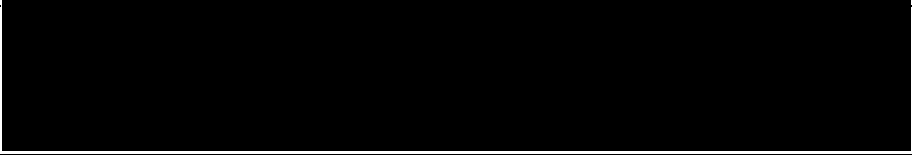


Clinical Trial Protocol

Document Number:		c03207491-01
EudraCT No.:	2015-002974-20	
BI Trial No.:	1237.28	
BI Investigational Product(s):	Tiotropium + olodaterol fixed dose combination solution for inhalation - Respimat [®]	
Title:	A randomised, double-blind, cross-over study to evaluate the effect of 6 weeks treatment of orally inhaled tiotropium + olodaterol fixed dose combination (5/5 µg) compared with tiotropium (5 µg), both delivered by the Respimat [®] Inhaler, on breathlessness during the three minute Constant Speed Shuttle Test (3min CSST) in patients with Chronic Obstructive Pulmonary Disease (COPD) [OTIVATO [™]]	
Brief Title:	Effect of tiotropium + olodaterol on breathlessness in COPD patients.	
Clinical Phase:	IV	
Trial Clinical Monitor:	<div style="background-color: black; width: 100%; height: 40px;"></div>	
	Phone:	Fax:
Coordinating Investigator:	<div style="background-color: black; width: 100%; height: 60px;"></div>	
Status:	Final Protocol	
Version and Date:	Version 1.0	Date: 15 APR 2016
Page 1 of 137		
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CLINICAL TRIAL PROTOCOL SYNOPSIS

Name of company:		Boehringer Ingelheim	
Name of finished product:		Not applicable	
Name of active ingredient:		Tiotropium + olodaterol fixed dose combination solution for inhalation - Respimat®	
Protocol date: 15 APR 2016	Trial number: 1237.28		Revision date:
Title of trial:	A randomised, double-blind, cross-over study to evaluate the effect of 6 weeks treatment of orally inhaled tiotropium + olodaterol fixed dose combination (5/5 µg) compared with tiotropium (5 µg), both delivered by the Respimat® Inhaler, on breathlessness during the three minute Constant Speed Shuttle Test (3min CSST) in patients with Chronic Obstructive Pulmonary Disease (COPD) [OTIVATO™]		
Principal Investigator			
Trial sites:	Multi-centre		
Clinical phase:	IV		
Objectives:	<p>The primary objective of the study is to evaluate the effect of tiotropium + olodaterol FDC compared to tiotropium monotherapy on the intensity of breathlessness during the 3min CSST.</p> <p>A secondary objective is to explore the relationship between reductions in breathlessness during the 3min CSST and reductions in breathlessness during activities of everyday living as measured by the dyspnea domain of the Chronic Respiratory Questionnaire (CRQ) following bronchodilator therapy.</p>		
Methodology:	Randomised, double-blind, active-controlled, cross-over design comparing two treatments after 6 weeks of treatment.		

Name of company:		Boehringer Ingelheim	
Name of finished product:		Not applicable	
Name of active ingredient:		Tiotropium + olodaterol fixed dose combination solution for inhalation - Respimat®	
Protocol date: 15 APR 2016	Trial number: 1237.28		Revision date:
No. of patients:	102		
total entered:	102		
each treatment:	102		
Diagnosis :	Chronic Obstructive Pulmonary Disease (COPD)		
Main criteria for inclusion:	Outpatients of either sex, aged ≥ 40 years and ≤ 75 years with a smoking history > 10 pack years, post-bronchodilator $30\% \leq FEV_1 < 80\%$ predicted, post-bronchodilator $FEV_1 / FVC < 0.70$, BDI < 8 , FRC $> 120\%$ predicted.		
Test products:	Tiotropium + olodaterol fixed dose combination solution for inhalation – Respimat®		
dose:	[5 µg tiotropium + 5 µg olodaterol] once daily		
mode of administration:	Oral inhalation		
Comparator products:	Tiotropium solution for inhalation – Respimat®		
dose:	5 µg once daily		
mode of administration:	Oral inhalation		








Name of company:		Boehringer Ingelheim	
Name of finished product:		Not applicable	
Name of active ingredient:		Tiotropium + olodaterol fixed dose combination solution for inhalation - Respimat®	
Protocol date: 15 APR 2016	Trial number: 1237.28		Revision date:
Duration of treatment:		2 x 6-week treatment periods (total treatment duration of 12 weeks)	
Endpoints		<p>The primary endpoint is the change from baseline in intensity of breathlessness measured using the Modified BORG Scale (MBS-S) at the end of the 3 minute Constant Speed Shuttle Test (3min CSST) after 6 weeks of treatment.</p> <p>Change from baseline is defined as change from patient baseline.</p> <p>Secondary Endpoints include:</p> <p>Change from baseline in Inspiratory Capacity (IC) measured prior to exercise, after 6 weeks of treatment.</p> <p>Change from baseline in IC measured at the end of exercise, after 6 weeks of treatment</p> <p>Change from baseline in 1 hour post-dose FEV₁, after 6 weeks of treatment.</p> <p>Change from baseline in 1 hour post-dose FVC, after 6 weeks of treatment.</p> <p>Change from baseline in intensity of Breathlessness (MBS-S) at 1, 2 and 2.5 min during the 3min CSST after 6 weeks of treatment.</p> <p>Change in CRQ-SAI dyspnea subscale score after 6 weeks of treatment.</p> <p>Change in CRQ-SAS dyspnea subscale score after 6 weeks of treatment.</p> <p>None of the primary or secondary endpoints are safety issues.</p>	
Safety criteria:		Heart rate, blood pressure and SpO ₂ in conjunction with lung function and exercise testing as applicable, adverse events and physical examination.	

Name of company:		Boehringer Ingelheim	
Name of finished product:		Not applicable	
Name of active ingredient:		Tiotropium + olodaterol fixed dose combination solution for inhalation - Respimat®	
Protocol date: 15 APR 2016	Trial number: 1237.28		Revision date:
Statistical methods:	<p>Restricted Maximum Likelihood 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 period baseline as well as patient baseline as covariates. The patient baseline will be obtained by calculating the mean of period baselines for each patient. Compound symmetry will be used as a covariance structure for within patient variation.</p> <p>Descriptive statistics for the safety analyses.</p>		

FLOW CHART

	Screening				Treatment Period ¹			Follow-up
Visit	0	1	2	3	4, 7	5, 8	6, 9 (V9-EOT)	10
Week of treatment	-	-	-	-	0	3	6	V9-EOT + 3 weeks
Day of treatment Time Window (days)	-	-21 to -14	-13 to -9	-8 to -1	1	22 +7	43 + 7	V9-EOT + 21 + 7
Informed consent, patient information	X ²							
Demographics		X						
Baseline Conditions		X						
COPD Characteristics		X						
Smoking status		X			X		X ³	
In-/Exclusion Criteria		X	X	X	X (visit 4 only)			
Physical examination		X					X ³	X ²⁶
Laboratory tests		X					X ³	X ²⁶
Pregnancy testing ⁴		X			X		X ³	X
12-lead ECG ⁵		X					X ³	X ²⁶
Body Plethysmography ⁶ (IC, FRC, TLC)		X						
Screening call (IRT)		X						
Training in use of Respimat [®] inhaler		X			X ⁷			
Randomisation (IRT)					X (visit 4 only)			

	Screening				Treatment Period1			Follow-up
Visit	0	1	2	3	4, 7	5, 8	6, 9 (V9-EOT)	10
Week of treatment	-	-	-	-	0	3	6	V9-EOT + 3 weeks
Day of treatment Time Window (days)	-	-21 to -14	-13 to -9	-8 to -1	1	22 +7	43 + 7	V9-EOT + 21 + 7
Assign and Dispense IMP (IRT)					X			
Dispense rescue medication (as needed)	X ⁸	X	X	X	X	X	X	
Administer trial medication at clinic					X	X	X	
Collect trial medication							X ^{3,9}	
Incremental Shuttle Walk Test (ISWT)		X ¹⁰						
3min Constant Speed Shuttle Test (3min CSST)			X ¹¹	X ¹²	X ¹³	■	X ¹⁴	
Breathing discomfort / ■ (Modified BORG Scale) during 3min CSST ¹⁵			X	X	X	■	X	
Inspiratory Capacity (IC) measurements ¹⁶			X	X	X	■	X	
■			■	■	■	■	■	
■		■		■	■	■	■	

	Screening				Treatment Period1			Follow-up
Visit	0	1	2	3	4, 7	5, 8	6, 9 (V9-EOT)	10
Week of treatment	-	-	-	-	0	3	6	V9-EOT + 3 weeks
Day of treatment Time Window (days)	-	-21 to -14	-13 to -9	-8 to -1	1	22 +7	43 + 7	V9-EOT + 21 + 7
								
Chronic Respiratory Questionnaire (CRQ)- dyspnea domain, self- administered, individualized and standardized					X		X	
Modified Medical Research Council (mMRC) Dyspnea Scale		X						
Baseline Dyspnea Index (BDI)	X ¹⁹							
								
Spirometry (FEV ₁ , FVC)		X ²⁰			X ²¹		X ^{3,22}	
Vital signs (seated) ²³		X			X	X	X ³	
Adverse events		X	X	X	X	X	X ³	X
Concomitant therapy		X	X	X	X	X	X ³	X
Medication wash-out		X	X	X	X	X	X	

	Screening				Treatment Period1			Follow-up
Visit	0	1	2	3	4, 7	5, 8	6, 9 (V9-EOT)	10
Week of treatment	-	-	-	-	0	3	6	V9-EOT + 3 weeks
Day of treatment Time Window (days)	-	-21 to -14	-13 to -9	-8 to -1	1	22 +7	43 + 7	V9-EOT + 21 + 7
Rescue Medication Use		X	X	X	X	X	X ³	
Trial Medication Adherence ²⁴						X	X ³	
Telephone contacts ²⁵		X	X	X	X	X	X	
Trial medication termination							X ³ (call IRT at V9 only)	
Trial completion								X

1. **Treatment Period:** In this cross-over design, each treatment period (period 1, period 2) will follow the same [flow chart](#):
 - procedures during visits 4 and 7 will be identical (except for inclusion/exclusion check, randomisation and BDI at V4 only)
 - procedures during visits 5 and 8 will be identical
 - procedures during visits 6 and 9 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 medication washout and restrictions.
3. **Procedures:** To be completed at the end of each treatment period and / or by all patients who took at least one dose of trial medication including those who discontinue early. PFTs are to be performed if possible.
4. **Pregnancy Testing:** Women of child-bearing potential: serum pregnancy test at visit 1; urine pregnancy test at visits 4, 6, 7, 9, 10.
5. **ECG:** 12-lead ECG recording at screening (visit 1) and end of treatment periods (visits 6 and 9) to be measured pre-dose.
6. **Body Plethysmography:** Conducted prior to dosing with salbutamol for inclusion.
7. **Device Training:** The patient will be instructed in the use of the Respimat® inhaler, but the patient **should not** inhale from the placebo inhaler at these visits.
8. **Rescue Medication:** To be supplied to all patients starting 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 Day 43. All medication is collected after this dosing.

10. Measurements during ISWT:

- BORG measurements conducted at rest, every 2 minutes during exercise and at the end of exercise. Refer to [Appendix 10.5](#) for further details.
- IC to be conducted at rest, every 2 minutes during exercise and at the end of exercise using mobile cardiopulmonary exercise equipment. IC measurements are to be done after the BORG measurements. Refer to [Appendix 10.7](#) and manual of procedures for further details.

11. V2 3min CSST: Speed to be determined at visit 2 by conducting up to three tests at select speeds.

12. V3 3min CSST: Practice test for the 3min CSST at speed selected from V2.

13. 3min CSST timing V4 and V7: 3min CSST conducted prior to dosing (period baseline).

14. 3min CSST timing V5, V6, V8 and V9: 3min CSST conducted 2 hours post-dose (+15 minutes).

15. BORG measurements during 3min CSST: BORG measurements conducted at rest, 1, 2, 2.5 minutes during exercise and at 3min or end of exercise (if 3 minutes not achieved). Refer to Appendix 10.5 for further details.

16. Inspiratory Capacity measurements: IC measurements performed at rest and at end exercise during 3min CSSTs using mobile cardiopulmonary exercise equipment. IC measurements are to be done after the BORG measurements. Refer to Appendix 10.7 and manual of procedures for further details.

19. BDI score: Score <8 is required for inclusion.

20. Reversibility Testing: Pre- and post-bronchodilator FEV₁ and FVC (400 µg salbutamol (albuterol)). [note: reversibility is not an inclusion criterion]

21. Baseline spirometry measurements: Conducted prior to exercise testing.

22. Post-dose FEV₁ and FVC: 1 hr post-dose (±10 minutes) and prior to exercise testing

23. Vital Signs: Immediately prior to PFTs.

24. Medication Use: Measured using the counter on the Respimat® device.

25. Telephone Contacts: Site staff will telephone the patient 1-2 days prior to clinic visits to remind them of medication washout and any other requirements.


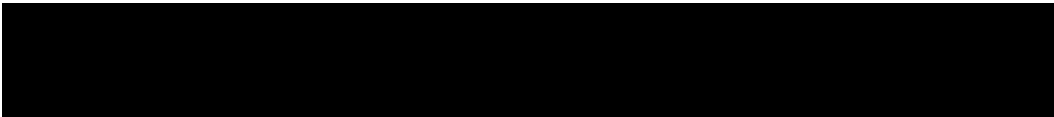
26. To be completed in the event of any clinically relevant findings at the End of Trial (EOT) visit.

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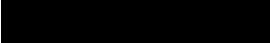
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ABBREVIATIONS

ACCP	American College of Chest Physicians
AE	Adverse Event
AESI	Adverse Event of Special Interest
AMP	Auxiliary Medicinal Products
ATS	American Thoracic Society
AUC	Area under the Curve
β-HCG	Beta-Human Chorionic Gonadotropin
BAC	Benzalkonium Chloride
BDI	Baseline Dyspnea Index
BI	Boehringer Ingelheim
bid	bis in die – twice daily
	
CA	Competent Authority
CI	Confidence Interval
CML	Local Clinical Monitor
COPD	Chronic Obstructive Pulmonary Disease
CPR	Cardiopulmonary Resuscitation
CRA	Clinical Research Associate
CRO	Contract Research Organization
CRQ-SAS	Chronic Respiratory Questionnaire - Self Administered Standardized
CRQ-SAI	Chronic Respiratory Questionnaire - Self Administered Individualized
CSST	Constant Speed Shuttle Test
CTP	Clinical trial Protocol
DOMS	Delayed Onset Muscular Soreness
eCRF	Electronic Case Report Form
ECG	Electrocardiogram
ECSC	European Coal and Steel Community
EDTA	Ethylenediaminetetraacetic acid
EELV	End expiratory lung volume
EOT	End of Trial
ERS	European Respiratory Society
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
Gamma-GT	Gamma-Glutamyl Transpeptidase
GOLD	Global Initiative for Chronic Obstructive Lung Disease

HFA	Hydrofluoroalkane
hrs	Hours
IB	Investigator's Brochure
IC	Inspiratory Capacity
ICH-GCP	International Conference on Harmonization - Good Clinical Practice
ICS	Inhaled corticosteroid
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISF	Investigator Site File
ISWT	Incremental Shuttle Walk Test
LABA	Long Acting β_2 -Agonists
LAMA	Long Acting Muscarinic Antagonists
LDH	Lactate Dehydrogenase
MBS-S	Modified BORG Scale
MCID	Minimum clinically important difference
MDI	Metered Dose Inhaler
MedDRA	Medical Dictionary for Drug Regulatory Activities
Min	Minute
mg	milligram
mMRC	Modified Medical Research Council Dyspnea Scale
mmHg	Millimetres mercury
MMRM	Mixed Effect Repeated Measures Model
MOP	Manual of Procedures
month	Month
PDE-4	Phosphodiesterase Type 4
PFT	Pulmonary Function Test
PRN	Pro re nata – as needed
qd	quaque die (once a day)
RDC	Remote Data Capture
REML	Restricted Maximum Likelihood
REP	Residual effect period
SAE	Serious Adverse Event
SGOT	Serum glutamic-oxaloacetic transaminase
SGPT	Serum glutamic-pyruvic transaminase
SOP	Standard Operating Procedure
SpO ₂	Oxygen saturation
SQ	Sensory Quality
TCM	Trial Clinical Monitor
TLC	Total Lung Capacity

TMF	Trial Master File
TS	Treated Set
TSAP	Trial Statistical Analysis Plan
ULN	Upper Limit Normal
	
wks	Weeks
w.o.	Washout

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.

1.2 DRUG PROFILE

Tiotropium

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

Tiotropium in the dry powder inhaler HandiHaler[®] has been approved in more than 100 countries worldwide. An alternative aqueous formulation for use in the Respimat[®] inhaler (tiotropium 5 μ g QD) is approved in more than 80 countries worldwide including European Union (EU), Japan, United States (US) and Canada. Further information about tiotropium can be found in the respective prescribing information for the product.

Tiotropium + olodaterol combination

Tiotropium + olodaterol FDC is an aqueous solution of tiotropium and olodaterol contained in a cartridge. It is administered by using the Respimat[®] inhaler. The same device is used for tiotropium (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) [[c01735218-03](#)/[c01735249-03](#)] tiotropium + olodaterol FDC showed statistically significant improvements in Forced Expiratory Volume in one 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.

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

For a more detailed description of the drug profile, please refer to the current Investigator's Brochure (IB) which is included in the Investigator Site File (ISF).

2. RATIONALE, OBJECTIVES, AND BENEFIT - RISK ASSESSMENT

2.1 RATIONALE FOR PERFORMING THE TRIAL

Breathlessness upon exertion is the most troublesome symptom reported by COPD patients. Furthermore, reduced breathlessness during exercise as a result of reductions in lung hyperinflation is believed to be the primary mechanistic explanation for increases in exercise endurance time in patients with COPD following treatment with bronchodilators. Previous studies have shown significant reductions in lung hyperinflation (increases in Inspiratory Capacity (IC)) for tiotropium + olodaterol FDC compared with placebo, tiotropium and olodaterol. However, while the improvement in IC with tiotropium + olodaterol FDC compared with placebo was associated with a reduction in breathlessness and an increase in symptom-limited endurance time, this was not the case for the increases in IC for tiotropium + olodaterol FDC compared with the monocomponents [[c02094185-02](#), [c02094318-02](#), [c01735246-02](#)]. Contrasting findings have been observed in the pivotal TONADOTM studies [[c01735218-03](#), [c01735249-03](#)], with significant increases in the Mahler TDI focal score for tiotropium + olodaterol FDC compared with tiotropium and olodaterol, providing evidence of incremental benefit in activity-related breathlessness for the combination over the monotherapies. Therefore, there is a need to better understand the relationship between improvements in lung function and activity-related breathlessness for tiotropium + olodaterol FDC compared to the monocomponents.

Traditional constant work rate exercise tests (e.g. endurance shuttle walking, constant work rate cycle ergometry) are conducted to the point of symptom limitation, which presents challenges regarding the evaluation of symptoms during exercise due to the open-ended nature of these tests. To address this issue, a novel exercise methodology, the 3min CSST, has been developed that allows specific focus on the assessment of activity-related breathlessness (using the MBS-S) at specific pre-defined timepoints in patients with COPD. The feasibility and reproducibility of the 3min CSST in providing a standardized physical stimulus and a measurable level of breathlessness in patients with moderate to severe COPD has been reported [[R15-4319](#)]. In one study, the responsiveness of the 3min CSST to bronchodilation was confirmed, with a statistically significant reduction in the intensity of breathlessness with ipratropium bromide compared to placebo [[P12-12739](#)].

Breathlessness or dyspnea¹ is characterised as “a subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity [and] vary in their

¹ In this protocol, the terms “breathlessness” and “dyspnea” are used interchangeably as the general term to describe the subjective experience of breathing discomfort [[R15-4208](#)]; the specific sensation that patients will be asked to attend to during the 3 min CSST is “breathing discomfort” (see [Appendix 10.5](#)). In the ATS statement on dyspnea, keywords are identified as “breathlessness”, “shortness of breath” and “respiratory sensation”.

unpleasantness and in their emotional and behavioral significance” [1]. There is increasing recognition that dyspnea is a multidimensional experience [R15-4209, R15-4207, R15-4211] and that, while unidimensional scales can capture the overall severity of dyspnea at a particular time-point (current or recalled), they do not capture information about the quality of breathing discomfort, its unpleasantness or the associated emotional responses. The recent development of a conceptual model for dyspnea (figure 1; [R15-4211]) suggests that clinical trials that specifically focus on exertional breathlessness should not limit the evaluation solely to the intensity dimension, but should conduct a comprehensive assessment that also attends to the sensory quality (SQ) and emotional impact of dyspnea in patients with COPD.

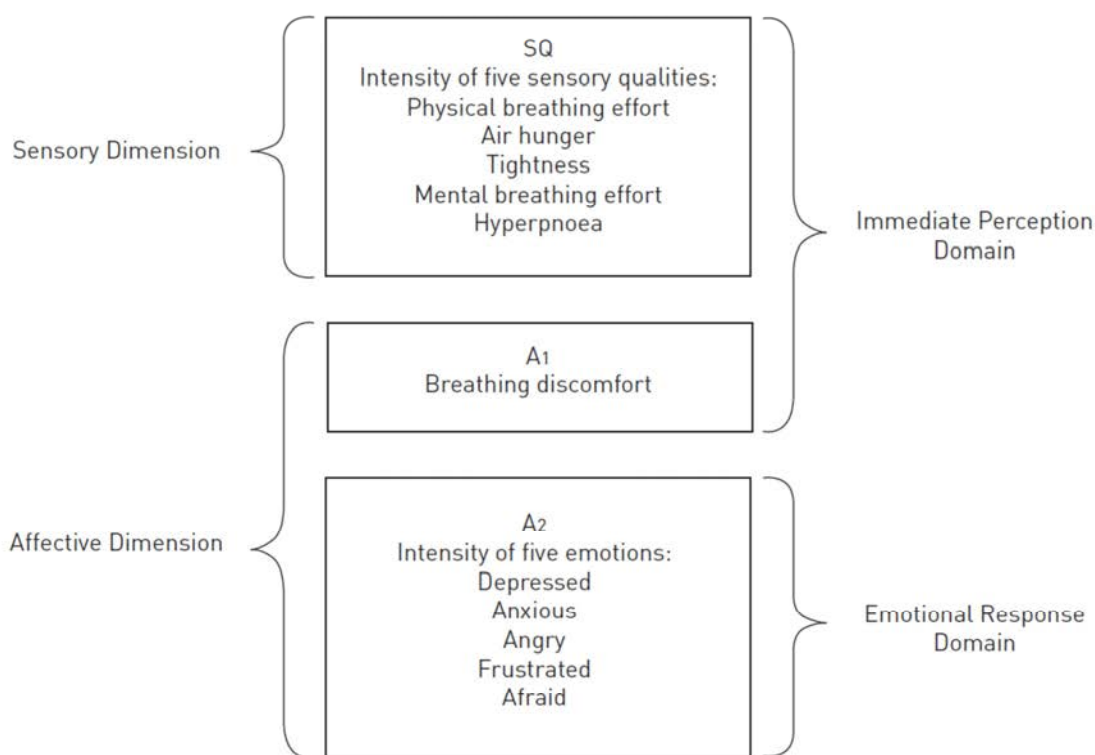


Figure 1 Model of the components of dyspnea underlying the Multidimensional Dyspnea Profile (MDP).

Reproduced from Banzett et al. Multidimensional Dyspnea Profile: an instrument for clinical and laboratory Research. [R15-4210]

2.2 TRIAL OBJECTIVES

The primary objective of the study is to evaluate the effect of tiotropium + olodaterol FDC compared to tiotropium monotherapy on the intensity of breathlessness during the 3min CSST.

A secondary objective is to explore the relationship between reductions in breathlessness during the 3min CSST and reductions in breathlessness during activities of everyday living as measured by the dyspnea domain of the Chronic Respiratory Questionnaire (CRQ) following bronchodilator therapy.

2.3 BENEFIT - RISK ASSESSMENT

The clinical trials conducted to date have shown tiotropium + olodaterol 5/5 µg 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 5/5 µg compared to the individual components translated into benefits that were meaningful to the patient, with improvements in several patient centred outcomes. As such, tiotropium + olodaterol 5/5 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, including Canada. At the time of the final protocol for 1237.28, marketing authorization has been granted in Belgium, Canada, Germany, Netherlands, as well as the US and several other countries.

Potential risks associated with exercise testing will be avoided by implementing standard monitoring procedures under appropriate supervision [[R13-2820](#), [R13-4694](#)].

The trial design requires that all eligible patients complete a 3 to 4 week screening period in which LABAs and LAMAs are withdrawn prior to randomisation. At the investigator's discretion, ipratropium may be provided to patients who are required to wash out LAMA during the washout period prior to randomisation and during the washout period prior to visit 7; Boehringer Ingelheim (BI) will provide open-label salbutamol (albuterol) as needed (PRN) rescue medication for all patients who have signed Informed Consent.

All patients will receive active treatment with either tiotropium + olodaterol FDC (5 µg / 5 µg) or tiotropium (5 µg) inhalation solution (control group) during the treatment periods. There is no placebo comparator in this trial.

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

The proposed medication restriction scheme is considered ethically acceptable given the availability of ipratropium metered dose inhaler (MDI) during the wash-out periods, salbutamol (albuterol) as rescue medication and permitted use of ICS during the treatment period.

Safety will be monitored (as described in [section 5.2](#)) at site visits and withdrawal criteria are provided for investigators' consideration (as listed in [section 3.3.4.1](#)).

According to the prescribing information for Spiolto[®] (Stiolto[®] in US, Inspiolto[®] in Canada), 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 (5/5 µg) FDC provided appropriate precautions are taken to minimize the risk of pregnancy. These precautions include pregnancy testing and use of a highly effective method of birth control. Continued testing and monitoring during the trial should be sufficient to ensure compliance with the measures not to become pregnant during the period of drug exposure (which may exceed the length of study until the follow-up visit at 21 days after discontinuation of study medication) [[R05-0370](#)].

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

This is a multi-centre, multi-national, randomised, double-blind, active-controlled, two-period cross-over, Phase IV study to evaluate the effects of once daily administration of orally inhaled tiotropium + olodaterol FDC (5 / 5 µg) (delivered by the Respimat® Inhaler) compared with tiotropium (5 µg) (delivered by the Respimat® Inhaler) on the intensity of breathlessness in patients with Chronic Obstructive Pulmonary Disease (COPD).

The trial consists of a run-in period, two 6-week treatment periods, each separated by a 3-week wash-out period and a follow-up period.

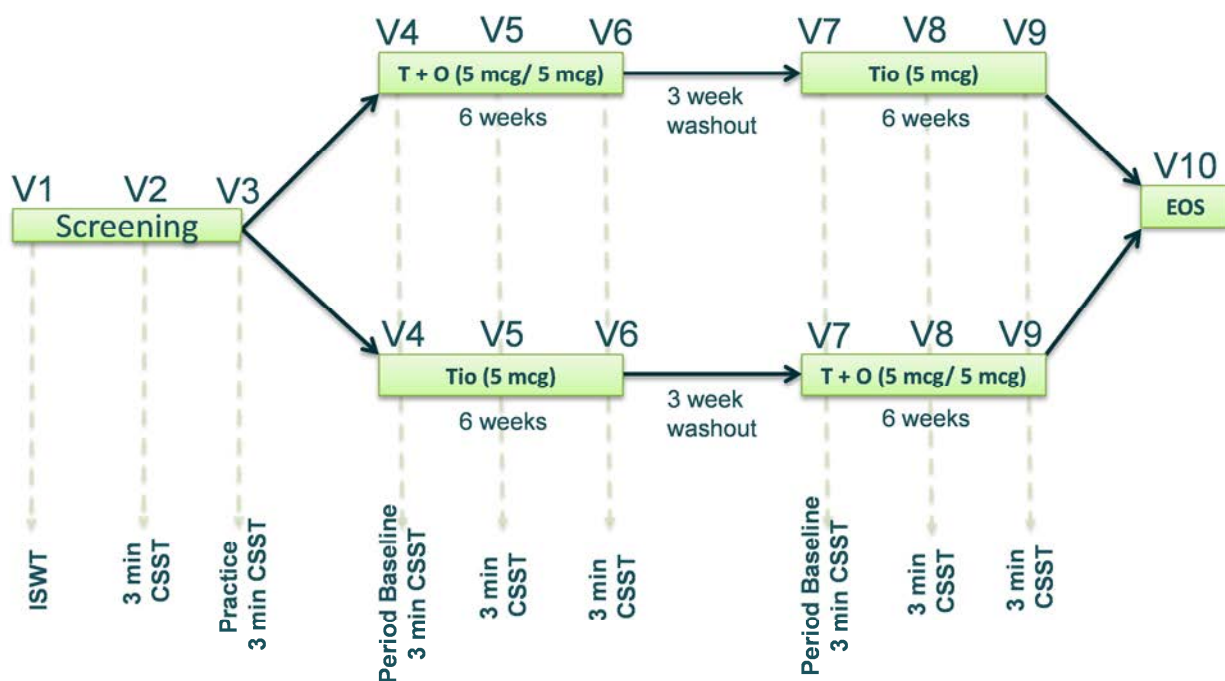


Figure 3.1:1. Overview of the trial design

After signing Informed Consent and completing an initial screening visit (visit 1), patients will enter a 3 to 4-week run-in period to ensure clinical stability (i.e. no exacerbations). During this screening period, they will conduct an Incremental Shuttle Walk Test (ISWT) at visit 1, up to three x 3min CSSTs to establish the shuttle test speed at visit 2 and a practice 3min CSST at visit 3.

Patients who meet all the inclusion criteria and none of the exclusion criteria will be randomised at visit 4 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 treatment sequences with the treatment codes as follows:

- A. tiotropium + olodaterol (5 / 5 µg) FDC inhalation solution, delivered once daily via the Respimat[®]
- B. tiotropium (5 µg) inhalation solution, delivered once daily via the Respimat[®]

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.

IRT will also be set-up to ensure that the number of GOLD Stage II patients is capped at approximately 50% and the number of GOLD Stage III patients is capped at approximately 50%. This will allow a better representation of the different stages of pulmonary impairment in the trial.

The patient's GOLD stage will be entered in IRT at the screening call that should take place at visit 1. The following classification of severity of airflow limitation should be used to determine the GOLD stage of the patient [[P11-05865](#)]:

GOLD Stage	Severity of Disease	Degree of airflow limitation (FEV ₁)
GOLD 2	Moderate	$50\% \leq \text{FEV}_1 < 80\%$
GOLD 3	Severe	$30\% \leq \text{FEV}_1 < 50\%$

Additional clinic visits will be scheduled after 3 and 6 weeks of treatment (visits 5 and 6 respectively). The first treatment period will be followed by a 3-week wash-out period and then the second treatment period will commence (visits 7-9). Patients will be evaluated for an additional 21 days following completion of the last 6-week treatment period, or, in case of early discontinuation, after the final dose of study medication. 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](#).

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

3.1.1 Administrative structure of the trial

The trial is sponsored by Boehringer Ingelheim (BI)

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

The organisation of the trial in the participating countries will be performed by the respective local or regional BI-organisation (Operating Unit, OPU) in accordance with applicable regulations and internal SOPs, or by a Contract Research Organisation (CRO) with which the responsibilities and tasks will have been agreed and a written contract filed before initiation of the clinical trial.

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 the ISF.

Targeted group of Investigators: Pulmonologists/qualified sites with experience in conducting studies involving exercise in patients with COPD and access to the desired patient population.

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

- scale and sphygmomanometer,
- a spirometer which meets ATS Criteria [[P05-12782](#)],
- a portable pulse oximeter for use during exercise testing,
- body plethysmograph,
- a standard 12-lead electrocardiogram (ECG),
- access to local lab facility for safety testing.

Staff training on exercise procedures: Given the importance to perform the shuttle test in a harmonised and standardised way in all participating countries and centers, a global exercise trainer has been contracted to advise the sponsor and trial team and assure that local training will be performed in a standardised way.

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

IRT: An IRT vendor will be used in this trial for randomisation to a treatment group 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 the ISF.

Mobile cardiopulmonary exercise equipment: Will be leased by the sponsor for all sites for the duration of the trial. The provision of this equipment will be handled by BI and an external vendor.

All contracts and relevant meeting minutes will be stored by BI in the TMF.

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

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 minimising 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 tiotropium + olodaterol FDC at pharmacodynamic steady state (based on results from previous studies evaluating the effects of tiotropium + olodaterol FDC on spirometric parameters).

The restriction of long-acting β_2 -agonist and a long-acting anti-cholinergic during the run-in period is necessary to determine the appropriate speed for the 3min CSST, perform the practice 3min CSST, and measures of breathlessness.

During the run-in and treatment periods, patients will continue to receive treatment with ICS as required. Short-acting β_2 -agonist medication (salbutamol / albuterol) will be provided to all patients for rescue use, and appropriate medications will be allowed to control acute exacerbations as medically necessary. Ipratropium may be provided to patients who are required to wash out of LAMAs during the run-in and washout periods.

Eligible patients may be randomised to a treatment arm that includes both a LABA(olodaterol) and a LAMA (tiotropium), therefore it is necessary to restrict the use of LABAs (e.g. salmeterol,

formoterol, indacaterol, olodaterol) and anti-cholinergics (e.g. tiotropium, ipratropium) during the treatment period.

The inclusion of the tiotropium 5 µg monotherapy treatment arm allows for an appropriate comparison of the combination product to the commonly used individual product to determine the additional effect of adding LABA to an anticholinergic on breathlessness.

3.3 SELECTION OF TRIAL POPULATION

A sufficient number of patients will be enrolled (sign informed consent) at approximately 15 sites to ensure that a minimum of 102 patients of either sex, 40 to 75 years of age, with a diagnosis of COPD are randomised into the study.

Enrolment will be competitive. Additional sites may be initiated and 'non-productive' sites may be closed to ensure sponsor's timelines. The distribution of patients between countries will be dependent on the access to the suitable patient population as well as the operational feasibility of performing the trial in the country. It is anticipated that each site will enrol an average of approximately 8 patients.

Patients will be required to perform shuttle tests on several occasions during the trial. For this reason, patients with any contraindication to exercise as stipulated in the ERS guidelines [[R98-0973](#)], and supported by the ATS/American College of Chest Physician (ACCP) guidelines [[P03-01262](#)] 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 moderate to severe pulmonary impairment (according to GOLD guidelines [[P11-05865](#)]), including hyperinflation at rest during screening and a reported degree of breathlessness are eligible for inclusion if they fulfill 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 International Conference on Harmonisation - Good Clinical Practice (ICH-GCP) guidelines prior to participation in the trial, which includes medication washout and restrictions.
2. All patients must have a diagnosis of COPD [[P11-05865](#)] and must meet the following spirometric criteria:

Patients must have relatively stable airway obstruction with a post-bronchodilator $30\% \leq FEV_1 < 80\%$ of predicted normal (European Coal and Steel Community (ECSC), [[R94-1408](#)] see [Appendix 10.3](#) for ECSC predicted normal equations); GOLD 2 - 3, [[P11-05865](#)] and a post-bronchodilator $FEV_1/FVC < 0.70$ at visit 1.

3. Male or female patients, between 40 and 75 years of age (inclusive) on day of signing informed consent.
4. Patients must be current or ex-smokers with a smoking history of more than 10 pack-years (see [Appendix 10.3](#) for calculations). Patients who have never smoked cigarettes must be excluded.
5. Patients with a score on the Baseline Dyspnea Index (BDI) < 8 at visit 0.
6. Patients with hyperinflation at rest, defined as Functional Residual Capacity (FRC) $> 120\%$ predicted at visit 1 (see [Appendix 10.7](#)).
7. BORG dyspnea score ≥ 4 at the end of 3min CSST at visit 2 (refer to [Appendix 10.4.2.2](#) and manual of procedures for further details).
8. Patients must be able to perform technically acceptable pulmonary function tests (PFTs) (spirometry and body plethysmography), must be able to complete multiple shuttle tests during the study period as required in the protocol.
9. Patients must be able to inhale medication in a competent manner from the Respimat[®] inhaler ([Appendix 10.1](#)) 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 haematology, blood chemistry, or creatinine >x2 Upper Limit Normal (ULN) will be excluded regardless of clinical condition (a repeat laboratory evaluation can be conducted if deemed necessary by the investigator).
3. Patients with a current documented diagnosis of asthma. For patients with allergic rhinitis or atopy, source documentation is required to verify that the patient does not have asthma.
4. Patients with a COPD exacerbation in the 6 weeks prior to screening (visit 1).

Patients with any of the following conditions:

5. A diagnosis of thyrotoxicosis (due to the known class side effect profile of β_2 -agonists).
6. A history of myocardial infarction within 6 months of screening visit (visit 1).
7. Life-threatening cardiac arrhythmia as judged by the investigator.
8. Known active tuberculosis.
9. Any malignancy unless free of disease for at least 5 years (patients with treated basal cell carcinoma or squamous cell skin cancers are allowed).
10. A history of cystic fibrosis.
11. Clinically relevant bronchiectasis, as judged by the investigator.
12. Patients with severe emphysema requiring endobronchial interventions within 6 months prior to screening.
13. A history of significant alcohol or drug abuse, as judged by the investigator.
14. Any contraindications for exercise testing as outlined below ([see section 3.3.3.1](#) below "Contraindications to exercise").
15. Patients who have undergone thoracotomy with pulmonary resection (patients with a history of thoracotomy for other reasons should be evaluated as per exclusion criterion No. 1).
16. Patients being treated with any oral or patch β -adrenergics.
17. Patients being treated with oral corticosteroid medication at unstable doses (i.e., less than four weeks on a stable dose prior to visit 1) or at doses in excess of the equivalent of 10 mg of prednisone per day or 20 mg every other day.

18. Patients being treated with antibiotics for any reason (not limited to exacerbation infection) within 4 weeks of screening visit (visit 1).
 19. Patients being treated with PDE4 inhibitors within 3 months of screening visit 1 (e.g. roflumilast) should not be enrolled and PDE4 inhibitors should not be withdrawn for the purpose of enrolling in this study.
 20. Patients who regularly use daytime oxygen therapy for more than one hour per day and in the investigator's opinion will be unable to abstain from the use of oxygen therapy during clinic visits.
 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 a limitation of exercise performance as a result of factors other than fatigue or exertional dyspnea, such as arthritis in the leg, angina pectoris or claudication or morbid obesity.
 23. Patients with an endurance time ≥ 12 minutes during the ISWT (visit 1).
 24. Patients with oxygen saturation $SpO_2 < 85\%$ (on room air) at rest or during exercise (no CSST will be conducted with supplemental oxygen).
 25. Patients who have taken an investigational drug within one month or six half-lives (whichever is greater) or in case the investigational drug (sub) class is listed within the washout period specified in [table 4.2.2.1](#) prior to screening visit (visit 1).
 26. Patients with known hypersensitivity to β -adrenergics and/or anticholinergic drugs, Benzalkonium Chloride (BAC), Ethylenediaminetetraacetic acid (EDTA) or any other component of the Respimat® inhalation solution.
 27. Women who are pregnant, nursing, or who plan to become pregnant while in the trial.
 28. Women of childbearing potential not using a highly effective method of birth control.*
Female patients will be considered to be of childbearing potential unless surgically sterilised by hysterectomy or bilateral tubal ligation, or post-menopausal for at least two years.
- *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.
29. Patients who have previously been randomised in this study or are currently participating in another study.

30. Patients who are unable to comply with pulmonary medication restrictions prior to randomisation.

3.3.3.1 Contraindications to exercise

Patients are not allowed to perform an exercise challenge if they are known to have or are suspected of having one of the following contraindications to exercise [[R98-0973](#)]:

- unstable angina,
- uncontrolled arrhythmias causing symptoms or haemodynamic compromise,
- active endocarditis,
- acute myocarditis or pericarditis,
- symptomatic severe aortic stenosis,
- uncontrolled heart failure,
- acute non-cardiac disorder that may affect exercise performance or be aggravated by exercise (i.e., infection, renal failure, thyrotoxicosis),
- thrombosis of lower extremities,
- left main coronary stenosis or its equivalent,
- moderate stenotic valvular heart disease,
- electrolyte abnormalities,
- severe untreated arterial hypertension (>200 mmHg systolic, >120 mmHg diastolic),
- significant pulmonary hypertension,
- tachyarrhythmias or bradyarrhythmias,
- hypertrophic cardiomyopathy,
- mental impairment leading to inability to cooperate,
- high-degree atrioventricular block.

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, AEs, 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 on pregnancy and the outcome of pregnancy, please see [section 5.3.7](#).

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

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

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

Given the patient's agreement, 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. AEs) must be recorded in the electronic case report form (eCRF). These data will be included in the trial database and reported.

3.3.4.2 Discontinuation of the trial by the sponsor

BI 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 ICH-GCP, the Clinical Trial Protocol (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 TREATMENTS TO BE ADMINISTERED

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

Patients will receive of the following treatments in random order:

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

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

4.1.1 Identity of BI investigational products and comparator products

Table 4.1.1: 1 Test products

Substance:	Tiotropium + 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: 1 Test products (cont'd)

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

4.1.2 Method of assigning patients to treatment groups

During visit 4 and after the patient's eligibility has been confirmed, the treatment sequence will be assigned via a third party phone/web-based system. This will involve the use of an IRT system which will implement a randomisation scheme generated using a validated system. Access to the codes will be controlled and documented. All necessary instructions for using the IRT system will be described in a user guide/manual, a copy of which will be available in the ISF.

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

4.1.3 Selection of doses in the trial

The clinical trials conducted during the Phase III program for tiotropium + olodaterol FDC 5/5 µg have shown that this dose is a safe, well tolerated and efficacious combination therapy. The observed incremental bronchodilator response for the combination compared to the individual components translated into benefits that were meaningful to the patient, with improvements in several patient centred outcomes.

At the time of the final protocol for 1237.28, tiotropium + olodaterol FDC (5/5 µg) delivered by the Respimat[®] Inhaler has been approved in Belgium, Canada, Germany, Netherlands, as well as

the US and several other countries. Therefore the marketed dose is considered to be the appropriate dose to be studied in this trial.

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

4.1.4 Drug assignment and administration of doses for each patient

Trial medication will be dispensed to the patient by the investigator/pharmacist or designee. At visit 4 eligible patients will be randomised to one of two double-blinded treatment sequences (1:1 ratio) by the IRT. At visits 4 and 7, the IRT will assign 3 Respimat[®] treatment boxes to each patient. Each Respimat[®] treatment box consists of a Respimat[®] inhaler and a cartridge and will have a unique medication number with 6 digits.

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

Site personnel will enter all medication numbers dispensed to each patient in the Medication Record page of the eCRF.

4.1.4.1 Priming of the Respimat[®] inhaler

Each newly assembled Respimat[®] inhaler has to be primed when appropriate. The Respimat[®] inhaler should be primed by actuating it until an aerosol is visible plus three additional actuations. All priming actuations should be directed to the ground and priming should NOT take place in the same room where the patient is inhaling trial medication.

Once assembled, the shelf-life of the Respimat[®] inhaler with study medication or training medication (placebo) is 3 months. Therefore it is important to ALWAYS enter the date of the cartridge insertion on the medication label of the Respimat[®] inhaler immediately after the cartridge is inserted.

For detailed priming instructions please refer to the Respimat[®] inhaler handling instructions in [Appendix 10.1](#)

4.1.4.2 Study medication administration

At visit 4 the study medication will be self-administered between 7:00 a.m. and 10:00 a.m. At subsequent clinic visits, study medication will be self-administered preferably within ± 30 minutes of time of administration at visit 4 AND between 7:00 a.m. and 10:00 a.m. The clock time of the start of inhalation of study medication will be captured on the source documents and in the eCRF.

The utmost care should be taken to ensure that during the treatment period, the study medication is not taken prior to coming to the site for a visit.

At visits 6 and 9 (last visit of each treatment period), the Respimat[®] Inhaler that is in current use, must be used for administration of the study medication at that visit since no new Respimat[®] treatment box will be assigned.

When planning the time of the morning dose of study medication at visit 4, site personnel should discuss with the patient about the preferred regular time of day that the patient will be taking the morning dose of study medication at home.

Study medication administration at clinic visits

Dispensation and Respimat[®] inhaler assembling

Trial medication will be dispensed at visits 4 and 7. 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.

Drug administration

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

Respimat[®] inhalers return

At visits 6 and 9 all used and unused Respimat[®] inhalers will be returned to the clinic by the patient. The reserve Respimat[®] inhaler should also be returned at each clinic visit to be replaced if it has been used or primed.

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

Study medication administration at home

Each morning, oral inhalation of two puffs on the study medication from the assigned Respimat[®] inhaler will be self-administered by the patient. Patients should be encouraged to take their study

medication at approximately the same time in the morning (morning dose window until noon). If a patient misses the daily dose he/she should take the next dose the day after. The patient must assemble and prime the Respimat[®] inhaler at home once the current used Respimat[®] inhaler is empty and the device is locked.

4.1.4.3 Inhaler devices training

SPECIAL CONSIDERATION:

Most severe to very severe COPD patients are currently using different inhalation medications at the same time. This may cause technical challenges and affect their treatment adherence.

Respimat[®]

Training on the use of the Respimat[®] inhaler will be provided to patients.

- At visit 1: The first patient's training session will be performed with the intention to familiarise the patient with the Respimat[®] inhaler training medication (placebo). Detailed written instructions for the use of the Respimat[®] inhaler will also be given. (See [Appendix 10.1](#)).
- At visit 4: After randomisation, the patient's training session will be performed from the new assigned Respimat[®] inhaler. Instructions on how to assemble and prime the Respimat[®] inhaler at home should also be reviewed.
- At visit 7: Observance of the inhalation procedure will occur. The correct inhalation technique should be reinforced in case of inadequate use of Respimat[®] inhaler. It is also important to remind the patient on how to assemble and prime the Respimat[®] inhaler at home.

Rescue medication

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

4.1.4.4 Respimat[®] malfunctioning

Any Respimat[®] inhaler that has been reported as malfunctioning by a patient or investigator will be returned to BI for investigation. See the ISF for specific instructions and for details regarding drug accountability requirements. Details of the procedure for the return of malfunctioning inhalers are provided in [Appendix 10.2](#).

4.1.5 Blinding and procedures for unblinding

4.1.5.1 Blinding

Patients, investigators and everyone involved in 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.

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 eCRF page along with the date and the initials of the person who broke the code. Patients unblinded to treatment will be withdrawn from the trial.

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

4.1.6 Packaging, labelling, and re-supply

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

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

Open-label supplies = Auxiliary Medicinal Products (AMPs)

- Training Respimat[®] inhaler, placebo cartridges and disposable mouthpieces for training purposes. A training device may be used for multiple training sessions. The training Respimat[®] inhaler can be used until 3 months after first insertion of the cartridge or until the device is empty. The date of the cartridge insertion should be entered on the medication label of the Respimat[®] inhaler immediately after the cartridge is inserted. A new mouthpiece should be used for each patient.

- Salbutamol (albuterol*) HFA MDI inhalation aerosol (100µg per actuation) for use during reversibility testing at V1 and as rescue medication during screening, treatment and follow-up periods. The rescue medication will be provided locally by BI.
- Ipratropium bromide to be dispensed at the discretion of the investigator. For use by patients on LAMAs during the screening period and during the wash-out period between the treatment periods. This medication will be provided locally by BI.

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

Blinded study medication= Investigational Medicinal Product (IMP)

- Packaging: the Respimat[®] treatment box will contain one Respimat[®] inhaler plus one drug-filled cartridge and contains sufficient medication for 30 days of treatment. The Respimat[®] inhaler will lock after 60 actuations have been administered and will no longer actuate any medication.
- Labelling: individual Respimat[®] treatment box will have a study specific booklet with a two-part tear-off label (including one extra portion). One part of each tear-off label should be attached to the drug accountability form which will be part of the ISF.

The investigator or designee should fill out the following information:

- Date of cartridge insertion should be entered at time of cartridge insertion on the inside page of the booklet on the Respimat[®] Inhaler.
- Investigator's name should be entered at time of dispense on the inside page of the booklet on the Respimat[®] treatment box.

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

Re-supply

Each site will receive a first supply at or after the initiation visit and resupply will be managed via an IRT system which will also monitor expiry dates of supplies available at the sites.

4.1.7 Storage conditions

Drug supplies will be kept in their original packaging and in a secure limited access storage area according to the recommended storage conditions on the medication label.

The Respimat[®] inhaler and cartridges and training kits should be stored as indicated on the country specific booklet page. A temperature log must be maintained at the site to make certain that the drug supplies are stored at the correct temperature. If the storage conditions are found to be outside the specified range, the CML (as provided in the list of contacts) must be contacted immediately.

Further details are provided in the IB (tiotropium + olodaterol), prescribing information (tiotropium) and on the country-specific labels, a sample of which will be part of the ISF.

4.1.8 Drug accountability

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

- Approval of the trial protocol by the institutional review board (IRB) / independent ethics committee (IEC).
- 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 (CA).
- Availability of the curriculum vitae of the principal investigator.
- Availability of a signed and dated CTP.
- Where applicable: availability of the proof of a medical license for the principal investigator.
- For USA availability of Form 1572.

The investigator / pharmacist / investigational drug storage manager must maintain records of the product's delivery to the trial site, the inventory at the site, the use by each patient, and the return to the Sponsor or warehouse / drug distribution centre or alternative disposal of used or unused products. If applicable, the sponsor or warehouse / drug distribution centre will maintain records of the disposal.

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

- dates (dispense and return),
- dispenser's initials,
- quantities,
- batch / serial numbers,
- expiry ('use- by') dates,
- the unique Respimat[®] treatment box number assigned by IRT,
- The trial patient number assigned by the RDC system.

For the rescue medication and ipratropium bromide, accountability form will be provided to the trial site. This record will include:

- dates (dispense and return),
- dispenser's initials,
- quantities,
- batch/serial numbers,

- expiry date,
- the trial patient number assigned by the RDC system.

The patient will be asked to return all used/unused rescue medication inhalers at each clinic visit. Patients will be asked to return all used/unused ipratropium bromide at the end of screening and washout periods. Source data documentation and full drug accountability in regard to dispensed and returned medication to investigational site and to patients are required. Only used inhalers will be replaced at each clinic visit. For further details, please refer to section 4.2.1 (Rescue medication).

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[®] inhaler.

4.2 CONCOMITANT THERAPY, RESTRICTIONS, AND RESCUE TREATMENT

4.2.1 Rescue medication, emergency procedures, and additional treatments

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 (100 µg per puff) will be provided as rescue medication by BI; only the salbutamol / albuterol MDI provided by BI is allowed for rescue medication use. If the patient requires rescue medication during the PFT days (visits 4 - 9), the PFTs will be discontinued. The exercise testing should be rescheduled if possible. The medication used, route and 24-hour clock time of administration will be recorded on the Rescue Medication eCRF page.

There are no special emergency procedures to be followed.

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

- Salbutamol inhalation aerosol from MDI for PRN use provided by BI.
- Temporary increases in the dose or addition of oral steroids are allowed during the treatment portion of the study. Pulmonary function testing should not occur within seven days of the last administered dose of an increase or addition of oral steroids. 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. Pulmonary function testing should not occur within seven days of the last dose. 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, the testing will be postponed for at least two days but not more than seven days after the last dose is given. Subsequent visits will be scheduled according to the patient's regular schedule.

4.2.2 Restrictions

Table 4.2.2:1 Restrictions regarding concomitant treatment

Drug Class	Sub-class	Prior to study	Study Period			
			Screening Period	Treatment Period	Wash-out Period	Follow up Period
Corticosteroids	Inhaled corticosteroids (stabilized 4 wks prior to V1)	Permitted ^{1&5}	Permitted ^{1&5}	Permitted ^{1&5}	Permitted ^{1&5}	Permitted ^{1&5}
	Oral corticosteroids [≤10 mg prednisone per day or ≤20 mg prednisone every other day (or equivalent); stabilized 4 wks prior to V1]	Permitted	Permitted	Permitted	Permitted	Permitted
	Injected Corticosteroids – local administration (for treatment of e.g. bursitis)	Permitted	Permitted	Permitted	Permitted	Permitted
	Nasal Corticosteroid sprays	Permitted ⁵	Permitted ⁵	Permitted ⁵	Permitted ⁵	Permitted ⁵
β-adrenergics	Inhaled short-acting β- adrenergics	Permitted ¹	Rescue 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	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 V4)	NOT permitted	NOT permitted	Permitted

Drug Class	Sub-class	Prior to study	Study Period			
			Screening Period	Treatment Period	Wash-out Period	Follow up Period
	Oral and patch beta-adrenergics	NOT permitted⁶	NOT permitted	NOT permitted	NOT permitted	NOT permitted
	Beta blockers (stabilized 6 wks prior to V1)	Permitted	Permitted	Permitted	Permitted	Permitted
Anti-cholinergics	Short-acting anticholinergics (inhalation aerosol, nasal spray)	Permitted ¹	Permitted ¹ (w.o. 8 hrs prior to V2, V3, V4)	NOT permitted	Permitted ¹ (w.o. 8 hrs prior to V7)	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 V4)	Study medication	NOT permitted	Permitted
Combinations	ICS/LABA (bid) (* switch to ICS mono-product, at the same or equivalent dose, at least 48 hrs prior to V1)	Permitted ¹	NOT permitted*	NOT permitted	NOT permitted	Permitted
	ICS/LABA (qd) (*switch to ICS mono-product, at the same or equivalent dose, at least 1 wk prior to V1) (e.g. fluticasone +vilanterol)	Permitted	NOT permitted*	NOT permitted	NOT permitted	Permitted
	ICS/SABA (* switch to ICS mono-product, at the same or equivalent dose, at least 8 hrs prior to V1)	Permitted ¹	NOT permitted*	NOT permitted	NOT permitted	Permitted
	short-acting anticholinergic/ SABA (* 8 hrs prior to V1)	Permitted ¹	NOT permitted*	NOT permitted	NOT permitted	Permitted

Drug Class	Sub-class	Prior to study	Study Period			
			Screening Period	Treatment Period	Wash-out Period	Follow up Period
	Long-acting anticholinergics/long-acting β-adrenergics² (e.g. glycopyrronium+indacaterol, umeclidinium+vilanterol)	Permitted (w.o. 1 week prior to V1)	NOT permitted (w.o. 3 wks prior to V4)	Study medication	NOT permitted	Permitted
Antibiotics	For respiratory infections The use of antibiotics is not restricted and may be prescribed as medically necessary for COPD exacerbation episodes and / or infections.	Permitted (w.o. 4 wks prior to V1)	Permitted (except antibiotics for prevention of exacerbation of COPD)			
	Any other infections	Permitted (w.o. 4 wks prior to V1)	Permitted	Permitted	Permitted	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	NOT permitted
	Cromolyn sodium / nedocromil sodium⁵	Permitted	Permitted	Permitted	Permitted	Permitted
	Antihistamines (including nasal route), antileukotrienes⁵	Permitted	Permitted	Permitted	Permitted	Permitted
	Methylxanthines⁵	Permitted ³	Permitted ³	Permitted ³	Permitted ³	Permitted ³
	Mucolytics (not containing bronchodilators; stabilized 4 wks prior to V1)	Permitted	Permitted	Permitted	Permitted	Permitted
	Mucolytics containing bronchodilators	NOT permitted⁶	NOT permitted	NOT permitted	NOT permitted	NOT permitted
	Phosphodiesterase type 4 (PDE4) inhibitor⁴ (e.g. roflumilast)	NOT permitted	NOT permitted	NOT permitted	NOT permitted	NOT permitted

- 1 Refer to [section 4.2.2.1](#) for washout period prior to PFTs.
- 2 Patients may be switched to bid LABA and short acting anticholinergic. Refer to section 4.2.2.1 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 PDE4-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 Permitted if prescribed for non-asthma condition
- 6 Not permitted within 4 weeks prior to screening visit (w.o. 4 wks prior to V1)

Refer to [section 4.2.1](#) for washout period prior to PFTs in case of treatment of a COPD exacerbation

4.2.2.1 Restrictions for PFT and shuttle tests

- At least an 8-hour washout of short-acting beta-adrenergic bronchodilators.
- At least an 8-hour washout of short-acting anticholinergic bronchodilators prior to visits 1, 2, 3 and 4 (Not allowed during treatment periods but permitted during the wash-out period, with at least an 8-hour washout prior to V7).
- At least a 1-week washout of long-acting anticholinergic bronchodilators twice daily (bid) or once daily (qd) prior to visit 1 and a 3-week washout prior to visit 4. (Not allowed between visits 1 to 9).
- At least a 1-week washout of long-acting beta-adrenergic bronchodilators (qd) prior to visit 1 and a 3-week washout prior to visit 4 (Not allowed between visits 1 to 9).
- At least a 48-hour washout of long-acting beta-adrenergic bronchodilators (bid) prior to visit 1 (Not allowed between visits 1 to 9).
- The morning dose of inhaled steroids should not be taken in the 1-hour period prior to PFTs.
- Morning doses of study medication should not be taken prior to test-day pre-dose PFT.
- 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. After this, a discussion with the Clinical Monitor should take place regarding the patient continuing in the trial

4.2.2.2 Restrictions on diet and life style

- Medication washout restrictions should be adhered to as described in [table 4.2.2.1](#).
- Patients must remain in the building where the exercise and lung function testing is performed and must return to the laboratory at least 10 minutes prior to the start of each test.

- On PFT and exercise testing days (including the screening visit), patients must refrain from strenuous activity for at least 2-3 days prior to pulmonary function and exercise testing 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 lung function and exercise testing. If a patient has smoked in the 30-minute period prior to lung function and exercise testing, the visit should be rescheduled.
- Coffee, tea, chocolate, cola and other caffeine-containing beverages and foods, and ice-cold beverages are not allowed the morning of and during the lung function and exercise testing period. Decaffeinated beverages are acceptable.

4.2.2.3 Restrictions regarding women of childbearing potential

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

4.3 TREATMENT COMPLIANCE

On visit days, compliance will be guaranteed by administration of the trial drug under supervision of the investigator or designee. Each patient will be trained in the correct use of the Respimat[®] Inhaler using the training Respimat[®] Inhaler with inserted placebo cartridge on visit 1.

Compliance will be measured using the counter on the Respimat[®] device. 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 (CML).

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

The primary endpoint is the change from baseline in intensity of breathlessness measured using the MBS-S at the end of the 3min Constant Speed Shuttle Test (CSST) after 6 weeks of treatment.

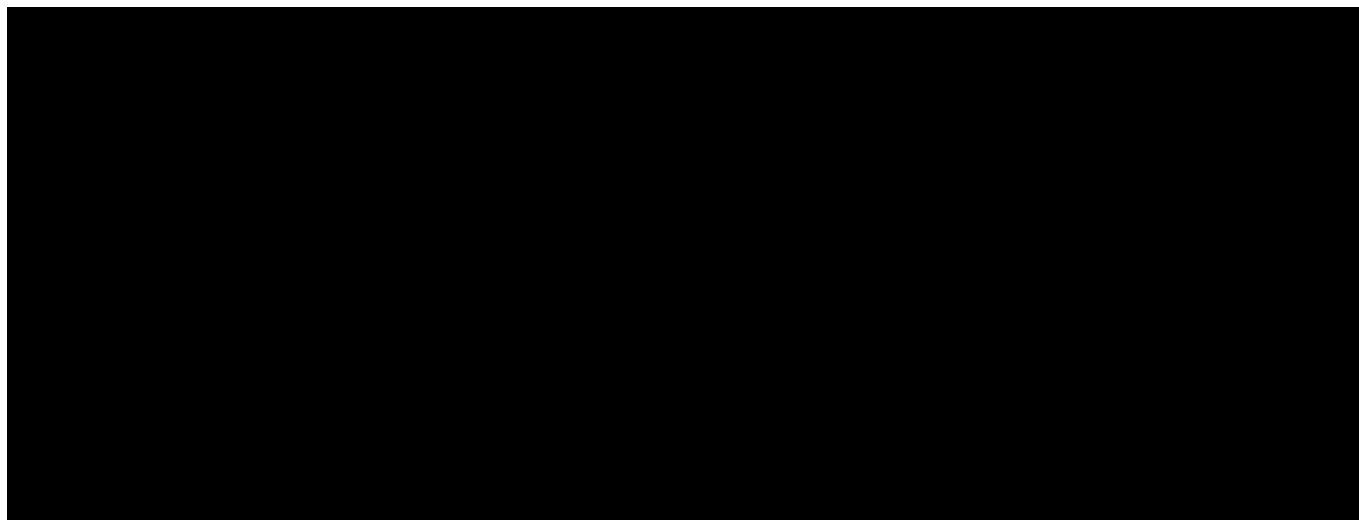
Change from baseline is defined as change from patient baseline. [See Section 7.3.1.](#)

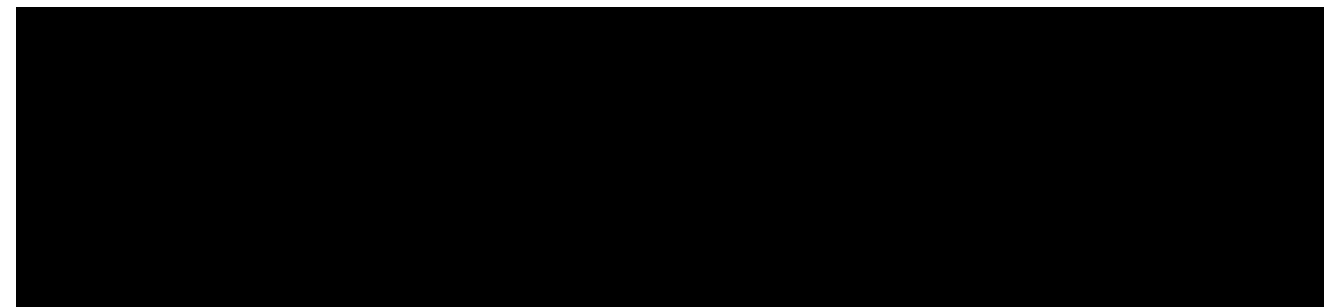
5.1.2 Secondary Endpoints

The following secondary endpoints will also be evaluated:

- Change from baseline in Inspiratory Capacity (IC) measured prior to exercise, after 6 weeks of treatment.
- Change from baseline in IC measured at the end of exercise, after 6 weeks of treatment
- Change from baseline in 1 hour post-dose FEV₁, after 6 weeks of treatment.
- Change from baseline in 1 hour post-dose FVC, after 6 weeks of treatment.
- Change from baseline in intensity of Breathlessness (MBS-S) at 1min, 2min, and 2.5min during the 3min CSST after 6 weeks of treatment.
- Change in Chronic Respiratory Questionnaire - Self Administered Individualized (CRQ-SAI) dyspnea domain score after 6 weeks of treatment.
- Change in Chronic Respiratory Questionnaire - Self Administered Standardized (CRQ-SAS) dyspnea domain score after 6 weeks of treatment.

None of the primary or secondary endpoints are safety issues.





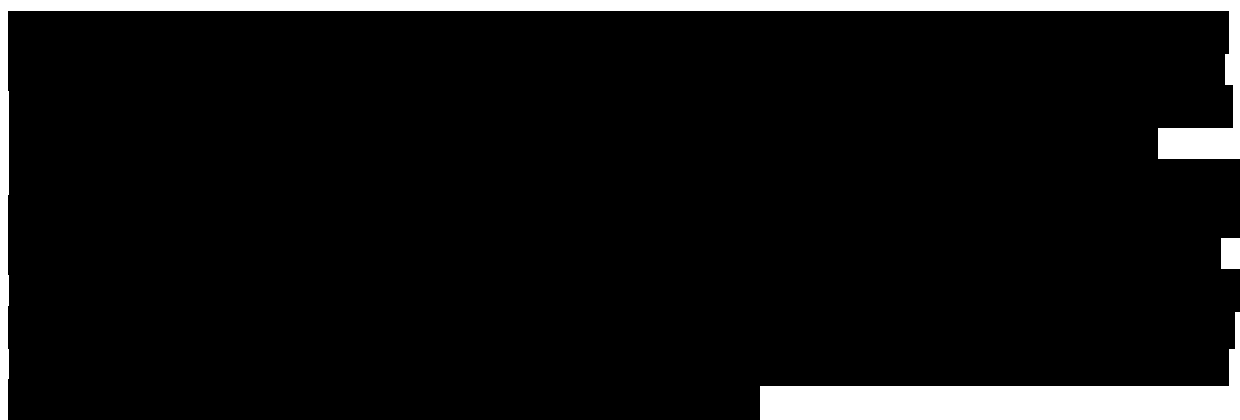
5.2 ASSESSMENT OF EFFICACY

Constant Speed Shuttle Test

At all sites, an ISWT will be performed at visit 1 for each patient. The test will be conducted according to the methodology described by Singh et al [[R04-4259](#)] with IC and physiological parameters measured using the mobile cardiopulmonary exercise equipment. At visit 2, starting at 4 km/h, the patient will complete up to three x 3min CSST at different sets of speeds (2.5, 3.25, 4, 5 or 6 km/h) to determine the highest speed that meet the following parameters:

- The patient can complete the entire three minutes of the test, and
- The patient achieves a BORG breathlessness rating of ≥ 4 .

The test will be conducted according to the methodology developed by Maltais et al, [[P12-12739](#)]. This speed selected at visit 2 will be used for all subsequent tests. At visit 3, a training 3min CSST will be performed using the speed selected at visit 2. At visits 4 and 7, a period baseline 3min CSST will be completed prior to dosing. At visits 5, 6, 8 and 9 a constant speed test will be conducted 2 hours (+ 15 minutes) after inhalation of the study medication.



The 3min CSST test methodology and speed selection is described in detail in [Appendix 10.4](#) and manual of procedures.

Modified BORG Scale

Before, during and at end-exercise, patients will be asked to estimate the intensity of breathing discomfort [REDACTED] that they are experiencing by matching their subjective estimate to descriptive phrases that best describe the intensity of each sensation using the MBS-S.

Details of the MBS-S are provided in [Appendix 10.5](#).

Pulmonary Function Testing

Spirometers and their use, including daily calibration, 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 CML 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](#). The post-bronchodilator measurements must meet the inclusion criteria specified in [section 3.3.2](#).

Inspiratory Capacity Measurements

IC measurements will be performed during exercise testing as follows:

- ISWT - at rest, during exercise and at the end of exercise
- 3min CSSTs – at rest and at the end of exercise

IC measurements will be taken using mobile cardiopulmonary exercise equipment capable of measuring IC during the shuttle tests.

For IC taken at rest prior to exercise, at least three reproducible measurements should be obtained with a maximum of 5 measurements to be performed. The resting IC should be recorded as the mean of the two highest acceptable efforts.

For additional details on the IC maneuvers, please refer to [Appendix 10.7](#) and manual of procedures.

Body Plethysmography

Constant-volume variable-pressure body plethysmography will be used in the trial at visit 1 to assess eligibility and parameters to be measured will be FRC, IC and total lung capacity (TLC).

Measurements should be done in triplicate. The mean FRC value from the three manoeuvres will be recorded. The largest IC will be recorded. TLC will be calculated as mean FRC + largest IC. Body plethysmography should be done before spirometry.

CRQ Questionnaires

The CRQ questionnaires should be administered at the visits outlined in the [FC](#) and completed by the patients. They should be completed first during a study visit, prior to dosing and all study procedures. The CRQ-SAI should be completed prior to the CRQ-SAS. Please see [Section 6.2](#) for the detailed order of administration of questionnaires at each visit.

The CRQ-SAS is a questionnaire that assesses the patients' perception of their COPD and measures the impact of COPD on their life. The CRQ-SAS refers to the CRQ-Self-administered format and contains 20 standardised dyspnea questions. The first part of the questionnaire contains 5 standardized activities and the patients must indicate how much shortness of breath they have experienced while performing each of the activities.

- Patients will also complete the CRQ-SAI questionnaire which contains a dyspnea domain that is individualized to each patient. Dyspnea items may be selected from a list of 26 suggested items or may be written in by the patients. The patients are asked to select the 5 activities associated with breathlessness that they perform frequently and are most important to them.
- Details of the CRQ-SAS are provided in [Appendix 10.9](#).
- Details of the CRQ-SAI are provided in [Appendix 10.10](#).

Mahler Dyspnea Indices [R96-2117]

[REDACTED] The BDI performed at visit 0 will be performed to determine eligibility. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Details of the Mahler Dyspnea Indices are provided in [Appendix 10.12](#).

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

5.3 ASSESSMENT OF SAFETY

5.3.1 Physical examination

Physical examinations are conducted at visit 1, at the end of each treatment period and at visit 10 in case of any findings at the end of treatment visit. 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 forced spirometry measurement (FEV₁ and FVC), 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 at visits 6 and 9 (or at the withdrawal visit if the patient does not complete all study visits). Follow-up clinical laboratory testing will be performed at visit 10 if there are any clinically significant findings at visit 9. The laboratory tests at visit 1 will be considered as the baseline measurements. Laboratory specimens will be collected in the morning prior to the exercise testing. Patients should be instructed not to do any unaccustomed physical exercise 36 hours prior to laboratory testing.

Haematology, blood chemistry and β -HCG will be analysed 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 or transferred to the sponsor. It is the 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 done at visit 1 in all females of childbearing potential. Urine pregnancy testing will be performed at visit 4, 6, 7, 9, and 10 in females of childbearing potential.

5.3.4 Electrocardiogram

A standard 12-lead ECG at rest will be performed on all patients at visits 1, 6 and 9. An ECG will be repeated at visit 10 in case of any findings at visit 9.

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 spirometry
- Heart rate, SpO₂, blood pressure in conjunction with exercise testing

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 patient administered a pharmaceutical 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 SAE is defined as any AE which:

- results in death,
- is life-threatening,
- requires inpatient hospitalisation or prolongation of existing hospitalisation,
- results in persistent or significant disability or incapacity,
- 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 jeopardize the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions.

Medical and scientific judgment 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 AEs, which by their nature, can always be considered to be “serious” even though they may not have met the criteria of an SAE as given above.

The latest list of “Always Serious AEs” can be found in the RDC. These events should always be reported as SAEs.

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 etiologies that could explain the event (e.g. pre existing or concomitant disease, or co-medications)
- The event is typically drug-related and infrequent in the general population not exposed to drugs (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 disease 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

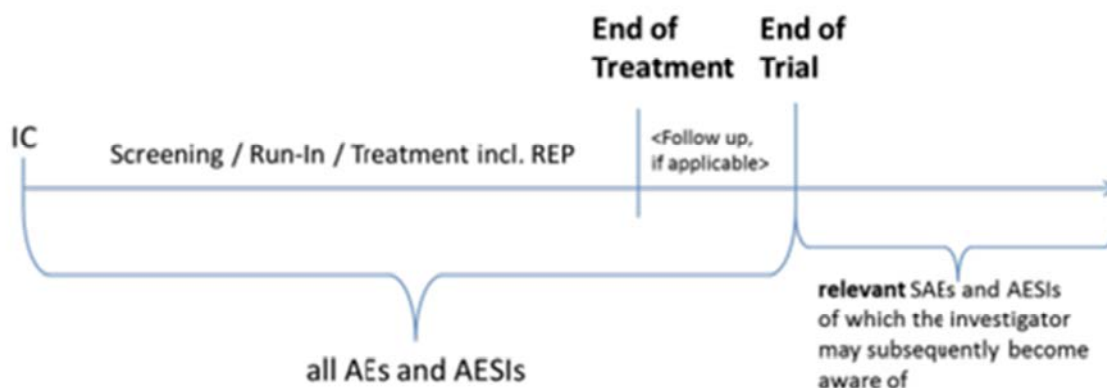
5.3.7 Adverse event collection and reporting

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 eCRF by the investigator:

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



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 7.3.3](#). 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 eCRF pages and the BI SAE form. The Investigator should determine the causal relationship to the trial medication and any possible interactions between the investigational drugs and a Non-Investigational Medicinal Product (NIMP)/Auxiliary Medicinal Product (AMP).

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

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

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

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

Pregnancy

In rare cases pregnancy might occur in a clinical trial. Once a patient has been enrolled into a clinical trial after having taken trial medication the investigator must report immediately (within 24 hours) a potential drug exposure during pregnancy 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 then the SAE has to be reported on the SAE form in addition.

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

5.4 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

5.4.1 This study will not analyse pharmacokinetic or pharmacodynamic parameters.

5.5 ASSESSMENT OF EXPLORATORY BIOMARKERS

This study will not analyse biomarkers.

5.6 OTHER ASSESSMENTS

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

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 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. Patients will be asked to score their dyspnea at Visit 1.

[REDACTED]

5.7 APPROPRIATENESS OF MEASUREMENTS

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

Shuttle Test

The ISWT will be conducted according to the methodology described by Singh et al [[R04-4259](#)]. The 3min CSST will be conducted according to the methodology developed by Maltais et al [[P12-12739](#)].

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 IC are standard measurements for the assessment of lung function.

Body Plethysmography

Constant-volume variable-pressure body plethysmography will be used in the trial following the methodology and calibration procedures described by Coates et al. 1997 [[R98-1487](#)].

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 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 4) 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 4), randomisation will be postponed until 6 weeks following recovery from the infection or exacerbation. To be eligible, patients should be clinically stable in the opinion of the investigator for 3 weeks prior to the randomisation visit.

If the screening period is extended by more than an additional 4 weeks, but not more than an additional 8 weeks, the screening examination has to be repeated prior to randomisation. The repeat screening examination will include a physical examination, vital signs (blood pressure and pulse rate), 12-lead ECG and clinical laboratory evaluation (haematology, serum chemistry, and pregnancy test). The patient should return for these evaluations 2 weeks prior to the re-scheduled randomisation visit (visit 4). All AEs and concomitant therapies will be recorded. If the screening period is to be extended more than an additional 8 weeks, the sponsor should be contacted. A decision whether the patient can continue in the trial will be made on a case by case basis. Clinically unstable COPD should be considered as a reason for discontinuation of the patient.

Refer to [sections 4.2.1](#) and [4.2.2](#) for details on medications allowed to control COPD exacerbations and restrictions for these medications prior to PFTs.

Rescheduling after randomisation

Subsequent visits should always be planned to take place to assure a minimum 6 week treatment period and a minimum 3 week wash-out period between treatment periods.

If rescheduling of visits after randomisation is necessary, the total daily doses of the Respimat[®] 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 CML.

Refer to [sections 4.2.1](#) and [4.2.2](#) for details on medications allowed to control acute COPD exacerbations and restrictions for these medications prior to PFTs.

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

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

6.2.1 Screening and run-in period

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 4 (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 6.1 for pulmonary test restrictions and section 3.3.3.1 for exercise test restrictions.
BDI	Completed to ascertain eligibility for the trial (Appendix 10.12).
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 (as rescue medication) that will be dispensed at this visit.
Ipratropium	Will be dispensed at the discretion of the investigator for patients washing out of LAMAs.

Patients will be contacted prior to each of the screening period visits to remind the patient of medication washouts and restrictions, and to bring back all rescue medication.

Visit 1 Procedures and Observations

Incremental Shuttle Walk Test and Reversibility Testing

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 Questionnaire	To be completed prior to study procedures. Refer to Appendix 10.8 .
Adverse Events	All AEs experienced since signing informed consent will be reviewed and 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) and ECG should be conducted following five

	minutes rest and prior to blood sampling and to salbutamol (albuterol) dosing.
Laboratory tests	<p>Will be collected and submitted to the local laboratory for haematology, serum chemistry and pregnancy testing (if applicable).</p> <p>A fasted condition is not required.</p> <p>Blood samples need to be taken prior to the salbutamol (albuterol) dosing.</p>
Body Plethysmography (Appendix 10.7)	Measurements (FRC, IC, TLC) will be taken prior to spirometry.
Vital Signs	Blood pressure and pulse rate will be measured immediately before PFTs with the patient seated and rested for at least five minutes.
Spirometry	<ul style="list-style-type: none"> • 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 (-10 min) and ≥ 10 minutes and up to 15 minutes after the inhalation of 4 puffs of salbutamol (albuterol). • Please refer to inclusion criteria 2 and Appendix 10.3.
ISWT	<p>To be performed 1 hour after spirometry. Please refer to Appendix 10.4.1. The duration and the number of shuttles for each patient will be recorded in the eCRF.</p> <p>The following will be measured during ISWT (please refer to FC):</p> <ul style="list-style-type: none"> • BORG measurements - at rest, every 2 minutes during exercise and at the end of exercise. Refer to Appendix 10.5 for further details. • IC - at rest, every 2 minutes during exercise and at the end of exercise using mobile cardiopulmonary exercise equipment. Refer to Appendix 10.7 for further details. • Physiological parameters using mobile cardiopulmonary exercise equipment. • MDP to be performed at end of exercise. Refer to Appendix 10.11. • Locus of Symptom Limitation Visual Analog Scale (VAS) to be administered at the end of exercise. Refer to Appendix 10.6.
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

	<ul style="list-style-type: none">Medication restrictions and washout requirements for the screening period and subsequent visitsReturning 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. The patient's GOLD stage will need to be entered into the IRT system. Please refer to section 3.1 .

Visit 2 Procedures and Observations

3 min CSST Speed Selection Visit

Medication washout	Medication washout compliance for prohibited medications will be verified and visits may be rescheduled as appropriate (section 6.1)
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.
3min CSST	<p>Patients will conduct the 3min CSST at various speeds as outlined in Appendix 10.4.2.2. The speed selected at this visit will be used for all subsequent visits.</p> <p>The following will be measured during 3min CSST (please refer to FC):</p> <ul style="list-style-type: none">BORG measurements - at rest, 1, 2, 2.5 minutes during exercise and at 3 min or the end of exercise. Refer to Appendix 10.5 for further details.IC - at rest and at end of exercise using mobile cardiopulmonary exercise equipment. Refer to Appendix 10.7 for further detailsPhysiological parameters using mobile cardiopulmonary exercise equipment.
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.

Visit 3 Procedures and Observations

Training 3min CSST Visit

Medication washout	Medication washout compliance for prohibited medications will be verified and visits may be rescheduled as appropriate (section 6.1).
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.
3min CSST	<p>A training 3min CSST will be conducted after spirometry using the speed selected at visit 2 (Appendix 10.4.2.2).</p> <p>The following will be measured during 3min CSST (please refer to FC):</p> <ul style="list-style-type: none">• BORG measurements - at rest, 1, 2, 2.5 minutes during exercise and at 3 min or the end of exercise. Refer to Appendix 10.5 for further details.• IC - at rest and at end of exercise using mobile cardiopulmonary exercise equipment. Refer to Appendix 10.7 for further details• Physiological parameters using mobile cardiopulmonary exercise equipment.• MDP to be performed at end of exercise. Refer to Appendix 10.11.
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.

6.2.2 Treatment periods

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 6 and 9

Visits 4 and 7 Procedures and Observations

First visit of each treatment period

Medication washout	Medication washout compliance for prohibited medications will be verified and visits may be rescheduled as appropriate (section 6.1)
Questionnaires	To be completed in the following order: CRQ-SAI (Appendix 10.10),

	CRQ-SAS (Appendix 10.9), [REDACTED] To be performed prior to dosing and study procedures. [REDACTED]
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 Visit 4 only	To be reviewed.
Smoking Status	Will be recorded
Urine Pregnancy	Will be performed if needed.
Vital Signs	Blood pressure and pulse rate will be measured immediately before PFTs with the patient seated and rested for at least five minutes.
Spirometry	Baseline spirometry measurements will be performed between 7:00 and 10:00am and prior to exercise testing. 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.
3min CSST	To be performed prior to dosing at the speed selected at visit 2. Please refer to Appendix 10.4.1 . The following will be measured during 3min CSST (please refer to FC): <ul style="list-style-type: none"> • BORG measurements - at rest, 1, 2, 2.5 minutes during exercise and at 3 min or the end of exercise. Refer to Appendix 10.5 for further details. • IC - at rest and at end of exercise using mobile cardiopulmonary exercise equipment. Refer to Appendix 10.7 for further details [REDACTED] [REDACTED]
Randomisation Call Visit 4 only	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.
Trial drug training and administration	<p>The patient will self-administer the trial drug (from the new assigned Respimat[®] inhaler) under the oversight of site staff. Instructions on how to assemble and prime the Respimat[®] inhaler at home should also be reviewed.</p> <p>Please refer to section 4.1.4.3.</p> <p>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 4 AND between 7:00 a.m. and 10:00 a.m.</p>
Training and Instructions	<p>Patients will receive training and instructions on</p> <ul style="list-style-type: none">• 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 will be issued additional rescue medication if needed and instructed to return all rescue medication to the clinic on the next scheduled visit.

Visits 5, and 8 Procedures and Observations

Clinic visits after 3 weeks of each treatment period

No new study medication will be dispensed at these visits.

Medication washout	Medication washout compliance for prohibited medications will be verified and visits may be rescheduled as appropriate (section 6.1)
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.
Trial Drug Administration	Study medication will be self-administered within ± 30 minutes of time of administration at visit 4 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.

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.

Visits 6 and 9 (EOT) Procedures and Observations

Clinic visits after 6 weeks of each treatment period

No new study medication will be dispensed at these visits.

Medication washout	Medication washout compliance for prohibited medications will be verified and visits may be rescheduled as appropriate (section 6.1)
Questionnaires	To be completed in the following order: CRQ-SAI (Appendix 10.10), CRQ-SAS (Appendix 10.9), [REDACTED] To be performed prior to dosing and study procedures.
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 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) and 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 haematology and serum chemistry. A fasted condition is not required.
Smoking Status	Will be recorded
Urine Pregnancy	Will be performed if applicable.
Trial Drug Administration	Study medication will be self-administered within ± 30 minutes of time of administration at visit 4 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 and pulse rate will be measured immediately before PFTs with the patient seated and rested for at least five minutes.
Spirometry	Lung function measurements will be performed 1-hour (± 10 minutes) post-dose and prior to exercise testing. 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.
3min CSST	<p>To be performed 2 hours (+15 min) post-dose using the speed selected at visit 2.</p> <p>Please refer to FC and Appendix 10.4.1.</p> <p>The following will be measured during 3min CSST (please refer to FC):</p> <ul style="list-style-type: none">• BORG measurements - at rest, 1, 2, 2.5 minutes during exercise and at 3 min or the end of exercise. Refer to Appendix 10.5 for further details.• IC - at rest and at end of exercise using mobile cardiopulmonary exercise equipment. Refer to Appendix 10.7 for further details <p>[REDACTED]</p> <p>[REDACTED]</p>
[REDACTED]	[REDACTED]
Training and Instructions	<p>Patients will receive training and instructions on</p> <ul style="list-style-type: none">• Medication restrictions and washout requirements for the wash-out period (visit 7) and subsequent visits• Returning all issued medication to the clinic on all subsequent visits.
Trial Drug Collection	All study medication will be collected at visits 6 and 9.
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.
IRT Visit 9 only	Call IRT to register the patient as completed.

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 and 12- Lead ECG	<p>The physical examination includes measurements of blood pressure and pulse rate. Refer to section 5.3.1.</p> <p>The vital signs (seated) and ECG should be conducted following five minutes rest and prior to blood sampling and to salbutamol (albuterol) dosing.</p>
Laboratory tests	<p>Will be collected and submitted to the local laboratory for haematology and serum chemistry.</p> <p>A fasted condition is not required.</p>
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.
Spirometry	<p>Will be conducted if possible. Refer to FC.</p> <p>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.</p>
Trial Drug Collection	All study medication will be collected.
IRT	Call IRT to register the patient as discontinued.

Follow-up Visit 10 Procedures and Observations

At the completion of Visit 9, 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 and 12- Lead ECG	<ul style="list-style-type: none">• The physical examination includes measurements of blood pressure and pulse rate. Refer to section 5.3.1.• The vital signs (seated) and ECG should be conducted following five minutes rest and prior to blood sampling and to salbutamol (albuterol) dosing.• To be completed in the event of any clinically relevant findings at the EOT visit.
Laboratory tests	<ul style="list-style-type: none">• Will be collected and submitted to the local laboratory for haematology and serum chemistry.• A fasted condition is not required.• To be completed in the event of any clinically relevant findings at the EOT visit.
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 a randomised, double-blind, cross-over study to determine the effect of 6 weeks treatment of orally inhaled tiotropium + olodaterol FDC (5/5 µg) delivered by the Respimat[®] Inhaler, on breathlessness during the three minute shuttle test in patients with COPD. The effect of two treatments (T+O vs. tiotropium) in this cross-over study will be compared.

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 will be 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 intensity of breathlessness measured using the MBS-S at the end of the 3min CSST - after 6 weeks of treatment.

H0: Mean MBS-S₃ for (Tiotropium + Olodaterol) = Mean MBS-S₃ for Tiotropium

H1: Mean MBS-S₃ for (Tiotropium + Olodaterol) \neq Mean MBS-S₃ for Tiotropium

Where MBS-S₃ is the primary endpoint, the MBS-S at the end of the 3 minute shuttle test 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. This set will be called Full Analysis Set (FAS).

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

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

7.3.1 Primary endpoint analyses

In the primary analysis, the two-sided hypotheses as given in [section 7.2](#) will be tested based on MBS-S using a restricted maximum likelihood (REML)-based MMRM. This model will include treatment and period as fixed effects, patient as a random effect and period baseline as well as patient baseline as covariates. Compound symmetry will be used as a covariance structure for within patient variation. The SAS procedure MIXED will be used involving the restricted maximum likelihood estimation and the Kenward-Roger approximation for denominator degrees of freedom. 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.

Period baseline

The period baseline is defined as the pre-dose measurement, the MBS-S at the end of the 3 minute CSST, performed prior to dosing on the first day of each period.

Patient baseline

The patient baseline is defined as the mean of non-missing period baselines for each patient.

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](#). 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.

7.3.3 Safety analyses

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary. Standard BI summary tables and listings will be produced. All adverse events with an onset between start of treatment and end of the residual effect period (REP), a period of 21 days after the last dose of trial medication, will be assigned to the treatment period for evaluation.

All 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.

Statistical analysis and reporting of adverse events will concentrate on treatment-emergent adverse events. To this end, all adverse events occurring between start of treatment and end of the residual effect period will be considered 'treatment-emergent'. The residual effect period is defined as 21 days after last dose of study medication (separately for each treatment period in the

crossover). Adverse events that start before first drug intake and deteriorate under treatment will also be considered as ‘treatment-emergent’.

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

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

7.3.4 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 Trial Statistical Analysis Plan (TSAP) prior to unblinding.

7.6 RANDOMISATION

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

IRT will also be set-up to ensure that the number of GOLD Stage II patients is capped at approximately 50% and the number of GOLD Stage III patients is capped at approximately 50%.

7.7 DETERMINATION OF SAMPLE SIZE

Based on a pilot study [[P12-12739](#)], the standard deviation of within-subject treatment difference (measured by 10-point modified BORG scale) for 3min CSST is approximately 1.776 for COPD patients. The pilot study was a placebo controlled, double-blind cross-over study in patients with COPD to investigate the effect of administration of 500 µg nebulized ipratropium bromide vs. saline placebo. It is deemed reasonable to assume that the variability for within-patients difference should be similar for this trial.

Assuming a delta of 0.5 BORG units and various choices of power, nQuery Advisor® 7.0 MOT0-1 (one-sample t-test) yielded the following results.

Table 7.7: 1 Total calculated sample size

Power	Std. Dev. (1.776)
80%	101
90%	135

Since patient drop out over 12 weeks of treatment is expected to be quite low and the MMRM model specified for the primary analysis naturally accounts for missing data, there has been no sample size inflation to account for patient attrition in the sample size calculations. Based on the standard deviation of 1.776 and a type one error rate of 0.05 (two-sided), the ability to detect a difference of 0.5 BORG units would require a sample size of 101 to maintain 80% power to reject the null hypothesis. Since there are two sequences of treatments, the sample sizes are rounded up to the nearest even number. The required sample size is 102.

8. INFORMED CONSENT, DATA PROTECTION, TRIAL RECORDS

The trial will be carried out in accordance with the Medical Devices Directive (93/42/EEC) and the harmonized standards for Medical Devices (ISO 14155-01 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), and relevant BI Standard Operating Procedures (SOPs), the EU regulation 536/2014 and other relevant regulations.

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

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

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

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

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

8.1 TRIAL APPROVAL, PATIENT INFORMATION, AND INFORMED CONSENT

This trial will be initiated only after all required legal documentation has been reviewed and approved by the respective IRB/ IEC and 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."

Re-consenting may become necessary when new relevant information becomes available and should be conducted according to the sponsor's instructions.

The consent and re-consenting process should be properly documented in the source documentation.

8.2 DATA QUALITY ASSURANCE

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

8.3 RECORDS

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.

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 pulmonary function testing reports, with proper documented medical evaluation
- 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 inhouse 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

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

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

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

8.6 TRIAL MILESTONES

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

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

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

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

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

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

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

A final report of the clinical trial data will be written only after all patients have completed the trial in all countries (EU or non-EU) to incorporate and consider all data in the report.

The sponsor will submit to the EU database a summary of the final trial results within one year from the end of a clinical trial as a whole, regardless of the country of the last patient (EU or non-EU).

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10. APPENDICES

10.1 THE RESPIMAT[®] INHALER

Instructions for Use

Respimat[®] inhaler

How to use your Respimat[®] inhaler

This leaflet explains how to use and care for your Respimat[®] inhaler. **Please read and carefully follow these instructions.**

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





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






Respimat[®] inhaler and the Respimat[®] cartridge

Inserting the cartridge and preparation for use

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

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


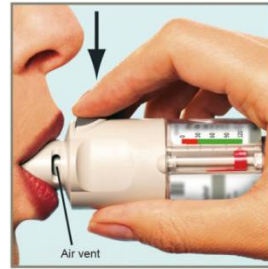
To prepare the Respimat[®] inhaler for first-time use

 <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 (30 medicinal doses).</p>


Daily use of your Respimat[®] inhaler

You will need to use this inhaler only ONCE A DAY.

Each time you use it take TWO PUFFS.

	<p>I Hold the Respimat[®] inhaler upright, with the grey cap (A) closed, to avoid accidental release of dose. Turn the base (G) in the direction of the red arrows on the label until it clicks (half a turn).</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 medicinal doses). The dose indicator shows approximately how much medication is left. When the pointer enters the red area of the scale, there is, approximately, medication for 7 days (14 puffs) left.</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>
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What if...

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

How to care for your inhaler

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

Any minor discoloration in the mouthpiece does not affect the performance of your Respimat[®] inhaler.

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

Further information


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

Do not touch the piercing element inside the base.

Keep out of the reach and sight of children.

Do not freeze.

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

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

10.2 RETURN OF INHALERS/CARTRIDGES

Return of Malfunctioning Respimat[®] Inhalers

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

10.3 ADDITIONAL INFORMATION REGARDING IN/EX CRITERIA

Reversibility testing [[P05-12782](#)]

At the screening visit (visit 1), following the completion of three acceptable pre-bronchodilator forced expiratory manoeuvres, salbutamol (albuterol) will be administered to each patient in order to document the degree of reversibility. Immediately after (within 10 min) pre-bronchodilator forced expiratory manoeuvres and after a gentle and incomplete expiration, a dose of 100 µg of salbutamol (albuterol) is inhaled in one breath to TLC. The breath is then held for 5–10s before the patient exhales. Four separate doses (total dose 400 µg) are delivered at approximately 30-second intervals (this dose ensures that the response is high on the salbutamol (albuterol) dose–response curve). Three additional, acceptable post-bronchodilator forced expiratory manoeuvre tests are recorded ≥10 min and up to 15 min later after the last dose of salbutamol (albuterol) is inhaled. !"# \$%&)*%+, "%-.0'%*1#0&2*#1#+&12&' 1##' ""# .+,/2&.%+*.'#*.0&\$#,3.#-.+ &#,'.%+45465

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

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

For height measured in inches

Males: $FEV_1 \text{ predicted (L)} = 4.30 \times [\text{height (inches)} / 39.37] - 0.029 \times [\text{age (yrs)}] - 2.49$

Females: $FEV_1 \text{ predicted (L)} = 3.95 \times [\text{height (inches)} / 39.37] - 0.025 \times [\text{age (yrs)}] - 2.60$

For height measured in meters

Males: $FEV_1 \text{ predicted (L)} = 4.30 \times [\text{height (m)}] - 0.029 \times [\text{age (yrs)}] - 2.49$

Females: $FEV_1 \text{ predicted (L)} = 3.95 \times [\text{height (m)}] - 0.025 \times [\text{age (yrs)}] - 2.60$

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

Calculation of number of pack years

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

10.4 EXERCISE TESTING – ISWT AND 3MIN CSST

To supplement the information on exercise testing using the ISWT and 3min CSST described in this chapter, a Manual of Procedures (MOP) has been developed. More detailed information on the procedure, on staffing, site and equipment requirements, patient preparation, IC measurements, and calculations etc. can be found in this MOP, which is filed in the ISF.

10.4.1 General considerations for exercise testing

Exercise performance variability

A number of physiological and psychological factors are known to affect exercise performance. Lack of attention to controlling these extraneous factors may result in an unacceptable degree of variability in exercise performance. As such, certain requirements have been put in place to reduce exercise performance variability:

Physiological:

Pre-exercise diet: Patients are to be encouraged to eat breakfast before coming to the clinic. However, patients should not eat within 2 hours of exercise tests.

- Hydration state: Patients are to be encouraged to maintain an adequate hydration state during the morning of the exercise tests (i.e., drink lots of water).
- Environmental conditions (temperature, humidity): Temperature and humidity should be controlled within the laboratory at comfortable levels, and should be recorded each testing day.

Previous exercise:

- Fatigue: Patients should be encouraged to stay well-rested and to refrain from any strenuous, fatiguing or exhausting activities (e.g., walking up hills, walking up many flights of stairs, running, cycling, shovelling snow, strenuous household chores) on the morning of exercise tests.
- Delayed onset muscular soreness (DOMS): Very strenuous, heavy type of activities, especially activities to which the patient is unaccustomed, can lead to muscle soreness 24-48 hours after the activity. Patients should be encouraged to refrain from any type of heavy lifting, exhaustive digging in the garden etc., for 2-3 days prior to each clinic visit, especially if the patient has not performed these activities recently.

Psychological:

- External motivational cues: Motivational cues provided to the patient can have profound effects on exercise performance. It is imperative that external motivational cues are controlled across patients and across sites.

- Time of exercise: No visual cues regarding the time of exercise should be provided to the patient. The patient's watch should be removed prior to exercise, and all other timekeeping devices (e.g., trial staff watches, wall clocks, stopwatch etc.) should be kept away from the patient's view.
- Verbal encouragement: During exercise testing, the wording and intensity of verbal encouragement provided to the patient will be standardized, and will preferably only be provided by one member of the trial team, who is blinded to the results of the lung function tests. Appropriate positive words should be used to encourage the patient to continue walking. The tone of the encouragement should be enthusiastic and supportive, but not overbearing, overly loud or coercive in nature. Examples would be "good work", "well done", "excellent job so far" and "keep up the good work". Reinforcement could also consist of "that's a good walking rate" or, if the walking rate is dropping, "keep up the walking rate - that's great".
- Familiarity with surroundings: Trial staff should allow as much time as necessary for the patient to become comfortable with the laboratory surroundings.
- Distractions: During the exercise tests, access to the laboratory should be restricted to trial staff as much as possible. The noise level in the laboratory should be kept to a minimum, except for those sounds specifically related to the conduct of the test. This will ensure that the patient is able to concentrate on the task at hand, and will also ensure that the patient is attentive to the verbal encouragement provided by the designated member of the trial team.
- Comfort with equipment: Patients should be appropriately dressed for exercise (e.g., shorts or track pants, gym shoes, T-shirt or sweat shirt), and trial staff should ensure that the patient is comfortable with the equipment prior to starting the exercise.
- Familiarity with test: Before starting exercise, a member of the trial team should make sure that the patient is completely familiar with the type of exercise that is to be performed; for the incremental test, patients should be told that during the test they will have to walk progressively faster. For the constant speed tests, patients should be told that the speed of walking will be constant throughout the test. It is important that the patient understands the difference between the incremental test and the constant speed tests.
- For the ISWT: It is extremely important that the patient understands that there is no specific time limit to the exercise test, and that the test will continue as long as the patient is able to. It must be stressed to the patient that the trial team will not stop the test unless there is concern for the patient's safety, or the patient is unable to maintain the required walking pace.

- Performance incentives: No external incentives for performance (i.e., rewards for performance) should be given to the patient, especially as the patient nears the point of limitation, but also prior to or at any time during the exercise.

Heart rate and safety monitoring:

- Heart rate and oxygen saturation will be monitored during shuttle tests using a mobile pulse oximeter.
- Blood pressure will be determined before exercise, at end-exercise, five minutes after termination of exercise and when, for clinical reasons, it is required.

Personnel qualifications:

- Exercise challenges should be conducted by adequately trained personnel with a basic knowledge of exercise physiology.
- Technicians familiar with normal and abnormal responses during exercise and trained in CPR should be present throughout the test.
- The supervising physician must be readily available to respond as needed. The degree of patient supervision should be increased if warranted by the clinical status of the patient.

Safety issues:

Cardiac (bradyarrhythmias, ventricular tachycardia, myocardial infarction, heart failure, hypotension, and shock) and non-cardiac (musculoskeletal trauma, severe fatigue, dizziness, fainting, body aches) complications of exercise challenges have been reported.

Consequently during the test, study personnel should be alert to any abnormal event.

Indications to stop the test must be clearly established and known by the personnel involved in testing.

Symptoms such as:

- acute chest pain,
- sudden pallor,
- loss of co-ordination,
- mental confusion,
- extreme dyspnea.

If the exercise test has been stopped for one of these reasons, the patient should be monitored in the laboratory until signs / symptoms / ECG modifications have completely cleared. Full CPR equipment should be available in the laboratory. The patient will be withdrawn from the study.

10.4.2 Shuttle Test

Shuttle tests will be performed in all patients of this trial. Selection of sites is based on past experience with the test and/or the availability of suitable infrastructure and qualified personnel.

The shuttle test is performed on a flat, straight walking track, in a quiet treatment area that is at least 12 meters in length and approximately 2 meters wide, and clear of hospital traffic and obstacles. The standard instructions are given by trained site staff. Patients are required to walk, jog or run back and forth, in loops of 10 meters long. Cones are placed half a meter from the end, so they are 9 meters apart. The patient must keep pace with the pre-recorded auditory signal such that he/she completes a turn as each audio signal sounds.

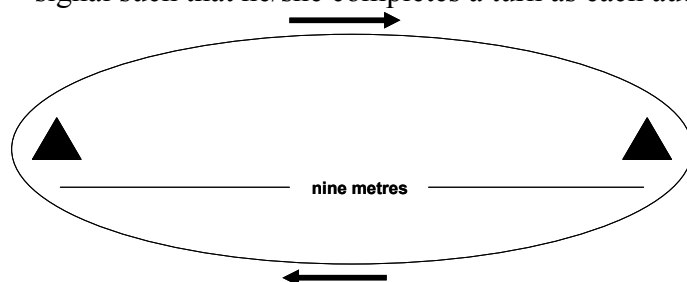


Figure 10.4.2:1: Set up for the shuttle test

During the test oxygen saturation and heart rate will be monitored using a pulse oximeter (fingertip or ear lobe sensor). Patients will also wear mobile cardiopulmonary exercise equipment. A chair should be placed in the immediate surroundings of the track for the patient to rest before and at the end of the test.

For the ISWT at visit 1, the end of the test will be signaled

- a) by the patient, when he feels too breathless or fatigued to continue at the required speed.
- b) by the operator when the patient fails to keep up to auditory signals after repeated warnings and encouragements (patient is more than 0.5 meter from the cone at the beep) and is unable to catch up within 3 shuttles.
- c) when the patient is unable to continue safely (in the opinion of the supervising technician or physician).

For the 3min CSST, the end of the test will be signaled

- a) by the patient, when he feels too breathless or fatigued to continue at the required speed.
- b) by the operator when the three minutes of testing is completed.
- c) by the operator when the patient fails to keep up to auditory signals after repeated warnings and encouragements (patient is more than 0.5 meter from the cone at the beep) and is unable to catch up within 3 shuttles.
- d) when the patient is unable to continue safely (in the opinion of the supervising technician or physician).

The test should also be interrupted when symptoms occur as described in the safety section above.

Patient preparation:

- Patients should not eat for at least 2 hours before any exercise challenge and should avoid caffeine-containing products the morning of and during the testing period.
- Patients should dress appropriately for the exercise challenge (i.e., comfortable shoes and clothing).
- On arrival in the laboratory, a detailed explanation of the testing procedure should be given to the patient, outlining the risks involved and potential complications (see safety issues section above).
- Before exercise, blood pressure and heart rate are measured; the pulse oximetry sensor is carefully placed and secured to ensure good recordings. Nail polish and acrylic nails do not allow correct measurements and should be removed.
- Good communication with the patient throughout the whole procedure increases the patient's confidence and helps to ensure a good effort by the patient. Standardized instructions from the CD/ instruction sheet should be used during the test. Standardized and continuous encouragement to the patient should preferably be provided by only one member of the trial team who is blinded to the results of the spirometry.

10.4.2.1 Incremental Shuttle Walk Test

In addition to adhering to the general considerations for exercise challenges described above, the following specific procedures should be adhered to during the ISWT at visit 1:

The ISWT is a progressive test: the patient walks/jogs/runs up and down a 10 meter course at a speed dictated by an audio signal. Every minute the speed increases. Every change in speed will be indicated by a triple audio signal (triple beep).

The test starts with a triple beep [start the stopwatch: Timing starts at the first triple beep, when the patient starts walking at the slowest speed (level 1)]; the patient starts at one of the cones. Thereafter, the CD emits a single beep at regular intervals; the patient is advised to walk at a steady pace, aiming to turn around at the cone at the opposite end of the course when he/she hears the signal (single beep). When the signal sounds the patient should be turning around the cone and proceed back down the course.

Each minute the speed of walking is increased by a small increment; a change of speed to the next level is indicated by a triple bleep from the CD, and the operator asks the patient to increase his speed slightly. There are 12 levels of speed beginning at 0.50 m/s and ending at 2.37m/s.

To help the patient to establish the routine of the test, the operator walks alongside the patient for the first minute (3 shuttles the first minute). When the patient reaches the cone before the signal, he/she is instructed to wait until the signal indicates that he/she can proceed. When the patient did not reach the cone within 0.5 meter when the signal sounds, the operator asks the patient to increase his speed (“You’re not going fast enough; try to make up the speed this time”); if the patient fails to keep up the required pace after repeated warnings and encouragements, the test ends.

During the test patients should be encouraged (in a standardized way) to keep the pace or to catch up when lagging behind.

Patients will be asked to rate the intensity of breathing and leg discomfort using the MBS-S (see [section 10.5](#)) prior to exercise, every two minutes during exercise and at end-exercise.

This is a maximal test. The patient will exercise until:

- limited by symptoms (i.e., is unwilling to continue exercising because of the discomfort associated with the exercise); OR
- unable to maintain the walking pace emitted by the CD (even with repeated encouragement): patient is not within 0.5 meter from the cone at the beep and not able to catch up within 3 shuttles; OR
- unable to continue safely (in the opinion of the supervising technician or physician).

The duration of exercise will be recorded using a stopwatch (in minutes and seconds).

At the end of exercise, after having taken the peak blood pressure measurement, the patient can rest on the chair, or walk around if he/she prefers.

At end-exercise the following parameters will be recorded immediately: oxygen saturation, (SpO₂%), blood pressure, heart rate and rating of the intensity of breathing discomfort and leg discomfort (MBS-S), followed by the MDP and locus of symptom limitation VAS ([Appendix 10.6](#)). Repeat blood pressure, heart rate and SpO₂% measurements will be taken five minutes later to assess recovery rate.

The number of completed shuttles is recorded on the ISWT recording sheet. One shuttle is 10 meters, the distance covered between two bleeps. The last shuttle is considered complete if at least $\frac{3}{4}$ of the distance was covered when the patient stopped the test. The total distance covered is calculated (distance in meters = number of complete shuttles x10).

The patient should remain in a clinical area for at least 15 minutes following an uncomplicated test or for at least 30 minutes after resolution of any symptoms.

Note that patients who complete level 12 will not be eligible to continue in the study ([exclusion criterion 22](#)).

10.4.2.2 Constant Speed Shuttle Test

The following procedure is to be followed for the 3min CSST conducted throughout the study.

Determination of speed for the 3min CSST:

The methodology for the execution of the 3min CSST is described by [REDACTED] group [P12-12739]. Based on the findings from the initial study, the current protocol was designed as described.

At visit 2, a test consisting of one bout of three minutes of walking at the initial speed of 4.0 km/h is completed. Thirty minutes after this first test, a second test will be performed at a speed of either 5.0 or 3.25 km/h.

The second walking rate will be determined by the ability to complete the full 3 minutes of the test at 4.0 km/h. If a patient cannot complete the first test, then the second speed will be stepped down to 3.25 km/h. If a patient is able to complete the full 3 minutes in the first test, then the second speed will be increased to 5.0 km/h. Patients will be asked to perform up to three tests at different speeds in order to determine, amongst the 3 different speeds, the highest speed that meet the following parameters:

- can be sustained for the entire 3 minutes, and
- achieves a BORG breathlessness rating of ≥ 4 .

In doing so, the objective is to induce a level of dyspnea that is sufficiently high to be amenable to therapy.

Depending on the patient's ability to complete 3 minutes OR achieve a BORG breathlessness rating ≥ 4 then the speed can be further adjusted up to 6.0 km/h or down to 2.5 km/h to achieve these requirements. Please consult the Manual of Procedures for more detailed instructions for speed selection.

An appropriate speed will be determined based on patients' ability to complete the entire 3 minutes of a speed and achieve a BORG rating ≥ 4 . If these 2 parameters are not fulfilled at any speed, the patient will be considered a screen failure.

These speeds are selected based on previous work by [REDACTED]' group showing that these were sufficiently demanding to induce measurable levels of dyspnea and that most moderate to severe patients with COPD are able to complete the test for the desired duration [[R15-4319](#)].

Patients will be directed to follow the audio signal for the entire 3 minutes of the test. They will be instructed to walk/jog/run around the two cones set-up in the hospital hallway pacing their walk/jog/run in a way not to wait at the cones for the following audio signal.

The values for the completed 3min CSST tests will be recorded in the eCRF, and will be used for all subsequent 3min CSSTs: the training 3min CSST (visit 3) and for the subsequent 3min CSSTs conducted.

No adjustments to the speed selected at visit 2 are permitted throughout the trial.

Physiological parameters will be taken during the 3min CSSTs using mobile cardiopulmonary exercise equipment.

10.5 MODIFIED BORG SCALE (MBS-S)

[\[R14-0975\]](#)

PATIENT INSTRUCTIONS

We will be using the BORG Scale to help us understand the intensity or severity of your breathing discomfort and the intensity or severity of your leg discomfort. We will ask you to use this scale to rate the intensity of your breathing discomfort and your leg discomfort before, during, and after your exercise test.

Please review the scale to see the various levels from which you can choose.

For breathing discomfort:

The top of the scale, “0 or nothing at all,” means *no breathing discomfort at all*.

The bottom of the scale, “10 or maximal,” means the *most severe breathing discomfort that you have ever experienced or could imagine experiencing*.

For leg discomfort:

The top of the scale, “0 or nothing at all,” means *no leg discomfort at all*.

The bottom of the scale, “10 or maximal,” means the *most severe leg discomfort that you have ever experienced or could imagine experiencing*.

When we ask you to rate the intensity of your breathing discomfort and your leg discomfort, please place the tip of your finger on the number that best describes the intensity that you are experiencing at that moment. You may also place a finger between 2 numbers if that better describes the intensity of your breathing discomfort or your leg discomfort.

Please let us know if you have any questions before we begin.

0	<i>Nothing at all</i>
0.5	<i>Very, very slight (just noticeable)</i>
1	<i>Very slight</i>
2	<i>Slight</i>
3	<i>Moderate</i>
4	<i>Somewhat severe</i>
5	<i>Severe</i>
6	
7	<i>Very severe</i>
8	
9	<i>Very, very severe (almost maximal)</i>
10	<i>Maximal</i>

Instructions for the Modified BORG Scale

Prior to the start of exercise test, each subject will be told that they will be asked to rate the intensity of [REDACTED] sensations at rest, during exercise and at end-exercise. The [REDACTED] sensations will be described to the subject as:

- Discomfort with your breathing

[REDACTED]

Use of the BORG Scale to rate these sensations will be explained to the subject. While showing the scale to the subject, the study coordinator or blinded tester will explain that the subject should relate the wording on the BORG Scale to the level of the sensation that he / she is experiencing, and then place the end of a finger on a number that best describes the intensity of the sensation - explain that placing a finger between 2 numbers is allowed. (BORG Scale numbers will be recorded to the nearest 0.5 units).

The study coordinator or blinded tester will anchor the endpoints of the scale for both sensations. The study coordinator or blinded tester will explain that for the sensation of “discomfort with your breathing”, “0 or nothing at all” corresponds to “no discomfort with your breathing” and “10 or maximal” corresponds to the “most severe discomfort with your breathing that you have ever experienced or could imagine experiencing”. [REDACTED]

[REDACTED]

Subjects are to be given no further information about these sensations. If a subject requests further clarification, he/she will be told to use his/her own individual interpretation as to the meaning of the sensory descriptors. This will ensure that the sensory descriptors are presented to each subject in a standard format.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

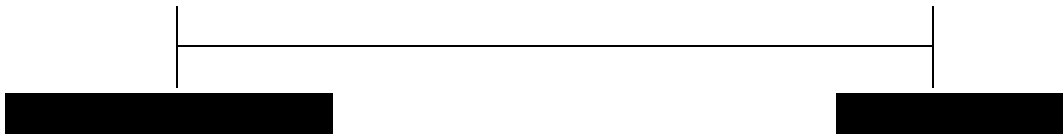
[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]



[REDACTED]

10.7 INSPIRATORY CAPACITY AND FRC

In this trial FRC measurements will be done at visit 1 in the body box to determine eligibility.

FRC predicted equations according to Crapo [\[R99-0401\]](#):

Males: $Y = 0.0472(\text{Ht in cm}) + 0.009(\text{Age}) - 5.29$

Females: $Y = 0.036(\text{Ht in cm}) + 0.0031(\text{Age}) - 3.182$

Inspiratory Capacity measurements:

IC measurements will be performed during exercise testing as follows:

- ISWT - at rest, during exercise and at the end of exercise
- 3min CSSTs – at rest and at the end of exercise

IC measurements will be taken using mobile cardiopulmonary exercise equipment capable of measuring IC during the shuttle tests.

To supplement the information on IC manoeuvres in this chapter, a manual of procedures has been developed. More detailed information on IC measurements, calculations and post-test corrections etc. can be found in this manual which is filled in the ISF.

Resting IC

At each required visit, IC maneuvers will first be fully explained to the patient and then practiced at rest to confirm proper technique. Patients will be given a few breaths warning before an IC maneuver, a prompt for the maneuver (i.e., “At the end of the next normal breath out, take a deep breath all the way IN”), and then strong verbal encouragement to make a maximal effort before relaxing.

The patient will be performing these IC maneuvers in the “Rest phase” of the exercise test using mobile cardiopulmonary exercise equipment. The patient should breathe quietly for a few breaths to achieve stable end expiratory lung volume (EELV) and then perform the inspiratory maneuver from EELV to TLC. The patient can be taken off the mouthpiece between maneuvers. The patient should return to stable EELV prior to performing the next maneuver. At least three reproducible IC measurements should be obtained (i.e., within $\pm 10\%$ or ± 100 mL whichever is larger) with a maximum of 5 measurements to be performed. The resting IC should be recorded as the mean of the two highest acceptable efforts.

Exercise IC for the ISWT

These IC maneuvers will be carried in a manner similar to that at rest. For the end-exercise IC maneuver specifically, the BORG scale intensity of breathing discomfort and leg discomfort ratings should precede IC maneuver by at least 5 breaths to avoid interfering with pre-IC breathing patterns.

End exercise IC

An IC maneuver should be performed directly after having performed the BORG scale measurements after end-exercise (i.e., first 15 seconds of recovery) and used as the “end-exercise” measurement. However, for the ISWT, if during the exercise test, a scheduled IC maneuver is performed within 30 seconds prior to the end of exercise, the final IC maneuver during exercise will be considered as the “end-exercise” measurement.

Analysis / acceptability of IC maneuvers

If the effort appears sub-maximal or if anticipatory changes in breathing pattern occur immediately preceding a maneuver, then the IC should not be accepted unless it can be corrected post-test.

10.8 MODIFIED MEDICAL RESEARCH COUNCIL DYSPNEA SCALE (MMRC)

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.

10.9 CHRONIC RESPIRATORY QUESTIONNAIRE – SELF ADMINISTERED STANDARDIZED - DYSPNEA DOMAIN ONLY

Instructions for the self-administered standardised CRQ

1. Please read these instructions carefully if you distribute the questionnaire to respondents in person.
2. This is a questionnaire that respondents should complete. It asks about breathing difficulties they might have experienced.
3. Please ask the respondent to take time, read over the instructions and answer the questions as best as they can by placing an “X” in the corresponding response box. Reassure them that this is not a test. There are no right or wrong answers to any of the questions, you would just like them to choose the best answer that describes how they have been feeling during the past 2 weeks.
4. If a question seems unclear to the respondent, we suggest that they read the question once or twice more. We have found that reading the question again helps understanding the questions.
5. In summary, we suggest that you tell the respondent the following when you give out the questionnaire: “This is a questionnaire that we would like you to complete. Please take your time, read over the instructions and answer the questions as best you can. It is not a test. There are no right or wrong answers to any of the questions, we would just like to you choose the best answer that describes how you have been feeling during the past 2 weeks. If a question seems unclear to you, we suggest that you read the question once or twice more. We have found that this helps understanding the questions.”
6. Please also review the detailed background information and instructions prior to start using the questionnaire.
7. Please remove this sheet if it is attached to the questionnaire prior to handing questionnaire to respondent for completion.



McMaster University
Canada

Chronic Respiratory Questionnaire

Self-Administered Standardised Format (CRQ-SAS)

First Administration

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CHRONIC RESPIRATORY QUESTIONNAIRE - SELF ADMINISTERED - STANDARDISED ACTIVITIES - "CRQ-SAS"

Date

<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
DAY		MONTH		YEAR

CHRONIC RESPIRATORY QUESTIONNAIRE -SAS- FIRST ADMINISTRATION 1(10)

This questionnaire is designed to find out how you have been feeling during the last 2 weeks. In the first section, you will be asked to answer questions about activities which make some people feel short of breath. In the next section, you will answer questions about your mood and how you have been feeling.

Please read these instructions for completing this questionnaire:

- Please read each question carefully and then place an "x" in the box beside the answer that best describes you. If you are unsure about how to answer a question, please give the best answer you can. If you would like to change an answer, put a line through the box you want to change. Place an "x" in the box beside the option you would like to choose instead.
- There are no right or wrong answers.
- Your answers to this questionnaire will be kept confidential.

Please continue on the next page.

CHRONIC RESPIRATORY QUESTIONNAIRE - SELF ADMINISTERED - STANDARDISED ACTIVITIES - "CRQ-SAS"

Date

DAY		MONTH		YEAR	

CRQ-SAS 1ST ADMINISTRATION 2(10)

Below is a list of activities which make some people with lung problems feel short of breath.

For each of the items below, place an "x" in the box that best describes how much shortness of breath you have had while doing that activity during the **LAST 2 WEEKS**.

The last column has been provided for you to indicate if you have **NOT DONE** an activity during the last two weeks.

(Place an "x" in one box on each line)

ACTIVITIES:	Extremely short of breath	Very short of breath	Quite a bit short of breath	Moderate shortness of breath	Some shortness of breath	A little shortness of breath	Not at all short of breath	Not Done
1 Feeling emotional, such as angry or upset	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2 Taking care of your basic needs (bathing, showering, eating or dressing)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
3 Walking	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
4 Performing chores (such as housework, shopping groceries)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
5 Participating in social activities	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>



McMaster University
Canada

Chronic Respiratory Questionnaire

Self-Administered Standardised Format (CRQ-SAS)

Follow-up Administration

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**CHRONIC RESPIRATORY QUESTIONNAIRE - SELF ADMINISTERED - STANDARDISED ACTIVITIES - "CRQ-SAS"
FOLLOW-UP ADMINISTRATION**

Date

DAY		MONTH		YEAR			

CHRONIC RESPIRATORY QUESTIONNAIRE -SAS- FOLLOW-UP 1(10)

You have previously completed a questionnaire containing questions on how you have been feeling and how your lung disease was affecting your life. This is a follow-up questionnaire designed to ask you how you have been since that time.

Please read these instructions for completing this questionnaire:

- Please read each question carefully and then place an "x" in the box beside the answer that best describes you. If you would like to change an answer, put a line through the box you want to change. Place an "x" in the box beside the option you would like to choose instead.
- If you are unsure about how to answer a question, please give the best answer you can.
- Remember there are no right or wrong answers.
- Your answers to this questionnaire will be kept confidential.

Please continue on the next page.

**CHRONIC RESPIRATORY QUESTIONNAIRE - SELF ADMINISTERED - STANDARDISED ACTIVITIES - "CRQ-SAS"
FOLLOW-UP ADMINISTRATION**

Date

DAY		MONTH		YEAR	

CHRONIC RESPIRATORY QUESTIONNAIRE -SAS- FOLLOW-UP 2(10)

This question is designed to find out how you have been getting on since the last time you saw us. You previously completed this questionnaire telling us how short of breath you were while performing the following activities.

For each of the activities below, place an "x" in the box that best describes how much shortness of breath you have had during the last two weeks while performing that activity.

The last column has been provided for you to indicate if you have NOT DONE an activity during the last two weeks.

(Place an "x" in one box on each line)

ACTIVITIES:	Extremely short of breath	Very short of breath	Quite a bit short of breath	Moderate shortness of breath	Some shortness of breath	A little shortness of breath	Not at all short of breath	Not Done
1 Feeling emotional, such as angry or upset	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
2 Taking care of your basic needs (bathing, showering, eating or dressing)	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
3 Walking	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
4 Performing chores (such as housework, shopping for groceries)	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
5 Participating in social activities	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>

Please continue on the next page.

**10.10 CHRONIC RESPIRATORY QUESTIONNAIRE – SELF ADMINISTERED
INDIVIDUALIZED**

**McMASTER UNIVERSITY
CANADA**

**CHRONIC RESPIRATORY QUESTIONNAIRE
SELF-ADMINISTERED INDIVIDUALIZED FORMAT**

(CRQ-SAI)

FIRST ADMINISTRATION

CHRONIC RESPIRATORY QUESTIONNAIRE
SELF-ADMINISTERED INDIVIDUALIZED FORMAT (CRQ-SAI)
FIRST ADMINISTRATION

Date completed:
DAY MONTH YEAR

This questionnaire is designed to find out how you have been feeling during the last 2 weeks. In the first section, you will be asked to answer questions about activities which make some people feel short of breath. In the next section, you will answer questions about your mood and how you have been feeling.

Please read these instructions for completing this questionnaire:

- Please read each question carefully and place an "x" in the box beside the answer that best describes you.
- If you are unsure about how to answer a question, please give the best answer you can.
- If you would like to change an answer, put a line through the box you want to change. Place an "x" in the box beside the option you would like to choose instead.
- There are no right or wrong answers.
- Your answers to this questionnaire will be kept confidential.

Please continue to the next page

1 of 8

CHRONIC RESPIRATORY QUESTIONNAIRE
SELF-ADMINISTERED INDIVIDUALIZED FORMAT (CRQ-SAI)
FIRST ADMINISTRATION

- i. Please read the following list of activities which make some people with lung problems feel short of breath. Place an "x" in the box beside each activity IF you answer YES to ALL of the following four statements: you have done the activity during the **LAST 2 WEEKS**
and it is something you do frequently
and it is important to your day to day life
and it makes you feel short of breath
- ii. If you have not done the activity during the **LAST 2 WEEKS** or it does NOT make you feel short of breath then leave it blank.
- iii. After you have read the list, please add any additional activities in the spaces provided. Only write down additional activities IF you answer YES to ALL of the following four statements: you have done the activity during the **LAST 2 WEEKS**
and it is something you do frequently
and it is important to your day to day life
and it makes you feel short of breath

PLACE AN "X" IN THE BOX BESIDE ANY ACTIVITIES THAT APPLY

- | | |
|---|---|
| 1 <input type="checkbox"/> BEING <u>ANGRY</u> OR UPSET | 13 <input type="checkbox"/> <u>PLAYING</u> WITH CHILDREN OR GRANDCHILDREN |
| 2 <input type="checkbox"/> HAVING A <u>BATH</u> OR SHOWER | 14 <input type="checkbox"/> <u>PLAYING</u> SPORTS |
| 3 <input type="checkbox"/> <u>BENDING</u> | 15 <input type="checkbox"/> <u>REACHING</u> OVER YOUR HEAD |
| 4 <input type="checkbox"/> <u>CARRYING</u> , SUCH AS CARRYING GROCERIES | 16 <input type="checkbox"/> <u>CLIMBING</u> , SUCH AS FOR A BUS |
| 5 <input type="checkbox"/> <u>DRESSING</u> | 17 <input type="checkbox"/> <u>SHOPPING</u> |
| 6 <input type="checkbox"/> <u>EATING</u> | 18 <input type="checkbox"/> <u>WHILE TRYING TO SLEEP</u> |
| 7 <input type="checkbox"/> <u>GOING</u> FOR A WALK | 19 <input type="checkbox"/> <u>STANDING</u> |
| 8 <input type="checkbox"/> DOING YOUR <u>HOUSEWORK</u> | 20 <input type="checkbox"/> <u>WALKING</u> |
| 9 <input type="checkbox"/> HURRYING | 21 <input type="checkbox"/> <u>WALKING</u> AROUND YOUR OWN HOME |
| 10 <input type="checkbox"/> <u>MAKING</u> A BED | 22 <input type="checkbox"/> <u>WALKING</u> UPSTAIRS |
| 11 <input type="checkbox"/> <u>MOPPING</u> OR SCRUBBING THE FLOOR | 23 <input type="checkbox"/> <u>WALKING</u> UPSTAIRS |
| 12 <input type="checkbox"/> <u>MOVING</u> FURNITURE | 24 <input type="checkbox"/> <u>WALKING</u> WITH OTHERS ON LEVEL GROUND |
| | 25 <input type="checkbox"/> <u>PREPARING</u> MEALS |
| | 26 <input type="checkbox"/> _____ (Additional activity) |
| | 27 <input type="checkbox"/> _____ (Additional activity) |
| | 28 <input type="checkbox"/> _____ (Additional activity) |
| | 29 <input type="checkbox"/> _____ (Additional activity) |

Please continue to the next page

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CHRONIC RESPIRATORY QUESTIONNAIRE
SELF-ADMINISTERED INDIVIDUALIZED FORMAT (CRQ-SAI)
FIRST ADMINISTRATION

We would now like you to look back at page 2 and from the list of activities where you have placed an "x" in the box, tell us which is the most important activity in your day to day life.

To help you do this:

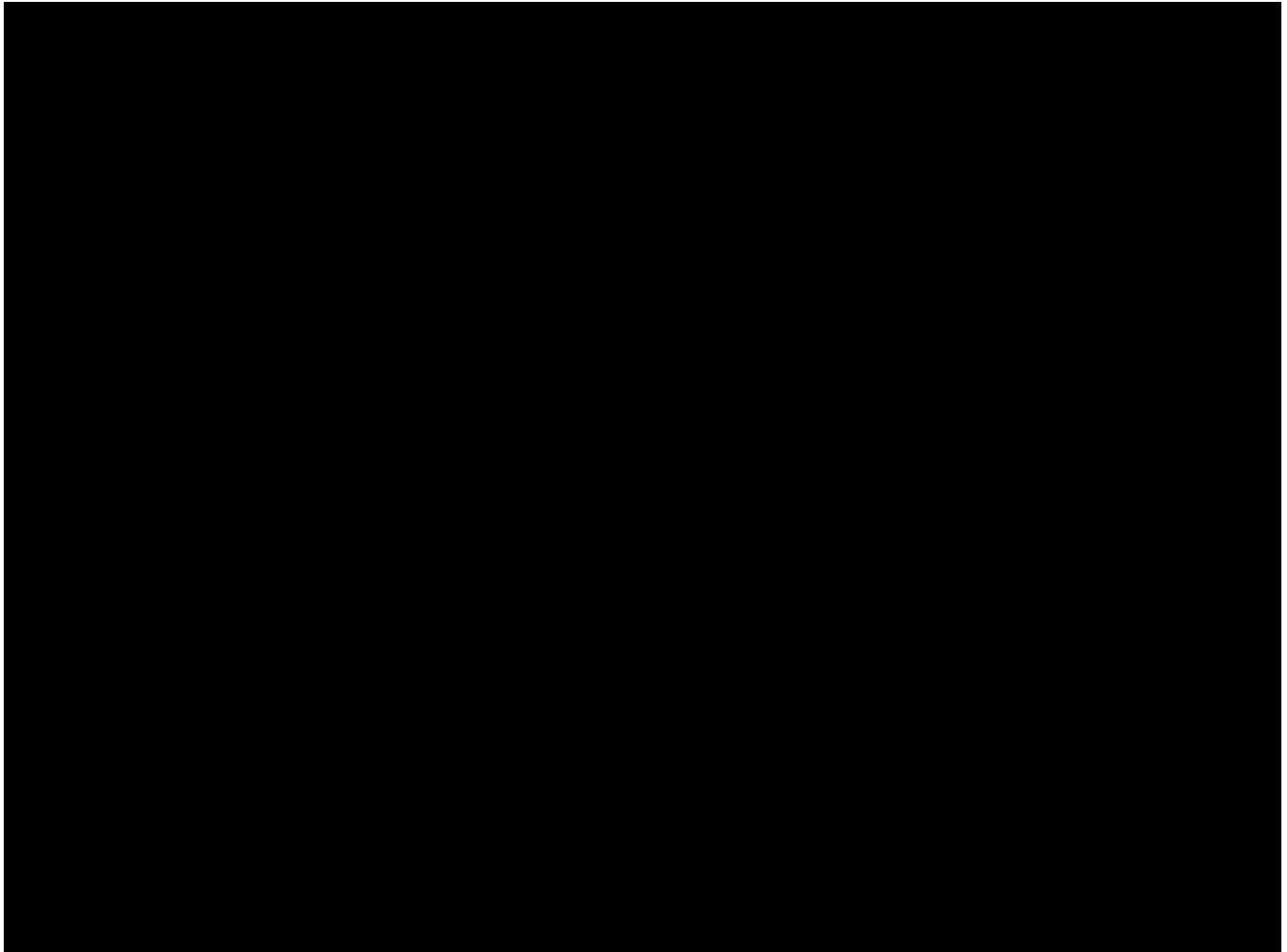
- Look at the activities that you have placed an "x" in the box beside. Decide which activity is the most important to you in your day to day life. To do this, ask yourself, "if I could choose one activity where I would no longer become short of breath doing which one would it be?"
- Decide which is the first most important activity and write it on line 1 below. Decide which is the 2nd most important activity and write in on line 2. Continue doing this until you have rated a maximum of 5 activities.
- For each of the most important activities that you have recorded below, place an "x" in the box that best tells how much shortness of breath you have had while doing that activity during the **LAST 2 WEEKS**.

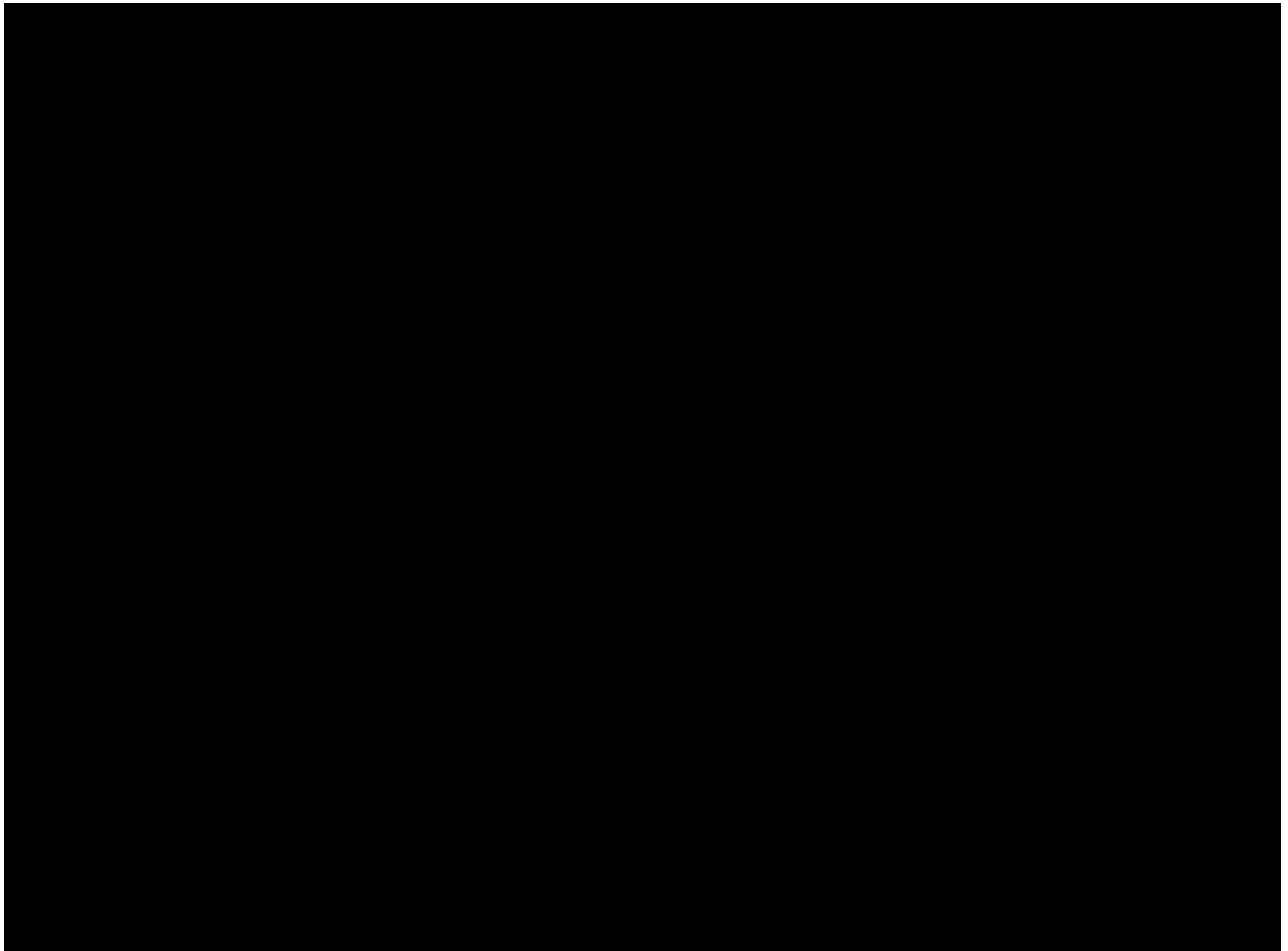
(Place an "x" in one box on each line)

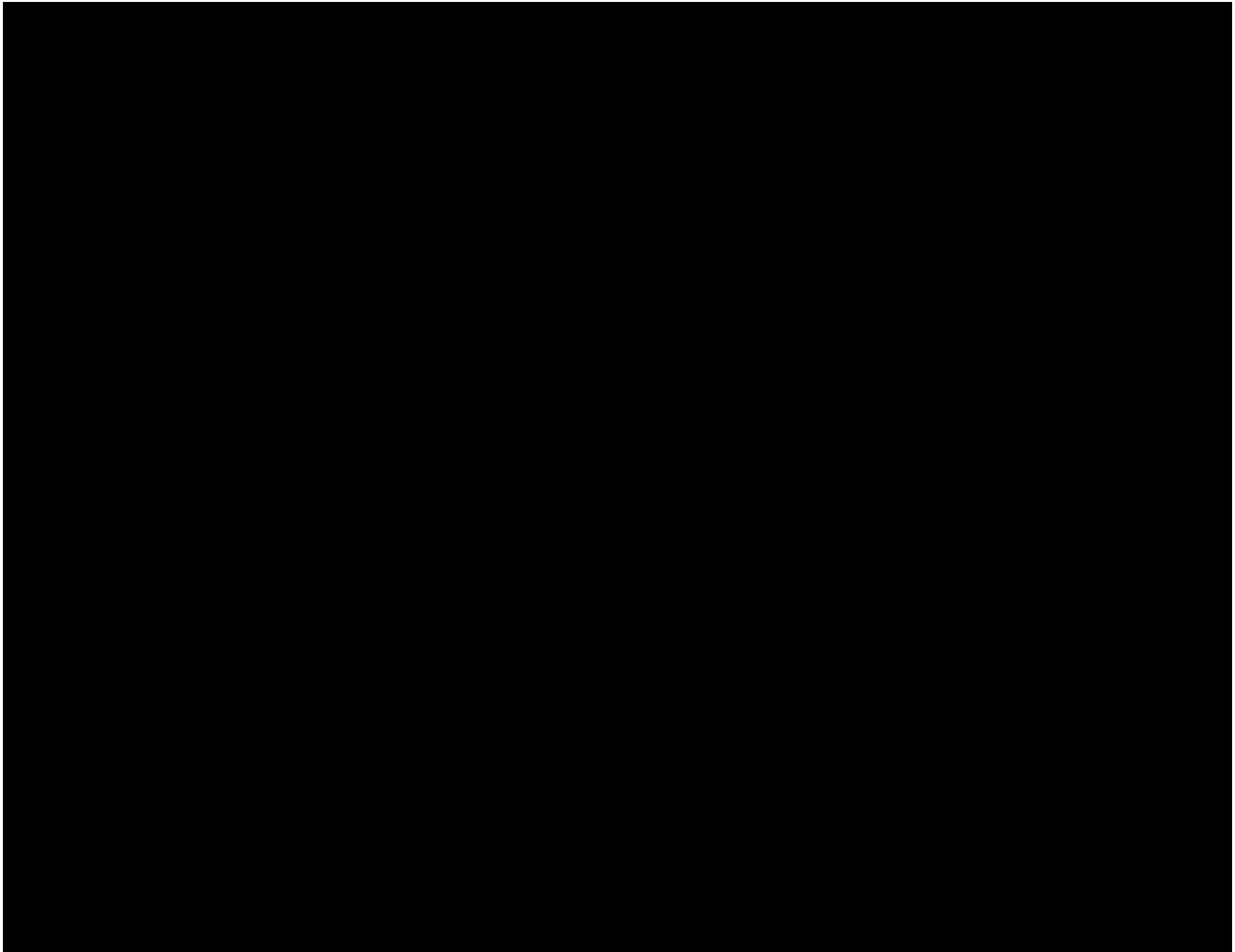
Activities	Extremely short of breath	Very short of breath	Quite a bit short of breath	Moderate shortness of breath	Some shortness of breath	A little shortness of breath	Not at all short of breath	
Activity	Name of activity							
1	<input type="checkbox"/> <input type="checkbox"/> _____	1 <input type="checkbox"/>	2 <input type="checkbox"/>	3 <input type="checkbox"/>	4 <input type="checkbox"/>	5 <input type="checkbox"/>	6 <input type="checkbox"/>	7 <input type="checkbox"/>
2	<input type="checkbox"/> <input type="checkbox"/> _____	1 <input type="checkbox"/>	2 <input type="checkbox"/>	3 <input type="checkbox"/>	4 <input type="checkbox"/>	5 <input type="checkbox"/>	6 <input type="checkbox"/>	7 <input type="checkbox"/>
3	<input type="checkbox"/> <input type="checkbox"/> _____	1 <input type="checkbox"/>	2 <input type="checkbox"/>	3 <input type="checkbox"/>	4 <input type="checkbox"/>	5 <input type="checkbox"/>	6 <input type="checkbox"/>	7 <input type="checkbox"/>
4	<input type="checkbox"/> <input type="checkbox"/> _____	1 <input type="checkbox"/>	2 <input type="checkbox"/>	3 <input type="checkbox"/>	4 <input type="checkbox"/>	5 <input type="checkbox"/>	6 <input type="checkbox"/>	7 <input type="checkbox"/>
5	<input type="checkbox"/> <input type="checkbox"/> _____	1 <input type="checkbox"/>	2 <input type="checkbox"/>	3 <input type="checkbox"/>	4 <input type="checkbox"/>	5 <input type="checkbox"/>	6 <input type="checkbox"/>	7 <input type="checkbox"/>

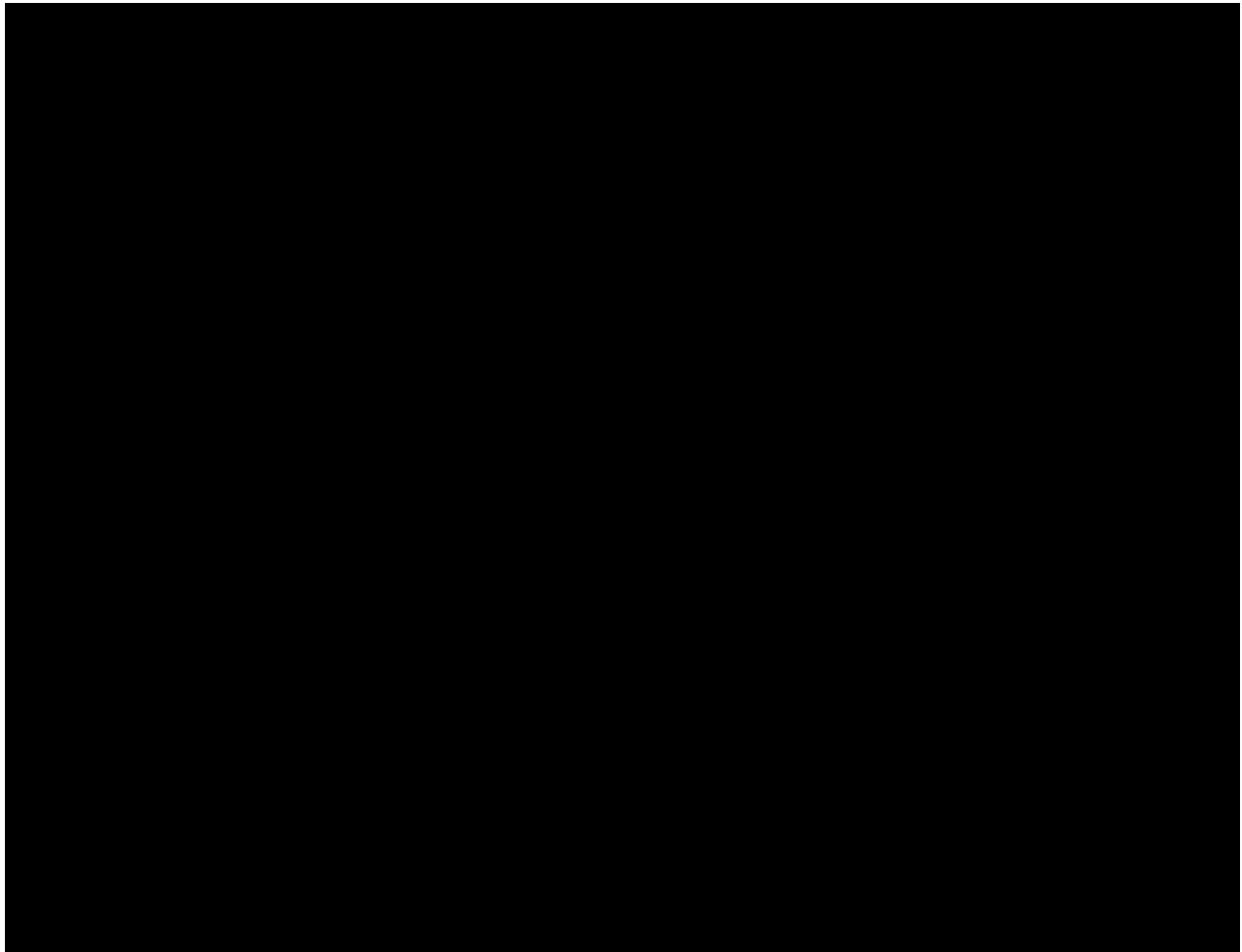
Please continue to the next page

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[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]		
[REDACTED]		
[REDACTED]		
[REDACTED]		
[REDACTED]		
[REDACTED]		
[REDACTED]		
[REDACTED]		
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]		

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]

[REDACTED]

[illegible]

[illegible]

[REDACTED]	[REDACTED]	[REDACTED] [REDACTED]
[REDACTED]	[REDACTED]	[REDACTED] [REDACTED]
[REDACTED]	[REDACTED]	[REDACTED] [REDACTED] [REDACTED]
[REDACTED]	[REDACTED]	[REDACTED] [REDACTED]
[REDACTED]	[REDACTED]	[REDACTED] [REDACTED] [REDACTED]
[REDACTED]	[REDACTED]	[REDACTED] [REDACTED]
[REDACTED]	[REDACTED]	[REDACTED] [REDACTED] [REDACTED]
[REDACTED]	[REDACTED]	[REDACTED] [REDACTED]

[REDACTED]

[illegible]

[illegible]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

“This is the original protocol.”

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



APPROVAL / SIGNATURE PAGE
Document Number: c03207491

Technical Version Number:1.0

Document Name: clinical-trial-protocol

Title: A randomised, double-blind, cross-over study to determine the effect of 6 weeks treatment of orally inhaled tiotropium + olodaterol fixed dose combination (5/5 µg) compared with tiotropium (5 µg), both delivered by the Respimat® Inhaler, on breathlessness during the three minute Constant Speed Shuttle Test (3min CSST) in patients with Chronic Obstructive Pulmonary Disease (COPD) [OTIVATO®]

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Approval-Trial Clinical Monitor		15 Apr 2016 19:52 CEST
Author-Team Member Medicine		15 Apr 2016 20:39 CEST
Approval-Therapeutic Area 		19 Apr 2016 09:32 CEST
Approval-Biostatistics		19 Apr 2016 15:35 CEST
Verification-Paper Signature Completion		19 Apr 2016 16:52 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
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