, cross-over treatment portion of the study, in which they will receive one of two treatments with the treatment codes as follows:

- A. tiotropium + olodaterol (5 µg / 5 µg) FDC inhalation solution, delivered once daily via the Respimat®
- B. fluticasone propionate + salmeterol (1000 µg / 100 µg) dry powder for inhalation, delivered twice daily via the Accuhaler®

The randomised treatment sequences are AB and BA. An interactive voice/web response

system named Interactive Response Technology (IRT) will be used for randomisation to a treatment sequence in this trial and for appropriate re-supply of medication to patients.

Patients will be evaluated for an additional 21 days following completion of the last 6-week randomised treatment period, or in case of discontinuation, after the final dose of study medication. In this follow-up period patients may return to their medication prescribed prior to participating in the study. The patient's trial participation will be concluded with the follow-up visit 21 days after the end of treatment. For visit details please refer to [Section 6.2](#).

3.1.1 Administrative structure of the trial

The trial is sponsored by Boehringer Ingelheim.

Sponsor: BI has appointed a Trial Clinical Monitor (TCM), responsible for coordinating all required activities, in order to

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

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

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

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

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 can be found in the ISF.

Coordinating Investigator: A Coordinating Investigator will be nominated and will be responsible to coordinate Investigators at different centres participating in this multicentre trial. Tasks and responsibilities will be defined in a contract. Relevant documentation on the participating (Principal) Investigators and other important participants, including their curricula vitae, will be filed in ISF.

Targeted group of Investigators: Pulmonologists/qualified sites with experience in conducting studies with own body plethysmography and spirometry equipment and access to the desired patient population of patients with COPD.

Local Facilities/Equipment: Sites should also have access to MRI facility that has capacity to conduct CMR for trial purpose. The following local facilities/equipment is required at the investigational site:

- scale and stadiometer
- a standard 12-lead electrocardiogram (ECG)
- a body plethysmograph which meets ATS/ERS Criteria [[R08-1121](#)]
- a spirometer which meets ATS/ERS Criteria [[P05-12782](#)]
- access to local lab facility for safety testing
- access to local radiology unit for CMR examination

Contract Research Organisation (CRO): A CRO will provide the device and staff training for peripheral blood pressure measurement and PWA for central blood pressure assessment for complete duration of the trial. A CRO will also provide logistical support for organizing and conducting centralized imaging service for timely assessment of CMR protocols and acquisition of parameters and support of the independent central reader.

Local Laboratory: Blood samples for safety evaluation will be analyzed at a local lab.

IRT: An IRT vendor will be used for randomisation to a treatment sequence AB or BA in this trial and for appropriate re-supply of medication to patients. The ability to unblind will be available to the investigator via the IRT. Details will be provided in IRT Manual available in ISF.

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

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

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

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

The cross-over design allows for each patient to serve as his/her own control. As such, treatment comparisons are within patient rather than between patients, which removes the inter-patient variability from the comparison between treatment regimens [[R94-1529](#)].

A 6 week treatment period is considered sufficient to evaluate the effects of both tiotropium + olodaterol FDC and of fluticasone propionate+salmeterol FDC at pharmacodynamic steady state (based on results from previous studies evaluating the effects of tiotropium + olodaterol FDC on spirometric parameters). A 6 week treatment period was therefore also accepted as sufficient for the evaluation of the longer term effects of the reduced lung hyperinflation on the cardiovascular changes.

The inclusion of the fluticasone propionate + salmeterol FDC allows a comparison of a LABA (in combination with an ICS), as used in previous positive study, to the combination product of both β_2 -agonist and anti-cholinergic. This selection will only allow us to explore the effect of two different combinations on the improvement of lung hyperinflation and cardiac function.

Pure placebo arm was not planned in this study. Based on the evidence of dual bronchodilation from previous similar comparisons the effect on reduction of lung hyperinflation is expected to be of similar size. How this translates in hemodynamic changes over longer treatment duration is presently unknown.

Because the duration of each treatment is 6 weeks, the pharmacodynamic steady state on lung function and hyperinflation would sufficiently be reached without the washout between the treatment periods. It is expected that in the treatment change from tiotropium + olodaterol to fluticasone propionate + salmeterol (AB sequence) there will be some additional bronchodilatory effect of tiotropium, lasting at most a couple of days that will rapidly and completely disappear when pharmacodynamic steady state of both treatments in the second treatment periods will be reached. No measurements are planned in this period but only at the end of each treatment period.

Since patients will be randomised to a treatment sequence AB or BA that includes either both a long-acting β_2 -agonist (olodaterol) and a long-acting anti-cholinergic (tiotropium) or an intermediate acting β_2 -agonist (salmeterol) and inhaled corticosteroid (fluticasone), it is necessary to restrict the use of long-acting β_2 -agonists (e.g. salmeterol, formoterol, indacaterol), anti-cholinergics (e.g. tiotropium, ipratropium) and inhaled corticosteroids (ICS) during the entire treatment phase. Short-acting β_2 -agonist medication (salbutamol / albuterol) and /or short acting anticholinergic (ipratropium; primarily to patients who are required to washout LAMAs during run-in periods) will be provided to patients for rescue use (as needed, PRN) in run-in and treatment periods with short washout of short-acting bronchodilators prior to CMR and PFT assessments.

3.3 SELECTION OF TRIAL POPULATION

A sufficient number of patients will be enrolled (sign informed consent) to ensure that approximately 74 patients of either sex, 40 to 75 years old, with a diagnosis of COPD are randomised into the study. All patients are expected to be randomised within eight months of overall trial initiation (i.e. initiation of the first site), which requires a minimum enrollment of 2 patients per month at each site.

Enrolment will be competitive and conducted at approximately 10 study sites. Additional

sites may be initiated and 'non-productive' sites may be closed to ensure sponsor's timelines. It is anticipated that each site will enroll an average of approximately 8 patients.

Patients will be required to perform lung function testing with body plethysmography on several occasions in the study. They will also be performing CMR 3 times in the trial. Each examination is estimated to last up to one hour and will be conducted as a non-contrast and non-stress MRI procedure. For this reason any patients with general contraindications to magnetic resonance procedure will be excluded from participation.

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

3.3.1 Main diagnosis for trial entry

Outpatients with a history of COPD with $FEV_1 < 70\%$ predicted, including hyperinflation at rest during screening, with documented reversibility of hyperinflation are eligible for inclusion if they fulfil all the inclusion criteria ([Section 3.3.2](#)) and do not present with any of the exclusion criteria ([Section 3.3.3](#)).

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

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. All patients must have a diagnosis of chronic obstructive pulmonary disease [[P16-13658](#)] for which they are treated with one or more long-acting inhaled bronchodilators prior to enrolment and must meet the following spirometric criteria:

Patients must have stable airway obstruction with a post-bronchodilator $FEV_1 < 70\%$ of predicted normal calculated with European Coal and Steel Community (ECSC) formulas, [[R94-1408](#)], and a post-bronchodilator $FEV_1/FVC < 70\%$ at Visit 1 (see [Appendix 10.3](#) for ECSC predicted normal equations).

3. Patients with hyperinflation at rest defined as $FRC > 120\%$ predicted, with post-bronchodilator reversibility which improves by greater than or equal to 7,5 percentage points at Visit 1 (see Appendix 10.3 for predicted normal FRC values).
4. Male or female patients between 40 and 75 years of age (inclusive) on day of signing informed consent.
5. Patients with a smoking history of more than 10 pack-years (see Appendix 10.3 for calculations).
6. Patients with Modified Medical Research Council Dyspnoea Scale (mMRC) score > 1 at Visit 1.
7. Patients must be able to perform technically acceptable pulmonary function tests (body plethysmography and spirometry), cardiac magnetic resonance, brachial blood pressure

measurements with PWA and other tests during the study period as required in the protocol.

8. Patients must be able to inhale medication in a competent manner, as assessed by the Investigator, from the Respimat[®] and Accuhaler[®] inhalers ([Appendix 10.1](#) and [10.2](#)) and from a MDI.

3.3.3 Exclusion criteria

1. Patients with a significant disease other than COPD; a significant disease is defined as a disease which, in the opinion of the investigator, may (i) put the patient at risk because of participation in the study, (ii) influence the results of the study, or (iii) cause concern regarding the patient's ability to participate in the study.
2. Patients with a, in the opinion of the investigator, clinically relevant abnormal baseline hematology, blood chemistry, or creatinine will be excluded regardless of clinical condition (a repeat laboratory evaluation will not be conducted in these patients).
3. Patients with a current diagnosis of asthma. For patients with allergic rhinitis or atopy, source documentation is required to verify that the patient does not have asthma.
4. Patients with a COPD exacerbation in the 6 weeks prior to screening (Visit 1) and patients who experience COPD exacerbation or respiratory tract infection during the washout phase prior to randomisation.
5. A history of myocardial infarction, cerebrovascular event or coronary artery intervention other than Coronary Artery Bypass Graft (CABG) within 1 year of screening Visit 1.
6. Abnormal and clinically significant 12-lead ECG (e.g. Left bundle branch block (LBBB) and left ventricular hypertrophy (LVH)).
7. Hospitalized for heart failure within the past year. Current severe heart failure (New York Heart Association (NYHA) class IV [New York Heart Association, 1994]. Ejection fraction $\leq 40\%$ from CMR baseline assessment.
8. Patients with systolic blood pressure > 140 mmHg and/or diastolic blood pressure > 90 mmHg at Visit 1.
9. A diagnosis of thyrotoxicosis (due to the known class side effect profile of β_2 -agonists).
10. Known active tuberculosis, cardiac sarcoidosis.
11. Any malignancy unless free of disease for at least five years (patients with treated basal cell carcinoma or squamous cell skin cancers are allowed).
12. A history of cystic fibrosis.
13. Clinically evident bronchiectasis, as judged by the Investigator.

14. Patients with severe emphysema requiring endobronchial interventions within 6 months prior to screening.
15. A history of significant alcohol or drug abuse as judged by the investigator.
16. 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).
17. Patients being treated with any oral β -adrenergics.
18. Patients being treated with oral corticosteroid medication within 6 weeks prior to Visit 1.
19. Patients being treated with Phosphodiesterase Type 4 (PDE-4) inhibitors within 3 months of screening Visit 1 (e.g. roflumilast) should not be enrolled and PDE-4 inhibitors should not be withdrawn for the purpose of enrolling in this study.
20. Patients being prescribed long-term home oxygen treatment and in the investigator's opinion will be unable to abstain from the use of oxygen therapy during clinic visits.
21. Patients who have completed a pulmonary rehabilitation program in the six weeks prior to the screening visit (Visit 1) or patients who are currently in a pulmonary rehabilitation program.
22. Patients who have taken an investigational drug within one month, six half-lives or (whichever is greater) or in case the investigational drug (sub) class is listed within the washout period specified in [Table 4.2.2.1:1](#) prior to screening Visit 1.
23. Patients with known hypersensitivity to β -adrenergics drugs, anticholinergic drugs, fluticasone propionate or to any of the excipients: Benzalkonium chloride (BAC), Disodium edentate (EDTA) or Lactose monohydrate (which contains milk proteins) or any other component of the Respimat[®] or Accuhaler[®] delivery systems.
24. Women who are pregnant, nursing, or who plan to become pregnant while in the trial.
25. Women of childbearing potential not using highly effective methods of birth control* during the period of drug exposure and until the follow-up visit at 21 days after the discontinuation of study medication. Female patients will be considered to be of childbearing potential unless permanently sterilised by hysterectomy, bilateral salpingectomy or bilateral oophorectomy, or post-menopausal (12 months with no menses without an alternative cause).

* 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. A list of contraception methods meeting these criteria is provided in the patient information.

26. Patients who have previously been enrolled in this study or are currently enrolled in another study.
27. Patients who are unable to comply with pulmonary medication restrictions, as per Investigator's judgment, prior to randomisation.
28. Patients with pacemakers and metal implants (i.e. vascular clips and stents, metal silver in patient's eye) and patients with claustrophobia, due to contraindications for CMR.

3.3.4 Removal of patients from therapy or assessments

3.3.4.1 Removal of individual patients

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

- The patient withdraws consent for study treatment or study participation, without the need to justify the decision.
- The patient needs to take concomitant drugs that interfere with the investigational product or other trial medication.
- The patient can no longer be treated with trial medication for other medical reasons (such as surgery, adverse events, other diseases, or pregnancy)
- The patient has repeatedly shown to be non-compliant with important trial procedures and, in the opinion of both, the investigator and sponsor representative, is not willing or able to stick to the trial requirements in the future.

If a patient becomes pregnant or a pregnancy is suspected during the trial, the patient will be permanently discontinued from study treatment and will be followed up until birth or otherwise termination of the pregnancy. For further information on reporting of pregnancy and the outcome of pregnancy, please see [Section 5.3.6.2](#).

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

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

Details of all COPD exacerbations will be captured in the source notes and on AE/SAE pages.

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

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

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

3.3.4.2 Discontinuation of the trial by the sponsor

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

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

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

4. TREATMENTS

4.1 INVESTIGATIONAL TREATMENTS

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

After screening, eligible patients will be randomly assigned to a treatment sequence AB or BA in two 6 week periods, with no washout in between the two treatment periods.

Patients will receive one of the following treatments:

A. Tiotropium + olodaterol FDC (2.5 µg / 2.5 µg) inhalation solution via Respimat[®] inhaler

followed by

B. Fluticasone propionate +salmeterol FDC (500 mcg / 50 mcg) inhalation powder via Accuhaler[®] inhaler

or vice versa, depending on randomized treatment sequence.

During each treatment period the patient will inhale two puffs from the Respimat[®] inhaler, once per day, in the morning immediately followed by one inhalation from the Accuhaler[®]. Each evening the patient will take one inhalation from the Accuhaler[®] only. The Respimat[®] inhaler is not to be used in the evening.

In order to assure blinded treatment during each treatment period with only one medication matching placebo will be used for both products for double dummy-design of the study.

4.1.1 Identity of the Investigational Medicinal Products

Table 4.1.1: 1 Test product 1:

Substance:	Tiotropium plus olodaterol FDC
Pharmaceutical formulation:	Inhalation solution
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG.
Unit strength:	2.5 µg / 2.5 µg per actuation
Posology	2 inhalations once daily (a.m. dosing)
Route of administration:	Oral inhalation via Respimat [®] inhaler (A5)

Table 4.1.1: 2 Placebo for test product 1:

Substance:	Placebo matching Tiotropium plus olodaterol FDC
Pharmaceutical formulation:	Inhalation solution
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG.
Unit strength:	Not applicable
Posology	2 inhalations once daily (a.m. dosing)
Route of administration:	Oral inhalation via Respimat [®] inhaler (A5)

Table 4.1.1: 3 Test product 2:

Substance:	Fluticasone propionate /salmeterol FDC
Pharmaceutical formulation:	Inhalation powder
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG.
Unit strength:	500 µg / 50 µg per inhalation
Posology	One inhalation in the morning and evening (a.m. and p.m. dosing)
Route of administration:	Oral inhalation via Accuhaler [®] inhaler

Table 4.1.1: 4 Placebo for test product 2:

Substance:	Placebo matching Fluticasone propionate /salmeterol FDC
Pharmaceutical formulation:	Inhalation powder
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG.
Unit strength:	Not applicable
Posology	One inhalation in the morning and evening (a.m. and p.m. dosing)
Route of administration:	Oral inhalation via Accuhaler [®] inhaler

4.1.2 Selection of doses in the trial

The clinical trials conducted during the Phase III program for tiotropium + olodaterol FDC 5 µg / 5 µg have shown that this dose is a safe, well tolerated and efficacious combination therapy. Tiotropium + olodaterol FDC 5 µg / 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 lower dose tiotropium + olodaterol FDC 2.5 µg / 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 observations, the tiotropium + olodaterol FDC 5 µg / 5 µg has been submitted for regulatory approval and was approved in this dosage and is therefore considered to be the most appropriate dose to be studied in this trial.

4.1.3 Method of assigning patients to treatment groups

Once the patient has provided written informed consent, the medication washout can occur according to [Table 4.2.2.1:1](#). When a patient is qualified for entry into the randomised treatment sequence, the intervention assignment will be by means of a third-party phone/web-based randomisation at Visit 2.

Patients will be assigned a unique patient number using the remote data capture system. During Visit 2 and after the patient's eligibility has been confirmed, one of the two treatment sequences will randomly be assigned via IRT. To facilitate the use of the IRT, the Investigator will receive all necessary instructions. Patients will then be assigned the alternative treatment again at Visit 3. Each time patients will be assigned treatment medication boxes and each medication box will have a unique number. Refer to [Section 4.1.6](#) for details on packaging and labelling.

Please note that the medication number is different from the patient number. Site personnel will enter all the medication numbers dispensed to each patient in the electronic case report form (eCRF).

Details on the IRT are provided in the ISF.

4.1.4 Drug assignment and administration of doses for each patient

4.1.4.1 Dispensing of trial medication

Trial medication will be dispensed to the patient by the investigator/pharmacist. At Visit 2 eligible patients will be randomised to one of two double-blinded treatment sequences AB or BA (1:1 ratio) by the IRT. IRT will assign three Respimat[®] kits (two for treatment and one for reserve) and three Accuhaler[®] kits (two for treatment and one for reserve). Matching placebo kits will be used in assignment so that in one treatment period only one product of the two will contain active substance (double-dummy design). This will be used for six weeks of treatment. At Visit 3, the IRT will assign additional Respimat[®] and Accuhaler treatment boxes so that alternate treatment sequence will be supported. Each Respimat[®] and Accuhaler[®] treatment box will have a unique medication number with 6 digits.

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

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

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. If the cloud of mist is not seen, the priming process shall be repeated until a cloud is visible. These steps will not affect the number of doses available and the Respimat[®] inhaler will deliver enough doses for 1 month supply.

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](#).

The Accuhaler[®] containing fluticasone propionate + salmeterol discus being a DPI does not require priming and has no shelf-life other than labeled Use-by date.

Testing of the MDI (rescue medication)

Before using for the first time, one actuation should be released into the air to make sure the device is working.

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 and 4 to avoid overdosing.

The last administration of the study medication will be taken at visit 4 (EoT) from the Respimat[®] inhaler and from Accuhaler[®] that is in current use since no new Respimat[®] and Accuhaler[®] treatment box will be assigned.

Study medication administration at clinic visits

Detailed written instructions and training for the use of the Respimat[®] inhaler and Accuhaler[®] will be given to the patient at Visit 1 (see [Appendix 10.1](#) and [10.2](#)). At Visits 2 and 3 detailed instructions on the use of the device will be repeated, but patient should not inhale from a training device that day. The investigator or qualified personnel will observe the inhalation procedure and will reinforce a correct inhalation technique. For training session please refer to [Section 4.1.4.3](#).

Trial medication will be dispensed at visits 2 and 3. Patients will receive 2 new Respimat[®] treatment boxes + 1 Respimat[®] inhaler reserve. 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. Patient will also receive 2 new Accuhaler[®] treatment boxes + 1 Accuhaler[®] inhaler reserve.

At each clinic visit and in this order, oral inhalation of two puffs of the trial medication from the assigned Respimat[®] inhaler followed by one puff of trial medication from the assigned Accuhaler[®] will be self-administered by the patient under the direct supervision of the investigating physician or designee. In addition, the evening dose of one puff from the Accuhaler[®] will be self-administered by the patient. The utmost care should be taken to ensure that during the treatment in the study medication is not taken prior to coming to the site. At treatment period end visits (Visit 3 and 4) the Respimat[®] and Accuhaler[®] that is in current use must be used for administration of the trial medication at that visit.

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

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

For rescue medication dispensation, please refer to [Section 4.2.1](#).

Study medication administration at the CMR visits prior to Visits 3 and 4

CMR assessment will be performed in a week prior to Visit 3 and Visit 4, 1 to 8 hours after self-administered morning medication dosing within ± 30 minutes of time of administration at visit 2 AND between 7:00 a.m. and 10:00 a.m.

Study medication administration at home

Each morning between clinic visits and in this order, oral inhalation of two puffs of the trial medication from the assigned Respimat[®] inhaler and one puff of trial medication from the assigned Accuhaler[®] (inhaled according to the instructions provided in [Appendix 10.1](#) and [10.2](#)) will be self-administered by the patient within ± 30 minutes of time of administration at visit 2 AND between 7:00 a.m. and 10:00 a.m.

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

If the patient forgot to take the trial medication within the specified time window, the patient is allowed to administer the morning dose up until 12:00 p.m. (morning dose window until noon). After 12:00 p.m. the patient should skip the dose and take the next dose at the next scheduled time the following day. If the patient forgot to take the evening trial medication within the specified time window, the patient is allowed to administer the evening dose up until 12:00 midnight (evening dose window until midnight). After midnight the patient should skip the dose and take the next dose at the next scheduled time the following day.

The patient must assemble and prime the Respimat[®] inhaler at home once the current used Respimat[®] inhaler is empty and the device is locked.

Respimat[®] and Accuhaler[®] inhalers return

The Respimat[®] and Accuhaler[®] dispensed for treatment periods can be used for approximately 30 days each. All used and unused trial medication must be returned to the patient treatment boxes and must be brought to the subsequent site visit by the patient. The reserve inhalers should also be returned at each clinic visit to be replaced if it has been used or primed.

All used and unused Respimat[®] and Accuhaler[®] inhalers dispensed at Visit 2 will be returned at Visit 3 at the end of first treatment period (and those newly dispensed at Visit 3 will be returned at Visit 4 respectively), after administration of morning trial medication at the site. This procedure allows for prompt recording on the drug accountability forms by the site staff and ensures that during the next treatment period trial medication of the previous treatment period could not be administered by the patient.

4.1.4.3 Inhaler devices training

Training on the use of the Respimat[®] and Accuhaler[®] inhalers 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 familiarize the patient with the Respimat[®] and Accuhaler[®] inhaler training medication (placebo). Detailed written instructions for the use of the inhalers will also be given ([Appendix 10.1](#) and [10.2](#)).

- Subsequent clinic visits: observance of the inhalation procedure. The correct inhalation technique should be reinforced in case of inadequate use of Respimat[®] and /or Accuhaler[®] inhalers. It is also important to remind the patient on how to assemble and prime the Respimat[®] inhaler at home.

4.1.4.4 Respimat[®] malfunctioning

Any Respimat[®] inhaler or Accuhaler[®] 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.

4.1.5 Blinding and procedures for unblinding

4.1.5.1 Blinding

Patients, Investigators and everyone involved in trial conduct or analysis or with any other interest in this double-blind trial will remain blinded with regard to the randomised treatment assignments until after database lock.

The randomisation code will be kept secret by Clinical Trial Support up to database lock. Boehringer Ingelheim will generate the randomisation scheme. Packaging and labelling of trial medication in a blinded fashion will be performed by a contractor. Trial supplies will be assigned to the patients via IRT.

4.1.5.2 Unblinding and breaking the code

Emergency unblinding will be available to the Investigator / Pharmacist / investigational drug storage manager via IRT. It must only be used in an emergency situation when the identity of the trial drug must be known to the Investigator in order to provide appropriate medical treatment or otherwise assure safety of trial participants. The reason for unblinding must be documented in the source documents and/or appropriate CRF page along with the date and the initials of the person who broke the code.

4.1.6 Packaging, labelling, and re-supply

Boehringer Ingelheim will provide all study supplies including blinded study medication, rescue medication and Respimat[®] and Accuhaler[®] inhaler training kits. Expiry date will be pre-printed on the trial supplies labels

- 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.

- Accuhaler[®] training: Training placebo Accuhaler[®] kits will be used for training purposes and can be used until empty or used by date is reached. The device should be cleaned with antiseptic wipes, followed by a dry tissue after each patient use.

Blinded study medication , Investigational Medicinal Product (IMP)

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

The boxes will have a two-part tear-off label. One part of each tear-off label will remain on the box, and the other part will be attached to a special drug dispensing log which will be part of the ISF. Examples of the labels are provided in the ISF.

Packaging

- The Respimat[®] treatment box will contain 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.
- The Accuhaler[®] treatment box will contain one Accuhaler[®] inhaler. Each Accuhaler[®] contains sufficient medication for 30 days of treatment.

Labelling

Individual treatment box will have a medical identification label and a two-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, patient number and visit number should be entered at time of cartridge insertion on the inside page of the cartridge booklet
- Investigator's name should be entered at time of dispense on the label of the booklet on the treatment box.

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

Medication dispensing

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

At randomisation (Visit 2), as well as at Visits 3 the site staff will phone IRT and obtain medication numbers for each of the 3 Respimat[®] treatment kits and 3 Accuhaler[®] treatment kits to be dispensed to the patient for daily use during the 6 weeks between visits. This will include one reserve Respimat[®] kit and one reserve Accuhaler[®]. The Respimat[®] and Accuhaler[®] medication and reserve kits will have unique medication numbers.

One Respimat[®] inhaler will be primed by the site staff (see [Section 4.1.4](#)) and used to dose the patient at that site visit, and will be continued to be used at home until 30 days of treatment has been reached. The Accuhaler[®] does not have to be primed and will be used for

30 days of treatment. The second Respimat[®] will be primed and used by the patient to cover the remaining few weeks until the next visit (end of treatment visit). The third Respimat[®] and Accuhaler[®] are reserve medication. This is to allow the patient the flexibility of not having to return to the site immediately to replace a lost or malfunctioning Respimat[®] or Accuhaler[®].

NOTE: The Respimat[®] and drug-filled cartridge that is not yet in use by the patient (including the reserve) should NOT be assembled prior to leaving the site. These devices must be assembled and primed by the patient at home when needed.

The investigator or designee should fill in investigator's name on the medication label of all three Respimat[®] and Accuhaler[®] treatment boxes at time of dispensing to the patient (Visit 2 and 3 respectively). In contrast, date of cartridge insertion should be entered (label of Respimat[®] inhaler only) at time of cartridge insertion only, i.e. for the first Respimat[®] inhaler this is entered by site staff (during Visit 2 and 3), for the second Respimat[®] inhaler the patient is advised to do so when assembling this device at home during the treatment period, as well as for the third (reserve) Respimat[®] device, if necessary.

Re-supply

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

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

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

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

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

4.1.8 Drug accountability

The Investigator / Pharmacist / investigational drug storage manager will receive the investigational drugs delivered by the Sponsor when the following requirements are fulfilled:

- Approval of the trial protocol by the IRB / ethics committee,

- Availability of a signed and dated clinical trial contract between the Sponsor and the head of the investigational site,
- Approval/notification of the regulatory authority, e.g. competent authority,
- Availability of the curriculum vitae of the principal Investigator,
- Availability of a signed and dated clinical trial protocol

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, and the return to the Sponsor or alternative disposal of used or unused products.

For the Respimat[®] and Accuhaler[®] Inhaler, these records for the drug accountability forms will include:

- dates (dispense and return),
- dispenser's initials,
- quantities,
- expiry ('use- by') dates,
- the unique Respimat treatment box number assigned by IRT
- patient number assigned by the remote data capture system.

For the rescue medication, one Non Investigational Medicinal Product (NIMP) accountability form will be provided for salbutamol and ipratropium to the trial site. This record will include:

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

The Investigator / Pharmacist / investigational drug storage manager will maintain records that document adequately that the patients were provided the doses specified by the CTP and reconcile all investigational products received from the Sponsor. At the time of return to the Sponsor or appointed CRO, the Investigator / pharmacist / investigational drug storage manager must verify that all unused or partially used drug supplies have been returned by the clinical trial patient and that no remaining supplies are in the Investigator's possession.

See [Section 4.1.2](#). It is important to enter the date of priming on the medication label of the Respimat[®].

4.2 OTHER TREATMENTS, EMERGENCY PROCEDURES, RESTRICTIONS

4.2.1 Other treatments and emergency procedures

Non Investigational Medicinal Product (NIMP) (open label supplies)

- Salbutamol (albuterol*) HFA MDI inhalation aerosol (100 µg per actuation) for use as rescue medication during screening and treatment (visit 0 to Visit 4) will also be used for reversibility testing at Visit 1. The rescue medication will be provided by BI.

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

- Ipratropium bromide HFA MDI inhalation aerosol (20 µg per actuation) will be provided to be dispensed at the investigators discretion primarily for use by patients on a LAMA during the 4-week washout period of the LAMA preceding Visit 2.

Administration of rescue medication can occur at any point during the trial as deemed necessary by the patient or the investigator. Open label salbutamol / albuterol MDI and/or ipratropium bromide MDI will be provided by BI and allowed for rescue medication use. If the patient requires rescue medication during the PFT days (Visits 2 - 4), the PFTs will be discontinued and PFTs repeated on another day. The medication used, route and 24-hour clock time of administration will be recorded on the Rescue Medication eCRF page.

Before using for the first time the salbutamol (albuterol) hydrofluoroalkane (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.

There are no special emergency procedures to be followed.

Medications Allowed to Control Acute Exacerbations as Medically Necessary during the Treatment Period (Refer to [Section 5.3.6.3](#) for definition of COPD exacerbations):

- Salbutamol inhalation aerosol and/or Ipratropium bromide inhalation aerosol, both from MDI for PRN use, provided by BI.
- Temporary addition of oral steroids is allowed during the treatment portion of the study. CMR assessment and pulmonary function testing should not occur within seven days of the last administered dose of an increase or addition of oral steroids. CMR assessment and subsequent pulmonary function testing may be postponed up to 14 days to meet this restriction. Subsequent visits will be scheduled according to the patient's regular schedule.
- Temporary additions of theophylline preparations are allowed during the treatment portion of the study. CMR assessment and pulmonary function testing should not occur within seven days of the last dose. CMR assessment and subsequent pulmonary function testing may be postponed up to 14 days to accommodate this restriction. Subsequent visits will be scheduled according to the patient's regular schedule.

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

Non study medication like oral steroids, theophylline preparations and antibiotics will not be provided by BI.

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

The following [Table 4.2.2.1:1](#) provides an overview of permitted and restricted medication.

Table 4.2.2.1: 1 Permitted medications and Medications Restrictions

Drug Class	Sub-class	Prior to study	Study Period		
			Screening Period	Treatment Period	Follow up Period
Corticosteroids	Inhaled corticosteroids (not allowed for 2 weeks prior to V1)	Permitted ¹	NOT permitted	NOT permitted	Permitted ¹
	Oral corticosteroids (not allowed for at least 6 weeks prior to Visit1; permitted intermittently during the treatment phase in a case of COPD exacerbation)	Permitted	NOT permitted	NOT permitted	Permitted
	Injected Corticosteroids – local administration (for treatment of e.g. bursitis)	Permitted	Permitted	Permitted	Permitted
β-adrenergics	Inhaled short-acting β-adrenergics	Permitted ¹	Rescue ¹	Rescue ¹	Permitted
	Inhaled long-acting β-adrenergics (bid) (e.g. formoterol / salmeterol)	Permitted ¹ (w.o. 48 hrs prior to V1)	NOT permitted	NOT permitted	Permitted
	Inhaled long-acting β-adrenergics (qd) (i.e. indacaterol, olodaterol)	Permitted ¹ (w.o.1 wk prior to V1)	NOT permitted (w.o.3wks prior to baseline CMR and V2)	NOT permitted	Permitted

Table 4.2.2.1: 1 Permitted medications and Medications Restrictions (cont.)

Drug Class	Sub-class	Prior to study	Study Period		
			Screening Period	Treatment Period	Follow up Period
	Oral and patch beta-adrenergics	Permitted ¹ (w.o.4 wks prior to V1)	NOT permitted	NOT permitted	NOT permitted
	Beta blockers (stabilized 6 wks prior to V1)	Permitted	Permitted	Permitted	Permitted
Anti-cholinergics	Short-acting anticholinergics (inhalation aerosol, nasal spray)	Permitted ¹	Rescue ¹	Rescue ¹	Permitted
	Long-acting anticholinergics (bid/qd) (i.e. tiotropium, aclidinium, glycopyrronium, umeclidinium)	Permitted (w.o. 1 wk prior to V1)	NOT permitted (3 wks prior to baseline CMR and V2)	NOT permitted	Permitted
Combinations	ICS/LABA (bid) (* switch to LABA mono-product 2 weeks prior to V1, and then discontinue LABA at least 48 hrs prior to V1) (if switched to e.g. salmeterol, formoterol)	Permitted ¹	NOT permitted*	Study medication	Permitted
	ICS/LABA (qd) (*switch to LABA mono-product 2 weeks prior to V1, and then discontinue at least 1 wks prior to V1) (if switched to e.g. indacaterol, olodaterol)	Permitted	NOT permitted*	NOT permitted	Permitted
	ICS/SABA (* switch to SABA only 2 weeks prior to V1, and then discontinue SABA at least 8 hrs prior to V1)	Permitted ¹	NOT permitted*	NOT permitted	Permitted

Table 4.2.2.1: 1 Permitted medications and Medications Restrictions (cont.)

Drug Class	Sub-class	Prior to study	Study Period		
			Screening Period	Treatment Period	Follow up Period
	short-acting anticholinergic/ SABA (* 8 hrs prior to V1)	Permitted ¹	NOT permitted*	NOT permitted	Permitted
	Long-acting anticholinergics/long-acting β-adrennergics ² (e.g. glycopyrronium+indacaterol, umeclidinium+vilanterol)	Permitted (w.o. 1 week prior to V1)	NOT permitted (w.o. 3 wks prior to baseline CMR and V2)	Study medication	Permitted
Miscellaneous	Other investigational drugs (* 1 mth or 6 half-lives (whichever is greater) prior to V1)	NOT permitted*	NOT permitted	NOT permitted	NOT permitted
	Cromolyn sodium / nedocromil sodium (* if prescribed for non-asthma condition)	Permitted*	Permitted*	Permitted*	Permitted*
	Antihistamines, antileukotrienes (* if prescribed for non-asthma condition)	Permitted*	Permitted*	Permitted*	Permitted*
	Methylxanthines* (* if prescribed for non-asthma condition)	Permitted ³	Permitted ³	Permitted ³	Permitted ³
	Mucolytics (not containing bronchodilators; stabilized 6 wks prior to V1)	Permitted	Permitted	Permitted	Permitted
	Phosphodiesterase type 4 (PDE-4) inhibitor ⁴ (e.g. roflumilast)	NOT permitted	NOT permitted	NOT permitted	NOT permitted
	Strong inhibitors of CYP3A4 ⁵	NOT permitted (w.o.4 wks prior to V2)	NOT permitted	NOT permitted	NOT permitted

- 1 Refer to [Section 4.2.2.2](#) for washout period prior to PFTs.
- 2 Patients may be switched to qid LABA and short acting anticholinergic. Refer to Section 4.2.2.2 for washout period prior to PFTs.
- 3 For theophyllines: Refer to [Section 4.2.2.1](#) for washout period prior to PFTs.
- 4 Patients currently using PDE-4-inhibitors (e.g. roflumilast) should not be enrolled and roflumilast should not be withdrawn for the purpose of enrolling in this study.
Patients who were using roflumilast in the past may be included if their last use was a minimum of 3 months prior to Visit 1. In the event a patient with prior use of roflumilast is enrolled, past medical records are required to support and document why and when roflumilast was stopped.
- 5 Strong CYP3A4 inhibitors e.g. boceprevir, danoprevir, elvitegravir, clarithromycin, cobicistat (GS-9350), conivaptan, grapefruit juice DS, idelalisib, indinavir, itraconazole, ketoconazole, LCL161, lopinavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, tipranavir, troleandomycin and voriconazole are not permitted 4 weeks prior to first trial drug administration (Visit 2) and during the trial. All concomitant medication has to be checked by the investigator whether it is a strong inhibitor of CYP3A4 based on the SPC, if applicable. Specific questions of eligibility based on this criterion should be clarified by the clinical monitor prior to inclusion.

4.2.2.2 Restrictions for pulmonary function testing and CMR assessment

- At least 2 weeks washout of inhaled steroids prior to PFT s at visit 1, (Inhaled steroids are not allowed after Visit 1)
- At least an 8-hour washout of short-acting beta-adrenergic bronchodilators and short-acting anticholinergic bronchodilators.
- At least a 1-week washout of long-acting anticholinergic bronchodilators (bid or qd) prior to Visit 1 and a 3-week washout prior to baseline CMR and Visit 2. (Not allowed between Visits 1 to 4)
- At least a 1-week washout of long-acting beta-adrenergic bronchodilators (qd) prior to Visit 1 and a 3-week washout prior to baseline CMR and Visit 2 (Not allowed between Visits 1 to 4).
- At least a 48-hour washout of long-acting beta-adrenergic bronchodilators (bid) prior to Visit 1 (Not allowed between Visits 1 to 4).
- At least a 4-week washout of oral and patch beta adrenergics prior to visit 1.
- At least a 24-hour washout of short-acting (bid or more frequent administration) theophylline preparations.
- At least a 48-hour washout of long-acting (qd administration) theophylline preparation.

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

4.2.2.3 Restrictions on diet and life style

- On pulmonary function testing days (including the Screening Visit), patients must refrain from strenuous activity for at least 2-3 days prior to pulmonary function and throughout the testing period. Patients should also avoid cold temperatures, environmental smoke, dust or areas with strong odours (e.g. perfumes).
- Smoking should be discouraged for the 12 hours prior to lung function testing and throughout the study day and will not be permitted in the 30-minute period prior to spirometry.
- Coffee, tea, chocolate, cola and other caffeine-containing beverages and foods, and ice-cold beverages are not allowed the morning of or during the lung function testing period. Decaffeinated beverages are acceptable.

4.3 TREATMENT COMPLIANCE

On visit days, compliance will be guaranteed by administration of the trial drug under supervision of the investigating physician or designee.

Each patient will be trained at the screening Visit 1 as to the correct priming and inhalation using a training Respimat® Inhaler and on use of the Accuhaler®, both containing placebo.

Compliance will be measured using the counter on the Respimat® and Accuhaler® devices. Patients are requested to bring all used and unused trial medication with them when attending visits. The Investigator or designee will review these records with the patient at all visits to

assess treatment compliance in treatment phase. However, randomised patients will not be discontinued for lack of compliance without prior discussion with the Sponsor.

$$\text{Treatment compliance(\%)} = \frac{\text{Number of inhalations actually taken} \times 100}{\text{Number of inhalations which should have been taken}}$$

If the number of doses taken is not between 80-120%, site staff will explain the patient the importance of treatment compliance.

5. VARIABLES AND THEIR ASSESSMENT

5.1 TRIAL ENDPOINTS

5.1.1 Primary Endpoint(s)

The primary endpoint is change from baseline in LVEDVI in the 6th week of treatment with tiotropium+olodaterol FDC versus fluticasone propionate+salmeterol FDC.

LVEDVI is normalized left ventricular end diastolic volume (LVEDV), divided by body surface area (BSA) ([Appendix 10.3](#)).

Baseline is defined as the value obtained during the assessment performed in a week prior to Visit 2. The change from baseline is calculated as the value obtained in a week prior to Visits 3 and 4 (end of each treatment periods) minus the baseline value.

5.1.2 Secondary Endpoint(s)

The following secondary endpoints will be evaluated, all calculated as a change from baseline after 6 weeks of treatment:

- Aortic distensibility and pulmonary artery (PA) pulsatility.
- Central systolic pressure, pulse pressure and augmentation index (AI).
- FRC_{pleth} % predicted.
- 1,5 hour post dose FEV₁.
- 1,5 hour post dose FVC.

None of the primary or secondary endpoints are safety issues.

5.2 ASSESSMENT OF EFFICACY

CMR imaging

The CMR at 1.5 or 3 Tesla will be performed as indicated in a flowchart at rest as non-enhanced, non-stress procedure lasting up to one hour in order to assess cardiac functional parameters and structure using a cardio-pulmonary acquisition protocol according to specifications detailed in the Imaging Manual prepared by a Central Imaging Vendor. Cardiac cine images will be acquired in two and four chamber view as well as in short-axis view. Strain and strain-rate of RV, LA and LV will be assessed.

Aortic distensibility and pulmonary artery pulsatility as measures of arterial stiffness will be derived from cine images acquired at end-expiration in planes perpendicular to the thoracic aorta at the level of the PA (ascending and descending section of thoracic aorta), abdominal aorta, and perpendicularly to the main, right, and left pulmonary arteries.

All scans on each subject will be completed on the same MR scanner used for the baseline MRI with the same settings and accredited for use by the Imaging Vendor. All scans should be performed preferably in a time window between 1 and 8 hours after morning trial medication dosing at visits 3 and 4.

All scans will be digitally transferred for central review performed by the independent reviewer within a pre-specified time period. All parameters will be captured and recorded at the Sponsor before the database lock and unblinding of the study. Further information is provided in a Study Procedure Manual filed in the ISF.

Pulse pulse wave analysis (PWA)

PWA will be performed with vendor device in conjunction with measurement of blood pressure at Visit 1 for inclusion and at Visit 2 to obtain baseline measurement and then it will be repeated at visits 3 and 4 at the end of each treatment period. Measurements will be batch uploaded from the vendor. All parameters will be captured and recorded at the Sponsor before the database lock and unblinding of the study. Further information is provided in a Study Procedure Manual filed in the ISF.

Body plethysmography

Body plethysmography will be done in line with ATS/ERS standards [[R08-1121](#)] using the device of the investigational site for assessment of lung volumes and capacities.

The measurement of functional residual capacity (FRC) will be repeated at least 3 times, until 3 obtained FRC values show $\leq \geq 5\%$ variability.

Expiratory reserve volume (ERV) will be measured immediately after the FRC, followed by slow inspiratory vital capacity (IVC) manoeuvre, without the subject coming off the mouthpiece prior to the completion (as a linked manoeuvre).

COPD patients who cannot perform linked manoeuvres will be instructed to have few cycles of quiet breathing before initiation of the ERV/IVC manoeuvres.

Mean FRC value of at least 3 technically satisfactory FRC measurements, linked to the technically satisfactory ERV and IVC manoeuvres used for calculating the RVol and TLC will be reported. RVol will be calculated as a difference between the reported FRC value and the mean of the technically acceptable ERV measurements, linked to technically acceptable FRC determinations. Total lung capacity (TLC) will be calculated by adding the reported value for RVol and the largest of the technically acceptable IVCs.

Inspiratory capacity (IC) will be derived from IVC and ERV, and IC/TLC will be calculated. RVol % predicted will also be reported.

Reversibility testing [[P05-12782](#)] will be performed for the qualifying PFT at the Screening visit (Visit 1): the procedure is described in [Appendix 10.3](#). The post-bronchodilator measurements for FRC must meet the inclusion criteria specified in [Section 3.3.2](#).

Pulmonary Function Testing

Spirometers and their use, including daily calibration on measurement days, must meet ATS/ERS criteria [[P05-12782](#)]. Spirometry will be conducted using the site's own equipment. Patient will be in a seated position and it is preferable that the same trained individual performs the PFT for a given patient. The best of three efforts will be defined as the highest FEV₁ and the highest FVC each obtained on any of three manoeuvres meeting the ATS criteria (to a maximum of five attempts). The highest FEV₁ and FVC will be selected regardless of whether they come from different spirometric manoeuvres or from the same manoeuvre.

Predicted normal FEV₁ values will be calculated for patients using the ECSC equations [[R94-1408](#)], see Appendix 10.3).

If a patient is unable to complete the PFTs during a visit, the Sponsor should be notified as soon as possible. The eCRF will be completed indicating the reason for stopping testing, rescue medication given (if any) and time of rescue medication. Patients who are unable to complete the study visit may leave the clinic only upon instruction from the supervising physician.

Reversibility testing [[P05-12782](#)] will be performed for the qualifying PFT at the Screening visit (Visit 1): the procedure is described in Appendix 10.3.

5.3 ASSESSMENT OF SAFETY

5.3.1 Physical examination

Physical examinations are conducted at visit 1, at the end of each treatment (Visits 3 and 4) and at Visit 5 (Follow-up Visit) in case of any findings at the end of treatment visit (Visit 4). The physical exam includes vital signs (blood pressure and pulse rate), height and weight.

5.3.2 Vital Signs

Measurements of heart rate and blood pressure will be obtained immediately prior to body plethysmography, with the patient seated and rested for a minimum of 5 minutes.

5.3.3 Safety laboratory parameters

Safety laboratory testing will be conducted (non-fasting) on all patients at the screening visit (Visit 1) and will be collected in the morning prior to the reduction of hyperinflation and reversibility testing.

Haematology, blood chemistry and β -HCG will be analyzed by the local laboratory of each participating site or, where appropriate, locally selected central laboratory. Laboratory data will be collected but not captured in the eCRF. It is responsibility of the investigator to evaluate changes in laboratory values and reporting of adverse event should be followed according to the definitions outlined in [Section 5.3.6.1](#).

Haematology

Haemoglobin, haematocrit, red blood cell count, white blood cell count including differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils), total eosinophil count and platelet count.

Blood chemistry

Alkaline phosphatase, Lactate Dehydrogenase (LDH), Gamma-Glutamyl Transpeptidase (Gamma-GT), Serum glutamic-oxaloacetic transaminase (SGOT), Serum glutamic-pyruvic transaminase (SGPT), glucose, calcium, inorganic phosphorus, uric acid, urea nitrogen, creatinine, total protein, potassium, sodium, chloride, total bilirubin, creatinine phosphokinase.

Pregnancy Testing

A serum human chorionic gonadotropin (HCG) test will be performed at visit 1 in all females of childbearing potential. Urine pregnancy testing will be performed at visits 2, 3, 4 and 5 in females of childbearing potential.

5.3.4 Electrocardiogram

A standard 12-lead electrocardiogram (ECG) at rest will be performed on all patients at the screening visit (Visit 1) for inclusion in the study.

The purpose of the screening ECG (Visit 1) is to obtain information about the patient's baseline conditions that may have not been elicited in obtaining the baseline conditions. Therefore, any significant findings from the examination are recorded on the Baseline Condition page.

ECG will be completed using site's own equipment and ECG data will not be collected or captured in the eCRF. It is the responsibility of the investigator to evaluate the ECG and reporting of adverse events should be followed using the definitions outlined in [Section 5.3.6.1](#).

In case of indication of a disease listed under the exclusion criteria, the patient should not be randomised for treatment.

5.3.5 Other safety parameters

- Heart rate, blood pressure in conjunction with body plethysmography and spirometry.

5.3.6 Assessment of adverse events

5.3.6.1 Definitions of AEs

Adverse event

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

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

Adverse reaction

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

Serious adverse event

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

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

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

AEs considered “Always Serious”

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

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

The latest list of “Always Serious AEs” can be found in the remote data capture system. These events should always be reported as SAEs as described in [Section 5.3.6](#).

Adverse events of special interest (AESIs)

No AESIs have been defined for this trial.

Intensity of AEs

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

- Mild: Awareness of sign(s) or symptom(s) that is/are easily tolerated
Moderate: Enough discomfort to cause interference with usual activity

Severe: Incapacitating or causing inability to work or to perform usual activities

Causal relationship of AEs

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

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

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.

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

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

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

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

5.3.6.2 Adverse event collection and reporting

AE Collection

The Investigator shall maintain and keep detailed records of all AEs in their patient files.

The following must be collected and documented on the appropriate CRF(s) by the Investigator:

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

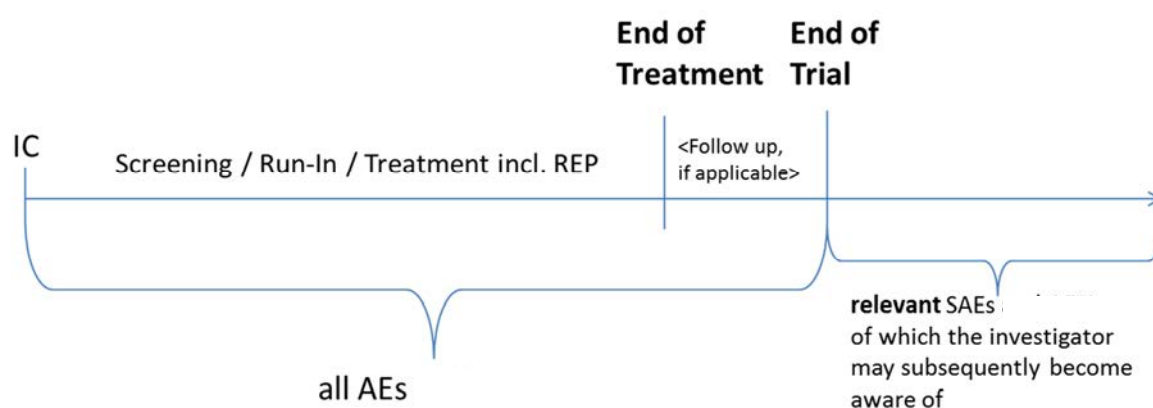


Figure 5.3.6.2: 1 AE collection in 1237.36

The REP is defined as 21 days after the last trial medication application. All AEs which occurred through the treatment phase and throughout the REP will be considered as on treatment please see [Section 7.3.4](#). Events which occurred after the REP will be considered as post treatment events.

AE reporting to sponsor and timelines

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

Information required

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

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

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

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

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

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

Pregnancy

In the rare case that a female subject participating in this clinical trial becomes pregnant after having taken trial medication, the investigator must report immediately (within 24 hours) the drug exposure during pregnancy (DEDP) to the Sponsor's unique entry point (country-specific contact details will be provided in the ISF). The Pregnancy Monitoring Form for Clinical Trials (Part A) should be used.

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

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

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

5.3.6.3 COPD Exacerbations

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

A complex of lower respiratory events 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.

5.4 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

5.4.1 Assessment of Pharmacokinetics

This study will not analyse pharmacokinetic or pharmacodynamic parameters

5.5 ASSESSMENT OF BIOMARKER(S)

5.6 OTHER ASSESSMENTS

Modified Medical Research Council Dyspnea Scale

The mMRC Dyspnea Scale uses a simple grading system to assess a patient’s level of dyspnea. All questions relate to everyday’s activities and are generally easily understood by patients. Scores range from 0 (none) to 4 (very severe) and are usually obtained in a few seconds ([Appendix 10.4](#)).

Patients will be asked to score their dyspnea first during an in-clinic visit, prior to pulmonary function testing and all other procedures (see [Section 6.2](#)). The results will be reported in the eCRFs.

New York Heart Association functional classification

The New York Heart Association (NYHA) functional classification will be used to check and classify the severity of the patients' function capacity ([Appendix 10.6](#)). The investigator should place the patients in one of the four categories based on how limited their physical activity is. Candidates for screening are required not to have a NYHA functional class IV.

The classification of patient's physical activity according to NYHA will be performed at Visit 1.

5.7 APPROPRIATENESS OF MEASUREMENTS

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

CMR

Cardiac magnetic resonance imaging will be performed according to current standardized protocols [[R16-3841](#)].

PWA

Non-invasive brachial cuff based assessment of central aortic pressure and waveform features will be used in this trial according to current recommendations [[R16-3840](#)]. The vendor device used provides measurements of brachial pressure and the estimation of central aortic pressure waveform by mathematical transformation of brachial artery tonometry. The method is reproducible and central pressure waveform indices correlate strongly with Doppler indexes of LV function [[R16-3842](#) and [R16-3843](#)].

Body Plethysmography

Body plethysmography will be conducted at clinic visits using the site's own equipment and used following the ATS/ERS methodology and calibration procedures [[R08-1121](#)].

Spirometry

PFTs are a validated and well established measurement tool for lung function testing. PFTs will be conducted at clinic visits using the site's own equipment which meets ATS/ERS criteria [[P05-12782](#)]. FEV₁, FVC and standard measurements for the assessment of lung function.

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

Patients should make every attempt to complete the protocol as specified. Investigators should encourage patient treatment compliance and adherence to other protocol specific activities. All deviations from the planned visit schedule will be documented. Refer to the [FC](#) for time windows for the visits. After this, a discussion with the Clinical Monitor should take place regarding the patient continuing in the trial.

Rescheduling in general

A patient visit may be rescheduled twice (within one week of the scheduled visit date) due to lack of medication washout compliance or no intake of study medication on the day preceding the clinic visit.

Rescheduling prior to randomisation

The screening period (between visit 1 and visit 2) may be extended by an additional 2 weeks for administrative reasons.

If a patient experiences a COPD exacerbation or respiratory tract infection in the 6 weeks prior to visit 1, the visit will be postponed until 6 weeks following recovery from the infection or exacerbation.

If a patient experiences a COPD exacerbation or respiratory tract infection during the screening period (between visit 1 and 2) washout should be stopped and patient will be assessed for severity and treated with bronchodilators, inhaled or systemic corticosteroids, antibiotics and other appropriate management interventions, as indicated according to current guidelines ([P16-13658](#)). Patient should also be excluded from further participation in the trial.

Rescheduling after randomisation

Subsequent visits should always be planned to take place to assure a minimum 6 week treatment period.

If rescheduling of visits after randomisation is necessary, the total daily doses of the Respimat[®] inhaler and/or Accuhaler[®] inhaler need to be obeyed. Reserve medication is dispensed at each treatment period to avoid intermediate visits.

If rescue medication is administered during a visit day within 8 hours prior to administration of trial medication, the visit will be rescheduled once. Further rescheduling should be discussed with the Sponsor.

Refer to [Section 4.2.2](#) for restrictions prior to PFTs and CMRs during study treatment.

In case a visit needs to be rescheduled outside the allowed time win Sponsor should be contacted.

Pulmonary function testing (PFT) and body plethysmography will be conducted at the screening visit (Visit 1) to determine patient eligibility. PFTs and body plethysmography will also be conducted at Visits 2, 3 and 4 during the treatment period; vital signs will be measured in conjunction with pulmonary function tests at all visits.

Physical examination will be performed together with an evaluation of the patient's smoking status and COPD background characteristics at Visit 1. A 12-lead ECG will be recorded at Visit 1 and blood samples for clinical laboratory testing will be obtained to evaluate the patient's eligibility. The physical exam will be repeated at Visit 3 and also at Visit 4 on completion of patient's participation in the randomised treatment period of the trial.

Serum pregnancy testing will be done at Visit 1 in females of childbearing potential. Urine pregnancy testing will be performed at Visit 2, 3, 4 and 5 in females of child bearing potential.

Peripheral blood pressure measurements together pulse wave analysis assessment will be obtained at Visit 1 for inclusion and on Visit 2 as baseline and at subsequent Visits 3 and 4 at the end of each 6 week treatment period.

CMR will be performed in a week prior to Visit 2 to obtain baseline parameters and then in a week prior to subsequent Visits 3 and 4, or at the latest on the day of respective visits, at the end of each treatment periods for assessment of left and right global and regional systolic and diastolic cardiac function and arterial stiffness.

Adverse events will be documented throughout the trial, i.e. starting with informed consent and ending 21 days after actual last administration of trial medication. COPD exacerbations according to protocol-specific definition ([Section 5.3.6.3](#)) will be documented together with additional observations including adverse events and concomitant therapies.

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

6.2.1 Screening and run-in period(s)

Screening Period

If there is any indication during the screening period that the patient is not stable enough, in the opinion of the investigator, to complete the trial or that the patient will be non-compliant with the trial medication or restrictions, the patient should not be randomised. This evaluation should be completed by the investigator.

Details of any patient who is screened for the trial but is found to be ineligible must be entered in the enrolment log and documented in the eCRF.

Patients must satisfy all inclusion and not meet any of the exclusion criteria prior to randomisation at visit 2 (see [Section 3.3.2](#) and [Section 3.3.3](#)).

Visit 0 Procedures and Observations

A preliminary check of in-/exclusion criteria is recommended at visit 0 to avoid unnecessary washout procedures in non-eligible patients.

Informed Consent	Informed Consent will be obtained prior to patient participation in the trial, which includes any medication washout procedures or restrictions. See Section 4.2.2.2 for pulmonary test restrictions.
Rescue Medication	Rescue medication will be issued to all patients. Please refer to Section 4.2.1 . The patient will receive directions on the as needed use of the salbutamol (albuterol) MDI and/or ipratropium (primarily to patients who are required to washout LAMAs during run-in periods) (as rescue medication) that will be dispensed at this visit.
IRT	Call IRT to register the patient in screening.

Visit 1 Procedures and Observations

Reversibility and Hyperinflation Testing

(Phone contact 1-2 days prior to the visit)

Medication washout	Medication washout compliance for prohibited medications will be verified and visits may be rescheduled as appropriate (Section 6.1)
Background information	Demographic data, COPD background characteristics, baseline conditions and smoking status will be recorded.
mMRC questionnaires	To be completed prior to study procedures. Refer to Appendix 10.5 and 10.6 .
Adverse Events	All AEs experienced since signing informed consent will be reviewed and recorded.
Smoking Status	Will be recorded.
Concomitant Therapy	Medication use for the previous 3 months will be recorded in the eCRF.
Inclusion/Exclusion	To be reviewed.
Physical Examination and 12-Lead ECG	The physical examination includes measurements of blood pressure and pulse rate. Refer to Section 5.3.1 . The vital signs (seated) with blood pressure measurement should be performed. ECG should be conducted following five minutes rest and prior to blood sampling and to salbutamol (albuterol) dosing.
Laboratory tests	Will be collected and submitted to the local laboratory for hematology, serum chemistry and pregnancy testing (if applicable). A fasted condition is not required. Blood samples need to be taken prior to the salbutamol (albuterol) dosing.

Vital Signs	Blood pressure (together with pulse wave analysis) and pulse rate will be measured immediately before body plethysmography with the patient seated and rested for at least five minutes.
Body Plethysmography followed by Spirometry (hyperinflation reduction and reversibility testing)	<ul style="list-style-type: none"> • Lung volumes including FRC measurement will be taken prior to spirometry. • The 24-hour clock time of the last cigarette smoked during the 12 hours prior to the start of lung function measurements will be recorded. • Will be conducted between 7:00 a.m.-10:00 a.m. immediately prior to (-30 min) and ≥ 10 minutes and up to 20 minutes after the inhalation of 4 puffs of salbutamol (albuterol). • Please refer to inclusion criteria 2 and Appendix 10.3.
Training and Instructions	<p>Patients will receive training and instructions on</p> <ul style="list-style-type: none"> • The use of rescue medication (salbutamol/albuterol) • The use of the RespiMat[®] Inhaler using the training kit • The use of the Accuhaler[®] Inhaler using the training kit • Medication restrictions and washout requirements for the screening period and subsequent visits • Returning all issued medication to the clinic on all subsequent visits.
Rescue Medication	Patients qualified to enter the 3-week screening period of the trial will be issued additional rescue medication if needed.
IRT	Call IRT to register the patient in screening (if not already done at Visit 0).
Plan for baseline CMR prior to Visit 2	Schedule for the baseline CMR assessment in coordination with the patient and the CMR unit. Assign patient a card for washout requirements and instructions for baseline CMR assessment. Instruct the patient about handling of the patient card.

6.2.2 Treatment period(s)

Patients will be contacted prior to each of the visits to remind the patient of medication washout requirements, and to bring back all study and rescue medication. Patients must return study medication at visits 3 and 4

Visit 2 Procedures and Observations

Randomisation, medication dispensing.

CMR baseline assessment will be performed in a week prior to Visit 2 but at the latest 3 days prior to the Visit 2 to allow for the assessment of ejection fraction level for inclusion.

(Phone contact prior to CMR and 1-2 days prior to the visit)

Medication washout	Medication washout compliance for prohibited medications will be verified and visits may be rescheduled as appropriate (Section 6.1)
mMRC questionnaires	To be completed prior to study procedures. Refer to Appendix 10.4 and 10.5 .
Adverse Events	All AEs experienced since the previous visit will be reviewed and documented.
Concomitant Therapy	Any changes in concomitant medications since the last visit will be reviewed and documented.
Inclusion / Exclusion	To be reviewed.
Smoking Status	Will be recorded.
CMR patient card	Evaluate patient card for baseline CMR issued at Visit 1.
Urine Pregnancy	Will be performed if needed.
Vital Signs	Blood pressure (together with pulse wave analysis) and pulse rate will be measured immediately before PFTs with the patient seated and rested for at least five minutes.
Body Plethysmography followed by Spirometry	Baseline pre-dose body plethysmography will be performed between 7:00 and 10:00 am (1 hour prior to inhalation of morning dose of study medication) followed by baseline pre-dose spirometry. Refer to FC . The 24-hour clock time of the last cigarette smoked during the 12 hours prior to the start of body plethysmography measurements will be recorded.
Randomisation Call (IRT)	To be performed by calling IRT.
Assignment and dispensing of trial drug	Allocate the appropriate medication kits using IRT. 2 Respimat [®] treatment boxes and 1 reserve Respimat [®] inhaler are assigned and 2 Accuhaler [®] treatment boxes and 1 reserve Accuhaler [®] inhaler
Trial drug training and administration	The patient will self-administer the trial drug (from the new assigned Respimat [®] inhaler followed by Accuhaler [®] inhaler) under the oversight of site staff. Instructions on how to assemble and prime the Respimat [®] inhaler at home should also be reviewed. Please refer to Section 4.1.4.3 . First dose of study medication for the treatment period will be self-administered between 07:00 and 10:00 a.m.; start-time of inhalation

	will be recorded. Note that at subsequent clinic visits, study medication will be self-administered preferably within ± 30 minutes of time of administration at Visit 2 AND between 7:00 a.m. and 10:00 a.m.
Training and Instructions	Patients will receive training and instructions on <ul style="list-style-type: none"> • Medication restrictions and washout requirements for subsequent visits • Returning all issued medication to the clinic on all subsequent visits.
Rescue Medication	Patients will be issued additional rescue medication if needed and instructed to return all rescue medication to the clinic on the next scheduled visit.
Plan for the second CMR prior to/at Visit 3	Schedule for the second CMR assessment in coordination with the patient and the CMR unit. Assign patient a card for washout requirements and time point of intake of morning study medication at the CMR assessment day. Instruct patient about handling of the patient card.

Visit 3 Procedures and Observations

End of first treatment period assessments and medication change.

CMR assessment will be performed in a week prior to or at the latest at Visit 3 (1 to 8 hours after morning medication dosing).

(Phone contact prior to CMR and 1-2 days prior to the visit)

Medication washout	Medication washout compliance for prohibited medications will be verified and visits may be rescheduled as appropriate (Section 6.1)
mMRC questionnaires	To be completed prior to study procedures. Refer to Appendix 10.4 and 10.5 .
Adverse Events	All AEs experienced since the previous visit will be reviewed and documented.
Concomitant Therapy	Any changes in concomitant medications since the last visit will be reviewed and documented.
Smoking Status	Will be recorded.
CMR patient card	Evaluate patient card for the second CMR issued at Visit 2.
Physical Examination	The physical examination includes measurements of blood pressure and pulse rate. Refer to Section 5.3.1 . The vital signs (seated) with blood pressure measurement should be performed.
Urine pregnancy	Will be recorded.

Trial Drug Administration	Study medication will be self-administered within ± 30 minutes of time of administration at visit 2 AND between 7:00 a.m. and 10:00 a.m.; start-time of inhalation will be recorded. Administration of trial medication during these visits will be done using medication that was dispensed at the beginning of the treatment period.
Vital Signs	Blood pressure (together with pulse wave analysis) and pulse rate will be measured immediately before body plethysmography with the patient seated and rested for at least five minutes.
Body Plethysmography followed by Spirometry	Post-dose plethysmography will be performed 1,5 hour post inhalation of morning dose of study medication followed by post-dose spirometry. Refer to EC . The 24-hour clock time of the last cigarette smoked during the 12 hours prior to the start of lung function measurements will be recorded.
Trial Drug Collection and Compliance check	Collect all dispensed trial medication and perform Compliance check.
IRT Call	Change of trial medication.
Assignment and dispensing of trial drug	Allocate the appropriate medication kits using IRT. 2 Respimat [®] treatment boxes and 1 reserve Respimat [®] inhaler are assigned and 2 Accuhaler [®] treatment boxes and 1 reserve Accuhaler [®] inhaler
Training and Instructions	Patients will receive training and instructions on <ul style="list-style-type: none">• Medication restrictions and washout requirements for subsequent visits• Returning all issued medication to the clinic on all subsequent visits.
Rescue Medication	Patients will be issued additional rescue medication if needed and instructed to return all rescue medication to the clinic on the next scheduled visit.
Plan for the third CMR prior to/at Visit 4	Schedule for the third CMR assessment in coordination with the patient and the CMR unit. Assign patient a card for washout requirements and time point of intake of morning study medication at CMR assessment day. Instruct patient about handling of the patient card.

If the patient is unable to complete the entire test-day visit, the eCRF will be completed indicating the reason for stopping testing, rescue medication given and time of rescue medication. Patients, who are unable to complete the test-day visit, may leave the clinic only upon instruction from the supervising physician.

Visit 4 (EoT) Procedures and Observations

End of second treatment period assessments and trial medication collection.

CMR assessment will be performed in a week prior to or at the latest at Visit 4 (1 to 8 hours after morning medication dosing).

(Phone contact prior to CMR and 1-2 days prior to the visit)

Medication washout	Medication washout compliance for prohibited medications will be verified and visits may be rescheduled as appropriate (Section 6.1)
mMRC questionnaires	To be completed prior to study procedures. Refer to Appendix 10.4 and 10.5 .
Adverse Events	All AEs experienced since the previous visit will be reviewed and documented.
Concomitant therapy	Any changes in concomitant medications since the last visit will be reviewed and documented.
Smoking Status	Will be recorded.
CMR patient card	Evaluate patient card for the third CMR issued at Visit 3.
Physical Examination	The physical examination includes measurements of blood pressure and pulse rate. Refer to Section 5.3.1 . The vital signs (seated) with blood pressure measurement should be performed.
Urine pregnancy	Will be recorded.
Trial Drug Administration	Study medication will be self-administered within ± 30 minutes of time of administration at Visit 2 AND between 7:00 a.m. and 10:00 a.m.; start-time of inhalation will be recorded. Administration of trial medication during these visits will be done using medication that was dispensed at the beginning of the treatment period.
Vital Signs	Blood pressure (together with pulse wave analysis) and pulse rate will be measured immediately before body plethysmography with the patient seated and rested for at least five minutes.
Body Plethysmography followed by Spirometry	Post-dose body plethysmography will be performed 1,5 hour post inhalation of morning dose of study medication followed by post-dose spirometry. Refer to FC . The 24-hour clock time of the last cigarette smoked during the 12 hours prior to the start of lung function measurements will be recorded.
IRT Call	Call IRT to register the patient as completed.
Trial Drug Collection and	All study medication will be collected at visit 4. Compliance check will be performed.

Compliance check	
Rescue Medication Collection	All study medication will be collected

If the patient is unable to complete the entire test-day visit, the eCRF will be completed indicating the reason for stopping testing, rescue medication given and time of rescue medication. Patients, who are unable to complete the test-day visit, may leave the clinic only upon instruction from the supervising physician.

6.2.3 Follow Up Period and Trial Completion

Premature discontinuation Procedures and Observations

These procedures should be performed after any premature withdrawal of patients that took at least one dose of trial medication.

Adverse Events	All AEs experienced since the previous visit will be reviewed and documented.
Concomitant therapy	Any changes in concomitant medications since the last visit will be reviewed and documented.
Physical Examination	The physical examination includes measurements of blood pressure and pulse rate. Refer to Section 5.3.1 . The vital signs (seated) with blood pressure measurement should be performed.
Smoking Status	Will be recorded.
Urine Pregnancy	Will be performed if applicable.
Vital Signs	Blood pressure and pulse rate will be measured immediately before PFTs with the patient seated and rested for at least five minutes.
Body Plethysmography followed by Spirometry	Will be conducted if possible. Refer to FC . The 24-hour clock time of the last cigarette smoked during the 12 hours prior to the start of lung function measurements will be recorded.
Trial Drug Collection	All study medication will be collected.
IRT Call	Call IRT to register the patient as discontinued.

Visit 5 (End of observation) Follow-up Procedures and Observations

At the completion of Visit 4, the follow-up visit should be performed as described in the FC. The investigator should make every effort to perform a follow-up visit 21 days after the last dose of study medication in patients that withdraw prematurely.

Adverse Events	All AEs experienced since the previous visit will be reviewed and documented.
Concomitant therapy	Any changes in concomitant medications since the last visit will be reviewed and documented.
Physical Examination	<p>The physical examination includes measurements of blood pressure and pulse rate. Refer to Section 5.3.1.</p> <p>The vital signs (seated) with blood pressure measurement should be performed.</p> <p>To be completed in the event of any clinically relevant findings at the EOT visit.</p>
Urine Pregnancy	Will be performed if applicable.
Trial Completion	Trial completion is defined as last dose of trial medication followed 21 days later by the follow-up visit.

The clinical monitor must be consulted on all persistently abnormal tests and SAEs until it is agreed that follow-up is no longer necessary.

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 STATISTICAL DESIGN - MODEL

This is an exploratory, randomised, double-blind, double-dummy, active-controlled, two period complete cross-over study to investigate the effect of 6 weeks treatment of orally inhaled tiotropium + olodaterol FDC (5 µg/5 µg) compared with fluticasone propionate + salmeterol FDC (1000 µg /100 µg) on left ventricular function and arterial stiffness in patients with COPD.

Based on these design considerations, a mixed effect repeated measures model (MMRM) with treatment and period as fixed effects and patient as a random effect will be used for the primary analysis. Detailed specifications are provided in [Section 7.3](#).

7.2 NULL AND ALTERNATIVE HYPOTHESES

The following hypotheses (two-sided $\alpha = 0.05$) will be tested for the primary endpoint – change from baseline in LVEDVI.

H_0 : Mean change from baseline in LVEDVI for (Tiotropium + Olodaterol) = Mean change from baseline in LVEDVI for (Fluticasone propionate + Salmeterol)

H_1 : Mean change from baseline in LVEDVI for (Tiotropium + Olodaterol) \neq Mean change from baseline in LVEDVI for (Fluticasone propionate + Salmeterol)

Where LVEDVI is the primary endpoint after 6 weeks of treatment.

7.3 PLANNED ANALYSES

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

The data from patients who have had an exacerbation during the treatments will be excluded from the analyses,

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

The handling of randomised patients who received the wrong treatment will be specified in the Trial Statistical Analysis Plan (TSAP).

7.3.1 Primary endpoint analyses

In the primary analysis, the two-sided hypothesis as given in [Section 7.2](#) will be tested based on adjusted mean change from baseline in LVEDVI, as listed in [Section 5.1.1](#), using a restricted maximum likelihood (REML)-based MMRM. This model will include treatment and period as fixed effects, patient as a random effect and baseline as covariate. Unstructured covariance structure will be used for within patient variation. If convergence is not achieved, the compound symmetry covariance structure will be used. The SAS procedure MIXED will be used involving the restricted maximum likelihood estimation and the Kenward-Roger approximation for denominator degrees of freedom. This approach is described in [\[R10-4391\]](#). Adjusted mean values as well as treatment contrasts will be presented together with the 95% confidence intervals (CI) and p-values.

Baseline

The baseline is defined as the (pre-dose) measurement in, the LVEDVI performed in a week prior to Visit 2 (or prior to dosing on the Visit 2).

7.3.2 Secondary endpoint analyses

The MMRM model described for the primary analysis will be performed for secondary endpoints as listed in [Section 5.1.2](#). Adjusted mean values as well as treatment contrasts will be presented together with the 95% CI. All calculated p-values should be considered descriptive for the analysis of the secondary endpoints.

7.3.4 Safety analyses

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary. Standard BI summary tables and listings will be produced. All adverse events with an onset between start of treatment and end of the residual effect period (REP), a period of 21 days after the last dose of trial medication, will be considered 'treatment-emergent'. Adverse events that start before first drug intake and deteriorate under treatment will also be considered as 'treatment-emergent'. Adverse events with an onset from the start of treatment to Visit 3 will be assigned to the first treatment, and adverse events with an onset on a day after Visit 3 to the end of REP to the second treatment.

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.

Frequency, severity, and causal relationship of adverse events will be tabulated by system organ class and preferred term after coding according to the current version of the MedDRA.

Blood pressure and pulse rate measured in conjunction with PFT testing will be presented for each treatment using descriptive statistics.

7.3.5 Pharmacokinetic analyses

No pharmacokinetic analysis is planned.

7.4 INTERIM ANALYSES

No interim analysis is planned.

7.5 HANDLING OF MISSING DATA

In general, missing data at a given visit will be imputed by the available data from the patient at that visit and completely missing visits will be handled through the statistical model.

Additional details on the imputation of missing data will be specified in the TSAP prior to unblinding.

7.6 RANDOMISATION

Approximately 74 patients will be randomised in blocks to double-blind treatment sequence so that approximately equal numbers of patients will be randomised to each treatment sequence. BI will arrange for the randomization and the packaging and labelling of trial medication. The randomization list will be generated using a validated system, which involves a pseudo-random number generator so that the resulting treatment will be both reproducible and non-predictable. The block size will be documented in the CTR. Access to the codes will be controlled and documented.

7.7 DETERMINATION OF SAMPLE SIZE

This is an exploratory trial and only limited data exist about LVEDVI. A cross-over study in COPD patients evaluated the effect of fluticasone furoate and vilanterol versus placebo on mean change from baseline in LVEDVI [R16-3512]. The mean difference was 3.63 mL/m² with a standard deviation of approximately 7.3 mL/m². Assuming a 2-sided alpha of 5% and a within-patient standard deviation of 7.5 mL/m², a sample size of approximately 74 patients would have 80% to 90% power to reject the null hypothesis if the true treatment difference is 2.5 to 3.0 mL/m². If the SD is 20% larger (9.0 mL/m²), then the power would still be 80% for a treatment difference of 3.0 mL/m². This results in a sample size of 74 patients.

Table 7.7: 1 Sample size for 80% and 90% power, 2-sided alpha= 0.05

Power	Difference [ml/m ²]	SD	Sample Size
80%	3.0	7.5	52
90%	3.0	7.5	68
80%	3.0	9.0	74
90%	3.0	9.0	98
80%	2.5	7.5	74
90%	2.5	7.5	98

Calculations were performed using nQuery Advisor[®] 7.0 statistical package by Statistical Solutions Ltd.

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

The trial will be carried out in accordance with the Medical Devices Directive (93/42/EEC) and the harmonised standards for Medical Devices (ISO 14155 and ISO 14155-02).

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

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

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

The BI transparency and publication policy can be found on the following web page: trials.boehringer-ingelheim.com. The rights of the Investigator and of the Sponsor with regard to publication of the results of this trial are described in the Investigator contract.

As a rule, no trial results should be published prior to finalization of the Clinical Trial Report.

The certificate of insurance cover is made available to the Investigator and the patients, and is stored in the ISF.

8.1 TRIAL APPROVAL, PATIENT INFORMATION, INFORMED CONSENT

This trial will be initiated only after all required legal documentation has been reviewed and approved by the respective Institutional Review Board (IRB) / Independent Ethics Committee (IEC) and competent authority (CA) according to national 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.

8.2 DATA QUALITY ASSURANCE

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

8.3 RECORDS

eCRF for individual patients will be provided by the Sponsor. See [Section 4.1.5.2](#) for rules about emergency code breaks. For drug accountability, refer to [Section 4.1.8](#).

8.3.1 Source documents

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

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

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

If the patient is not compliant with the protocol, any corrective action e.g. re-training must be documented in the patient file.

For the CRF, data must be derived from source documents, for example:

- Patient identification: gender, date or year of birth (in accordance with local laws and regulations)
- Patient participation in the trial (substance, trial number, patient number, date patient was informed)
- Dates of Patient's visits, including dispensing of trial medication
- Medical history (including trial indication and concomitant diseases, if applicable)
- Medication history
- Adverse events and outcome events (onset date (mandatory), and end date (if available))
- Serious adverse events (onset date (mandatory), and end date (if available))

- Concomitant therapy (start date, changes)
- Originals or copies of laboratory results and other imaging or testing results, with proper documented medical evaluation (in validated electronic format, if available)
- Completion of Patient's Participation in the trial" (end date; in case of premature discontinuation document the reason for it).
- Prior to allocation of a patient to a treatment into a clinical trial, there must be documented evidence in the source data (e.g. medical records) that the trial participant meets all inclusion criteria and does not meet any exclusion criteria. The absence of records (either medical records, verbal documented feedback of the patient or testing conducted specific for a protocol) to support inclusion/exclusion criteria does not make the patient eligible for the clinical trial.

8.3.2 Direct access to source data and documents

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

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

8.3.3 Storage period of records

Trial site(s):

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

Sponsor:

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

8.4 EXPEDITED REPORTING OF ADVERSE EVENTS

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

8.5 STATEMENT OF CONFIDENTIALITY AND PATIENT PRIVACY

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

Data protection and data security measures are implemented for the collection, storage and

processing of patient data in accordance with the principles 6 and 12 of the WHO GCP handbook.

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

8.6 TRIAL MILESTONES

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

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

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

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

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

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

The IEC / CA in Germany will be notified about the trial milestones according to the respective laws.

A final report of the clinical trial data will be written only after all patients have completed the trial to incorporate and consider all data in the report.

The Sponsor will submit to the EU database a summary of the final trial results within one year from the end of a clinical trial as a whole.

9. REFERENCES

9.1 PUBLISHED REFERENCES

- P05-12646 Pellegrino R, Viegi G, Brusasco V, Crapo RO, Burgos F, Casaburi R, Coates A, Grinten CPM van der, Gustafsson P, Hankinson J, Jensen R, Johnson DC, MacIntyre N, McKay R, Miller MR, Navajas D, Pedersen OF, Wanger J. Interpretative strategies for lung function tests. *Eur Respir J* 26 (5), 948 - 968 (2005)
- P05-12782 Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, Crapo R, Enright P, Grinten CPM van der, Gustafsson P, Jensen R, Johnson DC, MacIntyre N, McKay R, Navajas D, Pedersen OF, Pellegrino R, Viegi G, Wanger J; Standardisation of spirometry. *Eur Respir J* 26 (2), 319 - 338 (2005)
- P16-01440 Beeh KM, Derom E, Echave-Sustaeta J, Groenke L, Hamilton A, Bjemer L. The lung function profile of once-daily tiotropium and olodaterol vis Respimat is superior to that of twice-daily salmeterol and fluticasone propionate via Accuhaler (ENERGITO study). *Int J Chronic Obstruct Pulm Dis* 11, 193 – 205 (2016)
- P16-08905 Watz H. Chronic Obstructive Pulmonary disease: when Pulmologists do Something Good for the Heart. *Am J Respir Crit Care Med* 2016; 193(7): 703-716.
- P16-13658 Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease 2017 report. [http:// goldcopd.org/gold-2017-global-strategy-diagnosis-management-prevention-copd/](http://goldcopd.org/gold-2017-global-strategy-diagnosis-management-prevention-copd/) (access date: 22 November 2016); Global Initiative for Chronic Obstructive Lung Disease (GOLD) (2017).
- R03-2273 Draft consensus guideline: choice of control group in clinical trials (released for consultation at step 2 of the ICH process on 7 May 1999 by the ICH steering committee)
- R05-0370 ICH harmonised tripartite guideline: maintenance of the ICH guideline on non-clinical safety studies for the conduct of human clinical trials for pharmaceuticals M3(M) (recommended for adoption at step 4 of the ICH process on 16 July 1997 and amended on 9 November 2000 by the ICH

Steering Committee, Int. Conf Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use 2000)

- R06-1245 Mosteller RD. Simplified calculation of body-surface area. *N Engl J Med* 1987; 317(17):1098.
- R08-1121 Wanger J, Clausen JL, Coates A, Pedersen OF, Brusasco V, Burgos F, Casaburi R, Crapo R, Enright P, Grinten CPM van der, Gustafsson P, Hankinson J, Jensen R, Johnson D, MacIntyre N, McKay R, Miller MR, Navajas D, Pellegrino R, Viegi G. Standardisation of the measurement of lung volumes. *Eur Respir J* 26 (3), 511 - 522 (2005)
- R10-4391 Kenward MG, Roger JH. The use of baseline covariates in crossover studies. *Biostatistics* 11 (1), 1 - 17 (2010)
- R10-5669 ICH Expert Working Group; ICH harmonised tripartite guideline: guidance on nonclinical safety studies for the conduct of human clinical trials and marketing authorization for pharmaceuticals, M3 (R2) (current step 4 version, dated 11 June 2009). weblink: ich.org/LOB/media/MEDIA5544.pdf (access date:11.10.2010) (2009)
- R12-4840 Divo M, Cote C, Torres JP de, Casanova C, Marin JM, Pinto-Plata V, Zulueta J, Cabrera C, Zagaceta J, Hunninghake G, and Celli B; for the BODE Collaborative Group. Comorbidities and risk of mortality in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2012; 186: 155-161.
- R15-2161 Smith BM, Kawut SM, Bluemke DA, Basner RC, Gomes AS, Hoffman E, Kalhan R, Lima JAC, Liu CY, Michos ED, Prince MR, Rabbani L, Rabinovitz D, Shimbo D, Shea S, Barr RG, Pulmonary Hyperinflation and Left Ventricular Mass. The Multi-Ethnic Study of Atherosclerosis COPD Study, *Circulation* 2013; 127: 1503-1511.
- R16-3512 Stone IS, Barnes NC, James W-L, Midwinter D, Boubertakh R, Follows R, John L, Petersen SE. Lung deflation and cardiovascular structure and function in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2016; 193: 717-726.
- R16-3513 Negewo NA, McDonald VM, Gibson PG. Comorbidity in chronic pulmonary disease, *Respiratory Investigation* 2015; 53: 249-258.
- R16-3514 Chen W, Thomas J, Sadatsafavi M, FitzGerald JM. Risk of cardiovascular comorbidity in patients with chronic obstructive pulmonary disease: a systematic review and meta-analysis. *Lancet Respir Med* 2015; 3: 631-39.

- R16-3515 Cuttica MJ, Colangelo LA, Shah SJ, Lima J, Kishi S, Arynchyn A, Jacobs DR JR, Thyagarajan B, Liu K, Lloyd-Jones, and Kalhan R. Loss of Lung Health from Young Adulthood and Cardiac Phenotypes in Middle Age. *Am J Respir Crit Care Med* 2015; 192(1); 76-85.
- R16-3516 Watz H. The Lungs and the Heart. *Am J Respir Crit Care Med* 2015; 192(1); 7-8.
- R16-3517 Watz H, Waschki B, Meyer T, Kretschmar G, Kirsten A, Claussen M, Magnussen H. Decreasing cardiac chamber sizes and associated heart dysfunction in COPD; role of hyperinflation. *Chest* 2010; 138: 32-38.
- R16-3518 Smith BM, Hoffman EA, Basner RC, Kawut SM, Kalhan R, and Barr RG. Not all measures of Hyperinflation Are Created Equal. Lung structure and clinical Correlates of Gas Trapping and Hyperexpansion in COPD: The Multi-Ethnic Study of Atherosclerosis (MESA) COPD Study. *Chest* 2014; 145(6): 1305-1315.
- R16-3519 Smith BM Prince MR, Foffman EA, Bluemke DA, Liu CY, Rabinovitz D, Hueper K, Parikh MA, Gomes AS, Michos ED, Lima JAC, Barr RG. Impaired Left Ventricular Filling in COPD and Emphysema: Is It the Heart or the Lungs? The Multi-Ethnic Study of Atherosclerosis COPD Study. *Chest* 2013; 144(4): 1143-1151.
- R16-3528 Chirinos JA, Zamani P. The Nitrate-Nitrite-NO Pathway and Its Implications for heart Failure and Preserved Ejection Fraction. *Curr Heart Fail Rep* 2016; 13: 47. DOI 10.1007/s11897-016-0277-9.
- R16-3555 Frydrychowicz A, Wieben O. Safety issues in MRI. In: *ERS Monograph Imaging*. Edited by Ghram Barr R, Parr DG, Vogel-Claussen J. 2015; 70: 263-270.
- R16-3556 Caudron J, Fares J, Bauer F, Dacher JN. Evaluation of Left Ventricular Diastolic Function with Cardiac MR imaging. *Radiographics* 2011; 31: 239-261.
- R16-3557 Rutten FH, Voncken EJ, Cramer MJ, Moons KG, Velthuis BB, Niek HP, Lammers JW, Grobbee DE, Mali WP, Hoes AWH. Cardiovascular magnetic resonance imaging to identify left-sided chronic heart failure in stable patients with chronic obstructive pulmonary disease. *American Heart Journal* 2008; 156 (3), 506–512.
- R16-3558 Sanz J, Kariisa M, Dellegrottaglie S, Prat-Gonzales S, Garcia MJ, Fuster V, Rajagopalan S. Evaluation of Pulmonary Artery Stiffness in Pulmonary Hypertension With Cardiac Magnetic Resonance. *JACC: Cardiovascular Imaging* 2009; 2(3): 286-95.
- R16-3840 Townsend RR, Wilkinson IB, Schiffrin EL, Avolio AP, Chirinos JA, Cockcroft JR, Heffernan KS, Lakatta EG, McEniery CM, Mitchell GF, Najjar SS,

- Nichols WW, Urbina EM, Weber T. Recommendations for improving and standardizing vascular research on arterial stiffness. A scientific statement from the American Heart Association. Hypertension 2015; 66: 698-722.
- R16-3841 Kramer CM, Barkhausen J, Flamm SD, Kim RJ, Nagel E. Standardised cardiovascular magnetic resonance (CMR) protocols 2013 update. Journal of Cardiovascular Magnetic Resonance 2013; 15: 91 (<http://jcmr-online.com/content/15/1/91>).
- R16-3842 Cauwenberghs N, Knez J, Tikhonoff V, D'hooge JD, Kloch-Badek M, Thijs L, Stolarz-Skzypek K, Haddad F, Wojciechowska W, Swierblewska E, Casiglia E, Kawecka-Jaszcz K, Narkiewicz K, Staessen JA, Kuznetsova T. Doppler indexes of left ventricular systolic and diastolic function in relation to the arterial stiffness in a general population. J Hipertens 2015; 34: 762-771.
- R16-3843 Avolio A, Butlin M. Indices of central aortic pressure waveform and ventricular function: an intimate conversation changing direction with age. J Hipertens 2016; 34: 634-636.
- R94-1408 Quanjer PH, Tammeling GJ, Cotes JE, Pedersen OF, Peslin R, Yernault JC; Lung volumes and forced ventilatory flows. Report Working Party Standardization of Lung Function Tests, European Community for Steel and Coal. Official Statement of the European Respiratory Society. Eur Respir J 6 (Suppl 16), 5 - 40 (1993)
- R94-1529 Chow SC, Liu JP. Design and Analysis of Bioavailability and Bioequivalence Studies. New York: marcel Dekker Inc. (1992)

9.2 UNPUBLISHED REFERENCES

- c01735218 Clinical Trial Report: Tiotropium + olodaterol fixed dose combination inhalation solution – Respimat®. TOnado™ 1 1237.5. 10 April 2014.
- c01735249 . Clinical Trial Report: Tiotropium + olodaterol fixed dose combination inhalation solution – Respimat®. TOnado™ 2 1237.6. 10 April 2014.
- U13-1917 Randomised, double-blind, placebo-controlled, 6 treatment, 4 period, incomplete cross-over trial to characterise the 24-hour lung function profiles of tiotropium + olodaterol fixed dose combination (2.5/5 µg, 5/5 µg), tiotropium (2.5 µg, 5 µg) and olodaterol (5 µg) (oral inhalation, delivered by the Respimat® Inhaler) after 6 weeks once daily treatment in patients with Chronic Obstructive Pulmonary Disease (COPD) [VIVACITOTM] (1237.20).

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:


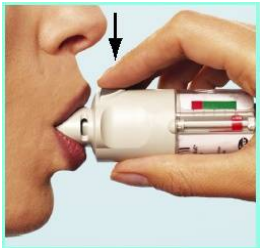
 <p>1</p>	<p>1 With the grey cap closed, press the safety catch € and pull the clear base (G).</p>
 <p>2a</p>	<p>2 Take the cartridge (H) out of the box. Push the narrow end of the cartridge into the inhaler until it clicks into place (2a). The cartridge should be pushed gently against a firm surface to ensure that it has gone all the way in (2b).</p> <p>Do not remove the cartridge once it has been inserted into the inhaler.</p>
 <p>2b</p>	
 <p>3</p>	<p>3 Replace the clear base (G).</p> <p>Do not remove the clear base again.</p>

To prepare the Respimat® inhaler for first-time use


 <p>4</p>	<p>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).</p>
 <p>5</p>	<p>5 Open the grey cap (A) until it snaps fully open.</p>
 <p>6</p>	<p>6 Point the Respimat® inhaler towards the ground. Press the dose release button (D). Close the grey cap (A).</p> <p>Repeat steps 4, 5 and 6 until a cloud is visible.</p> <p>Then repeat steps 4, 5 and 6 three more times to ensure the inhaler is prepared for use.</p> <p>Your Respimat® inhaler is now ready to use.</p> <p>These steps will not affect the number of doses available. After preparation your Respimat® inhaler will be able to deliver 60 puffs.</p>

Using the Respimat® inhaler

**You will need to use this inhaler only ONCE A DAY.
Each time you use it take 2 PUFFS.**

 <p>I</p>	<p>I Hold Respimat® inhaler upright, with the grey cap (A) closed, to avoid accidental release of dose. Turn the clear base (G) in the direction of the red arrows on the label until it clicks (half a turn).</p>
 <p>II</p>	<p>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.</p> <p>III Repeat steps I and II so that you get the full dose.</p> <p>You will need to use this inhaler only ONCE A DAY.</p> <p>Close the grey cap until you use your Respimat® inhaler again.</p> <p>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.</p>

When to get a new Respimat® inhaler

	<p>The Respimat® inhaler contains 60 puffs (30 doses). The dose indicator shows approximately how many doses are left. When the pointer enters the red area of the scale, there is, approximately, medication for 14 puffs (7 days) left.</p> <p>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.</p>
---	---

What if...

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

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

10.2 THE ACCUHALER® INHALER

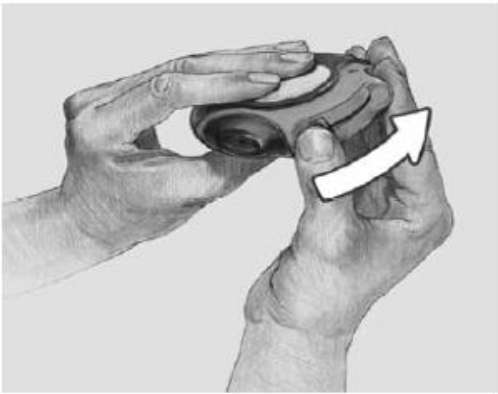

Version 1.0

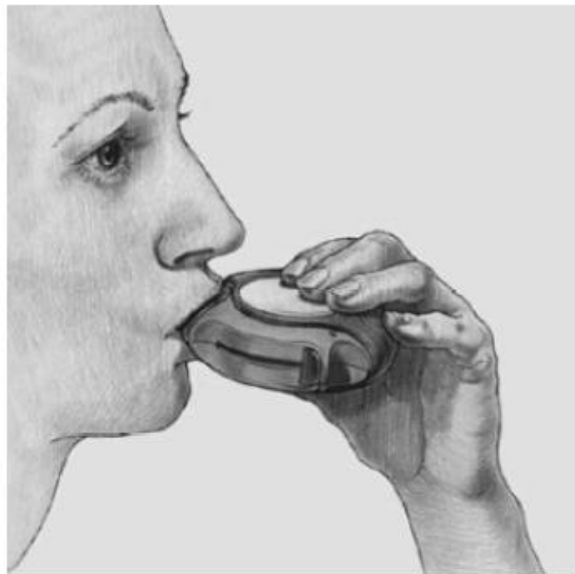
Instructions for use

Instructions for use

1. Your doctor, nurse or pharmacist will show you how to use your inhaler. They will check how you use it from time to time. Not using the Accuhaler® properly or as prescribed may mean that it will not help your COPD as it should.
2. The Accuhaler® device holds blisters containing a powder.
3. There is a counter on top of the Accuhaler® which tells you how many doses are left. It counts down to 0. The numbers 5 to 0 will appear in red to warn you when there are only a few doses left. Once the counter shows 0, your inhaler is empty.

Using your inhaler

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

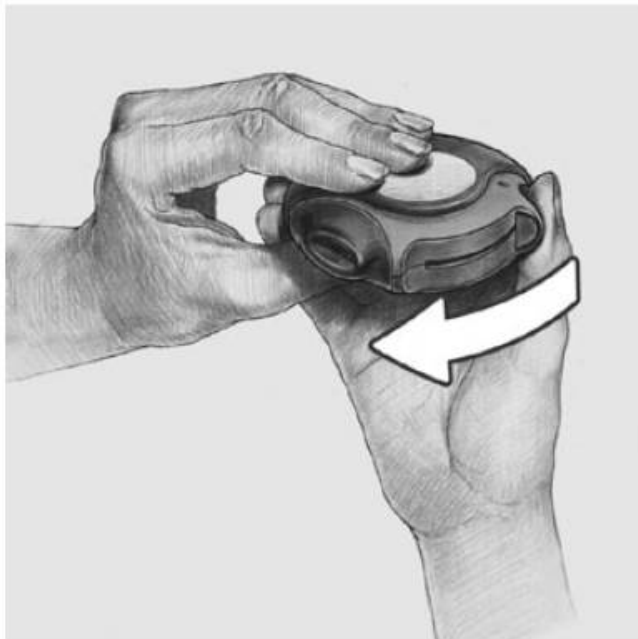


3

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

4

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



5

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

6

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

10.3 ADDITIONAL INFORMATION REGARDING IN/EX CRITERIA

Reversibility and reduction of hyperinflation testing [[P05-12782](#)]

At the screening visit (Visit 1) plethysmography is conducted first to obtain FRC measurement. Spirometry is conducted next and following the completion of three acceptable pre-bronchodilator forced expiratory manoeuvres, salbutamol will be administered to each patient in order to document the degree of reversibility. Immediately after (within 15 min) pre-bronchodilator forced expiratory manoeuvres and after a gentle and incomplete expiration, a dose of 100 µg of salbutamol is inhaled in one breath to total lung capacity (TLC). The breath is then held for 5–10s before the subject exhales. Four separate doses (total dose 400 µg) are delivered at approximately 30-s intervals (this dose ensures that the response is high on the salbutamol dose–response curve).

Post-bronchodilator plethysmography for the assessment of hyperinflation reduction (FRC_{pleth} reversibility) is conducted ≥10 min and up to 20 min later after the last dose of salbutamol (albuterol) is inhaled followed by three additional, acceptable post-bronchodilator forced expiratory manoeuvre tests.

Calculation of FEV₁ predicted normal values according to ECSC [[R94-1408](#)]

Males: $FEV_{1predicted} (L) = 4.30 \times Height (m) - 0.029 \times Age (yrs) - 2.49$

Females: $FEV_{1predicted} (L) = 3.95 \times Height (m) - 0.025 \times Age (yrs) - 2.60$

Ethnic adjustments of FEV₁ predicted may be made as appropriate as per ATS/ERS recommendations [[P05-12646](#), R94-1408].

Calculation of FRC predicted normal values according to ECSC [[R94-1408](#)]

Males: $FRC predicted (L) = 2.34 \times Height (m) + 0.009 \times Age (yrs) - 1.09$

Females: $FRC predicted (L) = 2.24 \times Height (m) + 0.001 \times Age (yrs) - 1.00$

Calculation of RVol predicted normal values according to ECSC [[R94-1408](#)]

Males: $RVol predicted (L) = 1.31 \times Height (m) + 0.022 \times Age (yrs) - 1.23$

Females: $RVol predicted (L) = 1.81 \times Height (m) + 0.016 \times Age (yrs) - 2.00$

Calculation of number of pack years

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

For calculation of Body Surface Area the following (Mosteller) formula should be used [[R06-1245](#)]

$$BSA (m^2) = \left(\frac{Height (cm) \times Weight (kg)}{3600} \right)^{1/2}$$

10.4 MODIFIED MEDICAL RESEARCH COUNCIL DYSPNEA SCALE

Grade	Description of Breathlessness
0	I only get breathless with strenuous exercise.
1	I get short of breath when hurrying on level ground or walking up a slight hill.
2	On level ground, I walk slower than people of the same age because of breathlessness, or have to stop for breath when walking at my own pace.
3	I stop for breath after walking about 100 yards or after a few minutes on level ground.
4	I am too breathless to leave the house or I am breathless when dressing.

10.6 NEW YORK HEART ASSOCIATION (NYHA) FUNCTIONAL CLASSIFICATION

Class	New York Association functional classification
I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea (shortness of breath) or anginal pain
II	Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea or anginal pain
III	Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea or anginal pain
IV	Unable to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency or of the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

Number of global amendment		3
Date of CTP revision		30 Nov 2017
EudraCT number		2015-002641-66
BI Trial number		1237.36
BI Investigational Product(s)		Tiotropium + Olodaterol fixed dose combination inhalation solution (Respimat®)
Title of protocol		An exploratory, randomised, double-blind, double-dummy, active-controlled, two period cross-over study to investigate the effect of 6 weeks treatment of orally inhaled tiotropium + olodaterol fixed dose combination (FDC) delivered by the Respimat® Inhaler with fluticasone propionate + salmeterol FDC delivered by the Accuhaler® Inhaler, on left ventricular function and arterial stiffness in patients with Chronic Obstructive Pulmonary Disease (COPD)
To be implemented only after approval of the IRB / IEC / Competent Authorities		<input type="checkbox"/>
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		<input type="checkbox"/>
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		<input checked="" type="checkbox"/> All changes have already been implemented in the trial conduct in the checklists and worksheets and in other parts of the protocol. The correction of FAS definition for secondary endpoints also is not a change of endpoints and considered rational approach in this exploratory trial.
Section to be changed		1. Abbreviations 2. Section 3.3.3 (Exclusion criteria) 3. Section 4.1.4.2 (Study medication administration) 4. Section 4.2.1 (Other treatments and emergency

		<p>procedures)</p> <p>5. Table 4.2.2.1: 1 (Permitted medications and Medication Restrictions)</p> <p>6. Section 5.1.1 (Primary Endpoint (s))</p> <p>7. Section 5.2 (Assessment of Efficacy)</p> <p>8. Section 6.2.1 (Screening and run-in period (s))</p> <p>9. Section 6.2.1 (Follow Up Period and Trial Completion)</p> <p>10. Section 7.3 (Planned analyses)</p>
Description of change		<p>2. Exclusion criterion 18 modified to match the restrictions Section 4.2.2 (detailed Table 4.2.2.1:1 Permitted medications and Medications Restrictions) and also washout worksheets.</p> <p>3. Use of paper diary removed.</p> <p>4. Time interval of CMR assessment and PFT testing after the use of antibiotics for acute COPD exacerbation treatment was modified.</p> <p>5. Table was corrected for:</p> <p>a. tio+olo was deleted as LAMA mono product.</p> <p>b. LABA mono product (qd) discontinuation corrected to 1 week prior to V1 also when switched from ICS/LABA (qd).</p> <p>c. LABA/LAMA combination discontinuation corrected to 3 weeks prior to baseline CMR and V2.</p> <p>6. Reference to Appendix section for calculation of BSA was corrected.</p> <p>7. Repeatability of FRC measurements requirement was corrected to lest than or equal to 5%.</p> <p>8. Training video replaced with training kit for the demonstration of Accuhaler[®] use.</p> <p>9. Missing text...and documented... entered under AEs procedure at the study site.</p> <p>10. FAS set definition extended to patients with</p>

		baseline and post baseline secondary endpoints.
Rationale for change		<ol style="list-style-type: none">1. Missing information in the Abbreviation list.2. Discrepancy to the detailed restriction Section 4 corrected.3. Medication diary not used in this trial.4. Restriction on assessments within one week of antibiotic use is not feasible due to other logistical requirements.5. Medication restrictions inconsistencies have been corrected.6. Reference corrected and hyperlink updated.7. Sign less than or equal to was corrected as required in guidelines and implemented in study LF calculator.8. Training video for comparator was not feasible for this study so training kits is used for this purpose.9. Missing text deleted in copying was entered.10. FAS definition based on primary endpoints was extended to secondary endpoints not to limit the exploratory analysis unnecessary (not a change in any endpoint).

Number of global amendment		2
Date of CTP revision		11 Jan 2017
EudraCT number		2015-002641-66
BI Trial number		1237.36
BI Investigational Product(s)		Tiotropium + Olodaterol fixed dose combination inhalation solution (Respimat [®])
Title of protocol		An exploratory, randomised, double-blind, double-dummy, active-controlled, two period cross-over study to investigate the effect of 6 weeks treatment of orally inhaled tiotropium + olodaterol fixed dose combination (FDC) delivered by the Respimat [®] Inhaler with fluticasone propionate + salmeterol FDC delivered by the Accuhaler [®] Inhaler, on left ventricular function and arterial stiffness in patients with Chronic Obstructive Pulmonary Disease (COPD)
To be implemented only after approval of the IRB / IEC / Competent Authorities		<input checked="" type="checkbox"/> Written to accommodate the requirements of CA (BfArM) and EC.
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. Synopsis (Main criteria for inclusion) 2. Flow chart footnote 3. Section 3.3 (Selection of trial population) 4. Section 3.3.2 (Inclusion criteria) 5. Section 3.3.3 (Exclusion criteria) 6. Section 4.2.2 (Restrictions) 7. Section 6.1 (Visit schedule) 8. Section 6.2.2 (Treatment period)

Description of change	<ol style="list-style-type: none"> 1. Patient age interval was limited to include patients only up to the age of 75 years (inclusive). 2. In footnote 13 timing of the post dose LF measurement was corrected. 3. Patient age interval was limited to include patients only up to the age of 75 years (inclusive). 4. Inclusion criterion number 2 was updated to include also the requirement that patients should be treated with one or more long-acting bronchodilators prior to enrolment. Inclusion criterion number 4 was updated to include patients only up to the age of 75 years (inclusive). 5. Exclusion criterion number 4 was updated to exclude patients who experience COPD exacerbation or respiratory tract infection during the washout phase prior to randomisation. Exclusion criterion number 28 was updated to exclude also patients with claustrophobia from the study due to contraindication for CMR assessment. 6. In Table 4.2.2.1:1 page 42 ICS/LABA (qd) washout was updated. 7. Updated to contain information that patients with COPD exacerbation or respiratory tract infection in the washout phase prior to randomization should be excluded from further participation in the trial. 8. Timing of the post dose LF measurement was corrected for Visits 3 and 4 to 1,5 hours post dose.
Rationale for change	<ol style="list-style-type: none"> 1. Request of CA and EC to limit the upper age level of participants. 2. Correction to match with the timing in the CTP text. 3. Same as 1. 4. Request of the CA and EC to include patients treated with long-acting bronchodilators and same as 1. 5. Request of CA and EC to exclude patients who

	<p>experience COPD exacerbation or respiratory tract infection during the washout phase prior to randomisation and to exclude patients with claustrophobia due to contraindication for CMR assessment.</p> <p>6. Discontinuation of LABA mono-product for V1 was corrected to match description in 4.2.2.2.</p> <p>7. Request of CA and EC to exclude patients who experience COPD exacerbation or respiratory tract infection during the washout phase prior to randomisation.</p> <p>8 Correction to match with the timing in the CTP text (Synopsis and Secondary endpoints description).</p>
--	--

Number of global amendment		1
Date of CTP revision		09 Dec 2016
EudraCT number		2015-002641-66
BI Trial number		1237.36
BI Investigational Product(s)		Tiotropium + Olodaterol fixed dose combination inhalation solution (Respimat®)
Title of protocol		An exploratory, randomised, double-blind, double-dummy, active-controlled, two period cross-over study to investigate the effect of 6 weeks treatment of orally inhaled tiotropium + olodaterol fixed dose combination (FDC) delivered by the Respimat® Inhaler with fluticasone propionate + salmeterol FDC delivered by the Accuhaler® Inhaler, on left ventricular function and arterial stiffness in patients with Chronic Obstructive Pulmonary Disease (COPD)
To be implemented only after approval of the IRB / IEC / Competent Authorities		<input checked="" type="checkbox"/> Written to accommodate the requirements of CA (BfArM) and EC.
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		<ol style="list-style-type: none"> 1. Flow chart (including footnote) 2. Section 2.3 (Benefit-risk assessment) 3. Section 3.1.1 (Administrative structure of the trial) 4. Section 3.3.3 (Exclusion criteria) 5. Section 4.2.1 (Other treatments and emergency procedures) 6. Table 4.2.2.1:1 (Permitted medications and

		<p>medications restrictions)</p> <p>7. Section 4.2.2.2 (Restrictions for pulmonary function and CMR assessment)</p> <p>8. Section 5.1.2 (Secondary Endpoints)</p> <p>9. Section 5.3.6.3 (COPD Exacerbations)</p> <p>10. Section 6.1 (Visit schedule)</p> <p>11. Section 6.2.1 (Screening and run-in period)</p> <p>12. Section 6.2.3 (Follow Up Period and Trial Completion)</p> <p>13. Section 9.1 (Published references)</p>
Description of change		<p>1. Trial follow-up time window was corrected to be aligned with the requirements in Section 5.3.6.2. Footnote number 11 was updated to clarify the timing of CMR assessments. Footnote number 12 to the flowchart was updated to contain percentage points as a required change of FRC.</p> <p>2. Washout required for baseline CMR and Visit 2. Update of existing CMR benefit-risk information.</p> <p>4. Exclusion criterion number 25 was updated to clarify the duration of highly effective birth control until the follow-up visit at 21 days after the discontinuation of study medication. Tubal occlusion was deleted as permanent sterilisation. An exclusion criterion 28 was added for CMR contraindications.</p> <p>5. Use of antibiotics restricted also prior to CMR assessment as for pulmonary function testing.</p> <p>6. Updated to contain also washout requirement for baseline CMR prior to Visit 2. Updated to contain restriction for strong and moderate inhibitors of CYP3A4 during the trial with additional footnote number 5 to address the restricted medications.</p> <p>7. Updated to contain also washout requirement of LAMAs for baseline CMR prior to Visit 2.</p>

	<p>8. 'Pressure' added for clarity.</p> <p>9. Description of mild COPD exacerbation added to classification.</p> <p>10. Updated to include more instructions on COPD exacerbation and potential withdrawal of the patient.</p> <p>11. IRT call added to Visit 0 to register the patient in screening. Details on planning of CMRs added.</p> <p>12. Laboratory testing deleted from description of visit 5 procedures.</p> <p>13. Updated reference to the new GOLD guideline 2017.</p>
Rationale for change	<p>1. Correction to align with BI standard. Clarification of timing of CMRs and of change in FRC for reversibility.</p> <p>2. Clarification of washout requirement for CMR assessment and risk-benefit in CMR assessment.</p> <p>4. Clarification on duration of contraception as required for this study.</p> <p>5. Clarification of antibiotic restriction prior to CMR assessment.</p> <p>6. Washout requirements for baseline CMR assessment and restriction of CYP3A4inhibitors during this study.</p> <p>7. Washout requirement for CMR assessment.</p> <p>8. Clarification.</p> <p>9. Correction to align with BI standard.</p> <p>10. To avoid prolonging unnecessary suboptimal treatment in screening due to intolerance of washout.</p> <p>11. Corrections and clarifications.</p> <p>12. Deleted to align with CTP text.</p> <p>13. Update of guideline reference.</p>

APPROVAL / SIGNATURE PAGE**Document Number:** c03560350**Technical Version Number:**4.0**Document Name:** clinical-trial-protocol-revision-03

Title: An exploratory, randomised, double-blind, double-dummy, active-controlled, two period cross-over study to investigate the effect of 6 weeks treatment of orally inhaled tiotropium + olodaterol fixed dose combination (FDC) delivered by the Respimat Inhaler with fluticasone propionate + salmeterol FDC delivered by the Acchaler Inhaler, on left ventricular function and arterial stiffness in ...

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Approval-Trial Clinical Monitor		30 Nov 2017 15:12 CET
Approval-Therapeutic Area		30 Nov 2017 16:38 CET
Approval-Team Member Medicine		30 Nov 2017 17:35 CET
Approval-Biostatistics		04 Dec 2017 05:44 CET
Verification-Paper Signature Completion		06 Dec 2017 11:03 CET

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
----------------------	-----------	-------------