CLINICAL TRIAL PROTOCOL

	Document Number:	**c03397161-01**
BI Trial No.:	1237.33	
BI Investigational Product:	Spiolto® Respimat®, Tiotropium+olodaterol RESPIMAT fixed dose combination inhalation solution	
Title:	A randomised, double-blinded, active-controlled 2-way cross over trial to assess the effects of 6 weeks treatment of once daily orally inhaled tiotropium + olodaterol fixed dose combination delivered by RESPIMAT Inhaler compared with tiotropium delivered by RESPIMAT Inhaler on lung hyperinflation, exercise capacity and physical activity in Japanese patients with Chronic Obstructive Pulmonary Disease (COPD)	
Brief Title:	Japanese Physical Activity Study [VESUTO™]	
Clinical Phase:	IIIb	
Trial Clinical Monitor:	[redacted] Phone: Fax:	
Coordinating Investigator:	[redacted] Phone: Fax:	
Status:	Final Protocol	
Version and Date:	**Version:**	**Date:**
	1.0	30 October 2015

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CLINICAL TRIAL PROTOCOL SYNOPSIS

Name of company:		**Boehringer Ingelheim**	
Name of finished product:		**Spiolto®**	
Name of active ingredient:		**Tiotropium + olodaterol fixed dose combination solution for inhalation**	
Protocol date: **30 OCT 2015**	**Trial number:** **1237.33**		**Revision date:**

Title of trial:	A randomised, double-blinded, active-controlled 2-way cross over trial to assess the effects of 6 weeks treatment of once daily orally inhaled tiotropium + olodaterol fixed dose combination (FDC) delivered by RESPIMAT Inhaler compared with tiotropium delivered by RESPIMAT Inhaler on lung hyperinflation, exercise capacity and physical activity in Japanese patients with Chronic Obstructive Pulmonary Disease (COPD)
Coordinating Investigator:	[redacted]
Trial sites:	Multi-centre trial in Japan
Clinical phase:	IIIb
Objectives:	The primary objective of this trial is to investigate the effect of 6 weeks treatment with tiotropium + olodaterol FDC therapy compared to tiotropium monotherapy on lung hyperinflation (measured by an inspiratory capacity [IC]) in Japanese patients with COPD The second objective is to evaluate the effect of 6 weeks treatment with tiotropium + olodaterol FDC compared to tiotropium monotherapy on exercise tolerability (measured by a 6-minute walk test [6MWT]) and amount of daily physical activity (measured by an activity monitor [3-axis accelerator]) in Japanese patients with COPD
Methodology:	Double-blinded, randomised, active-controlled, two-way cross over design
No. of patients:	
total entered:	180 patients (240 patients enrolled)
each treatment:	Tiotropium + olodaterol FDC: 180 patients Tiotropium : 180 patients
Diagnosis :	Chronic Obstructive Pulmonary Disease (COPD)
Main criteria for inclusion:	• Patients must have relatively stable airway obstruction with a post-bronchodilator FEV_1 < 80% of predicted normal and post-bronchodilator FEV_1/FVC < 70% at Visit 1. • Male or female patients, aged ≥ 40 years. • Patients must be current or ex-smokers with a smoking history of more than 10 pack years. • Patients with score on the modified Medical Research Council (mMRC) ≥1. • Patients who walk <400 meters of 6MWT and have a score on the modified Borg ≥4 at the end of 6MWT at Visit 2.

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Name of company:		**Boehringer Ingelheim**	
Name of finished product:		**Spiolto®**	
Name of active ingredient:		**Tiotropium + olodaterol fixed dose combination solution for inhalation**	
Protocol date: **30 OCT 2015**	**Trial number:** **1237.33**		**Revision date:**

Test product:	Tiotropium + olodaterol fixed dose combination (FDC) solution for inhalation
dose:	[5 µg tiotropium + 5 µg olodaterol] once daily
mode of administration:	Oral inhalation
Comparator product:	Tiotropium solution for inhalation
dose:	5 µg once daily
mode of administration:	Oral inhalation
Duration of treatment:	- Screening period (Visit 1 to Visit 2): 2 weeks - Double-blind treatment period: 12 weeks (2 x 6 weeks treatment periods) - Follow up period: 3 weeks
Endpoints	Primary Endpoint: · IC at rest measured at 60 minutes post-dose, after 6 weeks of treatment Secondary Endpoints · 6 minute walk distance (m) after 6 weeks of treatment · Average number of step per day (step/ day) measured by the activity monitor in the 2 weeks prior to Week 6 · Average daily duration (minutes) of ≥ 4 metabolic equivalents (METs) measured by the activity monitor in the 2 weeks prior to Week 6 · Average daily duration (minutes) of ≥ 3 METs measured by the activity monitor in the 2 weeks prior to Week 6 · Average daily duration (minutes) of ≥ 2 METs measured by the activity monitor in the 2 weeks prior to Week 6 · Average daily active strength (METs·minutes) of ≥ 3 METs measured by the activity monitor in the 2 weeks prior to Week 6 · 60 minutes post-dose Slow vital capacity (SVC), after 6 weeks of treatment · 30 minutes post-dose FEV_1, after 6 weeks of treatment. · 30 minutes post-dose FVC, after 6 weeks of treatment.
Safety criteria:	Adverse events, Physical examination, Heart rate and SpO_2 in conjunction with 6MWT
Statistical methods:	Primary endpoint will be analysed using a mixed effect repeated measures model, with treatment and period as categorical fixed effects, study baseline as a covariate and patient as a random effect. Secondary and further endpoints for efficacy will be analysed using the same model as the primary endpoint. Descriptive statistics will be used for safety and efficacy endpoints.

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FLOW CHART

Trial Periods	**Screening Period**		**Treatment period 1**				**Treatment period 2**			**Trial Follow-Up**
Visit Number	0[1]	1	2	☎	☎	3	☎	☎	4/ EOT	5
Week of treatment		-2	0	4	5	6	10	11	12	EOT+3
Day of treatment		-14	1	28	35	43	70	77	85	106
Visit window (days)		-7	N/A	-3	±1	+3	-3	±1	+3	+7
Informed consent	X[2]									
Demographics		X								
Medical history / concomitant diagnosis		X								
Smoking status		X							X[3]	
In-/ exclusion criteria[4]		X	X							
Physical examination		X	X			X			X[3]	X[5]
Laboratory tests		X							X[3]	X[5]
12-lead ECG		X	X			X			X[3]	X[5]
Pregnancy test[6]		X							X[3]	X[5]
Training in use of RESPIMAT[7]		X	X							
Dispense and explain use of rescue medication[8]	X	X	X			X				
Collect rescue medication/accountability check[8]		X	X			X			X[3]	
Medication washout check		X	X			X			X	
Administration (dosing) of trial medication at the site			X			X[18]			X[18]	
[redacted]			X			X			X	
mMRC[20]		X								
Pulmonary Function Testing (PFT); FEV_1/FVC and SVC/IC)		X[9]	X[10]			X[11]			X[3,11]	
Vital signs (seated)[12]		X	X			X			X[3]	X[5]
6MWT		X[21]	X			X			X	
[redacted]		X[21]	X			X			X	

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Trial Periods	**Screening Period**		**Treatment period 1**				**Treatment period 2**			**Trial Follow-Up**
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Day of treatment		-14	1	28	35	43	70	77	85	106
Visit window (days)		-7	N/A	-3	±1	+3	-3	±1	+3	+7
Physical activity monitoring[14]		X →	X	X	→	X	X	→	X	
[redacted]			X			X			X	
[redacted]			X			X			X	
Patient Diary[23]		X	X			X			X[3]	
[redacted]			X			X			X	
Muscle amount (% in BW)		X								
Telephone contacts[17]				X	X		X	X		
Patient registration (IRT)		X								
Randomisation (via IRT)			**X**							
Dispense double-blinded trial medication			X			X				
Collect double-blinded trial medication and accountability check						X			X[3]	
Adverse events		X	X	X	X	X	X	X	X[3]	X
Concomitant therapy		X	X	X	X	X	X	X	X[3]	X

EOT: End of Treatment, IRT: Interactive Response Technology, PFT: Pulmonary Function Testing, [redacted] mMRC: modified Medical Research Council, [redacted], 6MWT: 6 minute walk test

1 Visit 1 may be scheduled 1-28 days after Visit 0 (depending on medication washout requirement as described in Section 4.2.2.1. Patients who are treated with LABA and LAMA should be treated at least 3 weeks with one of its'component, i.e. LABA or LAMA.).

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

3 EOT examinations are completed by all patients who took at least one dose of trial medication and who discontinue early. Pulmonary Function Testing (PFT) is to be performed if possible.

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

5 To be performed only if relevant findings at Visit 4/EOT.

6 Women of child-bearing potential: pregnancy test at Visit 1 and Visit 4/EOT

7 The patient will be instructed in the use of the RESPIMAT, but patient **should not** inhale from the training inhaler at Visit 2.

8 Rescue medication as salbutamol is prescribed at visit 0. Rescue medication will be collected and prescribed on subsequent visits by investigators as needed. All rescue medication for the trial to be confirmed to be collected at Visit 4/EOT.

9 Pre- and post-bronchodilator (400 µg salbutamol) [note: reversibility is not an inclusion criterion], Spirometry measurement; FVC and FEV_1 only.

10 Baseline spirometry measurement FEV_1, FVC, SVC, and IC.

11 Morning post-dose spirometry

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- FEV_1 and FVC: 30 min post-morning dose as starting time
- IC and SVC measurement: 60 min post-morning dose as starting time

12 Prior to the start of PFTs are performed.

13 [redacted]

14 Patients should wear and measure activity monitor (3-axis accelerator) every day for 2 weeks prior to Visit 2, Visit 3 and Visit 4/EOT.

15 [redacted]

16 [redacted]

17 Site staff will telephone the patients 15 days and 8 days prior to the next planned Visit and remind them to wear physical activity monitor every day. An assessment of adverse events and of concomitant therapy should be performed from the last assessment.

18 Trial medication dispensed at Visit 2 should be administrated at clinic at Visit 3 and trial medication dispensed at Visit 3 should be administrated at clinic at Visit 4/EOT. Newly assigned trial medication at Visit 3 should be administered next day of Visit 3.

19 [redacted]

20 Refer to Appendix 10.8. mMRC

21 Training of 6MWT

22 Refer to Appendix 10.11

23 Training of patient diary at Visit 1. Dispense of the diary at Visit 1, Visit 2 and Visit 3. Reviewing and collection of the diary at Visit 2, Visit 3 and Visit 4/EOT.

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TIMING OF PROCEDURES: VISIT1 _SCREENING

	Start time					
	-	**More than 30 min prior to Pre-dosing PFT**	**-10 to 0 min prior to administration salbutamol**	**administration salbutamol (0 min)**	**10 to 15 min after administration salbutamol**	**-**
Medication washout compliance	**X**					
mMRC[1]	**X**					
Physical examination, vital sign and 12-lead ECG[2]	**X**					
Laboratory test and Pregnancy test	**X**					
6MWT (training)		**X**				
Breathlessness/leg discomfort (modified Borg scale)[3]		**X**				
Pre-dosing PFT (FEV_1, FVC)			**X**			
Administration 400 µg salbutamol[4]				**X**		
Post-dosing PFT (FEV_1, FVC)					**X**	
Administration current medication[5]						**X**

1 mMRC questionnaires will be completed prior to all other procedures after medical washout compliance.
2 The vital signs (seated) and ECG should be conducted following 5 minutes rest and prior to blood sampling
3 Patients will be asked to rate breathing discomfort and leg discomfort using the modified Borg Scale before, during every 1 minute, and at the end of the 6MWT as outlined in Appendix 10.7.
4 The inhalation of 4 puffs of salbutamol will be conducted between 7:00 a.m.-10:00 a.m.
5 Administration current medication will be done after post-dosing PFT before at noon

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TIMING OF PROCEDURES: VISIT2 _BASELINE

	Start time				
	-	**0 min**	**30 min (± 5 min)**	**60 min (+ 10 min)**	**-**
Medication washout compliance	**X**				
[redacted]	**X**				
Physical examination, vital sign and 12-lead ECG	**X**				
PFT (FEV_1, FVC)		**X**			
PFT (IC, SVC)			**X**		
6MWT				**X**	
[redacted]				**X**	
Administration trial medication[3]					**X**

1 [redacted]

2 [redacted]

3 First administration trial medication will be done after 6MWT before at noon

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TIMING OF PROCEDURES: VISIT3, VISIT 4_ENDPOINT

	Start time				
	-	**Administration of medication (0 min)**	**30 min (± 5 min)**	**60 min (± 10 min)**	**90 min (+ 15 min)**
Medication washout compliance	**X**				
[redacted]	**X**				
Physical examination, vital sign and 12-lead EGC[2]	**X**				
Laboratory test and Pregnancy test (only Visit 4/EOT)	**X**				
Administration trial medication[3]		**X**			
PFT (FEV1, FVC)			**X**		
PFT (IC, SVC)				**X**	
6MWT					**X**
[redacted]					**X**

1 [redacted]

2 The vital signs (seated) and ECG should be conducted following 5 minutes rest and prior to blood sampling.

3 Study medication will be administration within ± 30 min of administration time of next day at Visit 2 and between 07:00 and 10:00 am.

4 [redacted]

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ABBREVIATIONS

ACCP	American College of Chest Physician
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AMP	Auxiliary Medicinal Product
ATS	American Thoracic Society
AST	Aspartate aminotransferase
AUC	Area under the Curve
BAC	benzalkonium chloride
BI	Boehringer-ingelheim
b.i.d	bis in die (twice daily dosing)
BIRDS	Boehringer Ingelheim Regulatory Documents for Submission
CA	Competent authority
[redacted]	[redacted]
CCDS	Company Core Data Sheet
CI	Confidence Interval
CML	Local Clinical Monitor
COPD	Chronic Obstructive Pulmonary Disease
CRA	Clinical Research Associate
CRO	Contract research organization
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
[redacted]	[redacted]
DEDP	Drug exposure during pregnancy
DILI	Drug induced liver injury
DMC	Data Monitoring Committee
eCRF	Electronic Case Report Form
ECG	Electrocardiogram
EDC	Electronic Data Capture
EELV	End expiratory lung volume
EOT	End of Treatment
ePRO	Electronic Patient Reported Outcome
ERS	European Respiratory Society
EudraCT	European Clinical Trials Database
FAS	Full Analysis Set
FDC	Fixed dose combination
FEV_1	Forced expiratory volume in one second
FVC	Forced vital capacity
GCP	Good Clinical Practice
GOLD	Global initiative for chronic Obstructive Lung Disease
[redacted]	[redacted]

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HPC	Human Pharmacology Center
HR	Heart Rate
IB	Investigator's Brochure
IC	Inspiratory capacity
ICS	Inhaled corticosteroids
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISF	Investigator Site File
i.v.	Intervenous
IVRS	Interactive Voice Response System
IWRS	Interactive Web-based Response System
LABA	Long acting β_2-agonists
LAMA	Long acting muscarinic antagonist
LDH	Lactate dehydrogenase
LoEE	List of Essential Element
MACE	Major adverse cardiovascular event
MCID	Minimal clinically important difference
MDI	metered dose inhaler
MedDRA	Medical Dictionary for Drug Regulatory Activities
METs	Metabolic equivalents
MST	Medical Sub team
mMRC	modified Medical Research Council
MMRM	mixed model repeated measures
OPU	Operative Unit
PA	Physical activity
PEFR	Peak expiratory flow rate
PFT	Pulmonary function testing
p.o.	per os (oral)
PPS	Per–Protocol Set
q.d.	quaque die (once a day)
RDC	remote data capture
REP	Residual effect period
SABA	Short-acting β_2–agonist
SAE	Serious Adverse Event
SAMA	Short-acting anticholinergic
[redacted]	[redacted]
SOP	standard operation procedure
6MWD	Six-minute walk distance
6MWT	Six-minute walk test
SPC	Summary of Product Characteristics
SUSAR	Suspected serious unexpected adverse reactions
SVC	Slow vital capacity
TCM	Trial Clinical Monitor
TDMAP	Trial Data Management and Analysis Plan

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TLC	Total lung capacity
TMF	Trial Master File
TS	Treated set
TSAP	Trial Statistical Analysis Plan
ULN	Upper limit of normal

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1. INTRODUCTION

1.1 MEDICAL BACKGROUND

Global initiative for chronic Obstructive Lung Disease (GOLD) treatment guidelines [P14-01052] place bronchodilators as the foundation of pharmacologic management of COPD. In patients with moderate to very severe pulmonary impairment (i.e., GOLD Stage II to IV) 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. Several recent studies have provided evidence in support of this increased bronchodilatory effect when LABAs are added to LAMAs.

When beta-agonists and muscarinic antagonists with similar or equivalent posologies are combined, the opportunity exists for offering a simpler and more convenient administration regimen with the development of fixed combinations within the same inhaler device. The development of the novel once daily LABA olodaterol (quaque die [q.d.]) now offers the opportunity for a once daily (FDC) LABA/LAMA including the well-established LAMA tiotropium.

The complementary modes of action of tiotropium and olodaterol have previously been demonstrated in human clinical trials. The application for marketing authorisation has been approved in the EU, US, Japan and a number of other countries.

1.2 DRUG PROFILE

Tiotropium

Tiotropium is an established once-daily 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 patients with GOLD Stage II [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 5µg q.d..) is approved in more than 80 countries worldwide including EU, US and Japan. Further information about tiotropium can be found in the Investigators Brochure (IB) for the product.

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Olodaterol

Olodaterol is a highly selective and nearly full β_2 agonist [P10-07776, P11-07720] that provides 24-h bronchodilation in patients with COPD [P13-11467, P13-14112, P13-11346, P13-11345] Olodaterol is also associated with symptomatic benefit [P13-11341] and enhanced exercise capacity [P13-14109]. Olodaterol RESPIMAT 5 µg once daily has so far been approved in more than 40 countries worldwide (Olodaterol is not approved in Japan).

Tiotropium + olodaterol fixed dose combination

Tiotropium + olodaterol FDC is an aqueous solution of tiotropium and olodaterol. It is administered by using the RESPIMAT inhaler.

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

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

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

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

In conclusion, the clinical trials conducted to date have shown tiotropium + olodaterol FDC to be a safe, well tolerated and efficacious combination therapy according to treatment guidelines in a moderate to very severe COPD patient population that included patients with concomitant cardiovascular diseases. The observed incremental bronchodilator response for

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the combination compared to the individual components translated into benefits that were meaningful to the patient, with improvements in several patient-reported outcomes. For further information please refer to the IB for the Tiotropium + olodaterol FDC.

RESPIMAT Inhaler

Boehringer Ingelheim's RESPIMAT Inhaler will be used for administration of tiotropium + olodaterol FDC and tiotropium. One cartridge is used per inhaler, which is inserted into the device prior to first use. In pivotal clinical trials and for the intended marketed product, the clinical dose consists of two actuations once daily. The RESPIMAT inhaler uses mechanical energy to create a soft mist which is released over a period of approximately 1.5 seconds. The fraction of fine particles accessible to lungs and airways is very high compared with many metered dose aerosols or dry powder devices. The solution is adjusted to pH 2.9 because the drug in solution is stable at acidic pH values. Due to the multi-dose characteristics of the RESPIMAT Inhaler, the drug formulation contains the chelating agent disodium edentate (EDTA) and the antimicrobial preservative benzalkonium chloride (BAC). However, the concentrations of EDTA and BAC in tiotropium + olodaterol FDC solution and tiotropium solution for inhalation with the RESPIMAT Inhaler are well below the levels, which have been reported to induce bronchospasms in some patients inhaling aerosols of solutions from a nebulizer.

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2. RATIONALE, OBJECTIVES, AND BENEFIT - RISK ASSESSMENT

2.1 RATIONALE FOR PERFORMING THE TRIAL

Lung hyperinflation is an important factor to cause exercise-associated symptoms such as dyspnea and fatigue. These symptoms as a result of lung hyperinflation are believed to induce a reduction of exercise tolerability and daily physical activity (PA) being strong predictors of the rise of mortality in patients with COPD. Therefore, an improvement in lung hyperinflation is one of desirable therapeutic goals for the COPD patients with symptomatic dyspnea.

Previous global Phase III studies including Japanese COPD patients, tiotropium + olodaterol FDC were shown to be superior in improving airflow over 24 hours, QOL, and breathlessness compared with tiotropium or olodaterol monotherapy (ref 1237.5/6). Moreover, the other studies (ref 1237.13/14) have shown statistically significant improvement of lung hyperinflation (i.e. an increase in inspiratory capacity, IC) for tiotropium + olodaterol FDC compared with tiotropium or olodaterol monotherapy. However, no Japanese patients with COPD have participated in these two studies: trial 1237.13/14. As a consequence, the pharmacological impact of these bronchodilators on lung hyperinflation in Japanese patients with COPD has not been demonstrated yet.

In this trail, we are planning to investigate the effects of tiotropium + olodaterol FDC compared with tiotropium on IC as an index of lung hyperinflation in Japanese patients with COPD. Moreover, the effect of these bronchodilators on exercise tolerability and amount of daily physical activities are also evaluated in parallel. For purpose of evaluation of exercise tolerability and daily physical activity, we will perform a 6-minute walk test (6MWT) and activity monitor (3-axis accelerator) assessment, respectively.

2.2 TRIAL OBJECTIVES

The primary objective of this trial is to demonstrate investigate the effect of 6 weeks treatment with tiotropium + olodaterol FDC therapy compared to tiotropium monotherapy on lung hyperinflation (measured by IC) in Japanese patients with COPD

The secondary objective is to evaluate the effect of 6 weeks treatment with tiotropium + olodaterol FDC therapy compared to tiotropium monotherapy on exercise tolerability (measured by 6MWT) and amount of daily physical activities (measured by activity monitor) in Japanese patients with COPD

2.3 BENEFIT - RISK ASSESSMENT

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The potential benefits of a treatment with tiotropium + olodaterol FDC (5 µg/5 µg) and tiotropium from the RESPIMAT have been described in Section 1.2. Tiotropium is a well-established maintenance treatment for patients with COPD across broad severities.
The clinical trials conducted to date have shown tiotropium + olodaterol FDC (5 µg/5 µg) to be a safe, well tolerated and efficacious combination therapy in a moderate to very severe COPD patient population (including patients with concomitant cardiovascular diseases). The observed incremental bronchodilator response for the combination compared to the monotherapy translated into benefits that were meaningful to the patient, with improvements in several patient-reported outcomes.

Potential risks associated with administration of the combination of tiotropium and olodaterol include the listed adverse events for the IB for the Tiotropium + olodaterol FDC.

Women of childbearing potential may be included in clinical trials for tiotropium + olodaterol FDC (5 µg/5 µg) provided appropriate precautions are taken to minimize the risk of pregnancy. These precautions include pregnancy testing and use of a highly effective method of birth control. Continued testing and monitoring during the trial should be sufficient to ensure compliance with the measures not to become pregnant during the period of drug exposure (which may exceed the length of study until the follow-up visit at 21 days after discontinuation of study medication [R05-0370]).

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

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

At Visit 3, the patients will receive the other treatment which has not been received in previous treatment without any washout period. There is no placebo comparator in this trial.

Patients receiving inhaled corticosteroids before enrolment will continue their treatment (or the inhaled corticosteroids component alone if taken as a fixed combination with bronchodilator) at an equivalent dose and regimen by the end of treatment period. The only medications that are excluded during the treatment period are anticholinergic and long-acting β_2-adrenergic other than the study drugs.

During the whole course of the trial, salbutamol is prescribed to be used as rescue medication for all patients after they have signed their informed consent. The proposed medication restriction scheme is considered ethically acceptable given the availability of rescue short-acting β2-adrenergic (SABA) and permitted use of the other maintenance medications.

Patients who treat with LAMA/LABA combination at informed consent are desired to switch to LAMA or LABA monotherapy after informed consent, but patient' safety are secured since SAMA or SABA are available at least during the screening period.

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Safety will be monitored (as described in Section 5.3) at site visits as well as at each telephone contact. Patients will be contacted by site staff and asked for adverse events and change in concomitant therapy.

Given the good tolerability seen in the clinical trials for the combination of tiotropium and olodaterol and the careful monitoring during the study visits and phone contacts, the sponsor considers the risks to the participating patients would be minimised.

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3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

This is a multi-centre, randomised, double-blinded, active-controlled, 2-way cross over trial to assess the effects of once daily administration of orally inhaled tiotropium + olodaterol FDC 5 µg/5 µg or tiotropium 5 µg (both delivered by the RESPIMAT Inhaler) on pulmonary function (lung hyperinflation), exercise capacity (6-minute walk distance [6MWD]) and physical activities after 6 weeks of treatment in Japanese patients with COPD.

After signing Informed Consent (Visit 0) and completing an initial screening visit (Visit 1) after appropriate stable treatment with LAMA or LABA mono therapy (In case, patients who treated with combination of LABA and LAMA need to be treated at least 3 weeks with only monotherapy component.) and ensuring clinical stability (i.e. no exacerbations), patients will start a 2-week screening period. During the screening visit (Visits 1), they will conduct baseline physical activity assessments (between Visit 1 to Visit 2) and baseline IC (Visit 2) and 6MWT (Visit 1 and Visit 2).

Patients who meet all the inclusion criteria and none of the exclusion criteria will be randomised (1:1 ratio) at Visit 2 into the 2-period 6-week double-blind, cross-over treatment portion of the study, in which they will receive one of two treatment sequences as follows:

Sequence AB; Tiotropium followed by Tiotropium + olodaterol FDC

Sequence BA; Tiotropium + olodaterol FDC followed by Tiotropium

for a total of 12 weeks of treatment (Figure 3.1: 1).

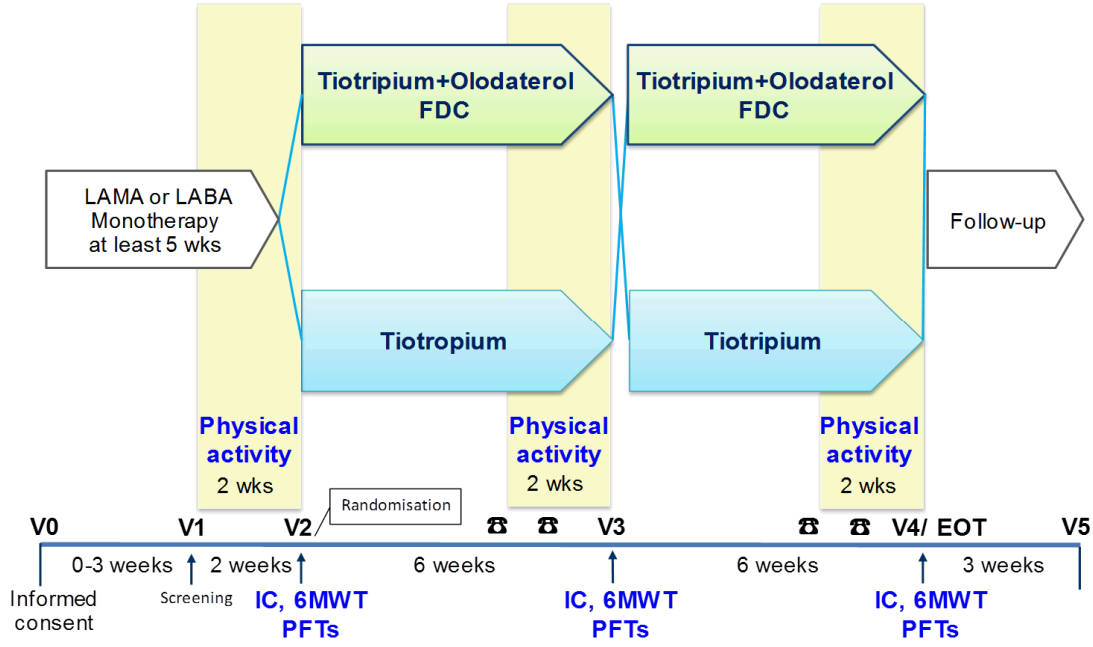

Figure 3.1: 1 Trial design

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An 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.

In this trial, patients who complete first 6-week treatment period will subsequently start second 6-week treatment period. There is no washout period between each treatment periods.

Pulmonary function testing (PFT) will be conducted at Visit 1, just before (within 10 min) and 10-15 min after inhalation of sulbtamol for inclusion, at Visit 2 for baseline and at Visit 3 and Visit 4/EOT during the treatment period (30 min post-dosing and 60 min post-dosing)

Physical examination will be performed together with an evaluation of the patient's smoking status and COPD background characteristics at Visit 1. Blood samples for clinical laboratory testing will be obtained and a 12-lead ECG will be recorded at Visit 1 to evaluate the patient's eligibility. Pregnancy testing will be performed at Visit 1 and 4/EOT in females of child bearing potential.

A 6MWT will be performed at Visit 1 (more than 30 min before PFT of post-dose salbutamol inhalation) for training in the study. The 6MWT will also be performed at Visit 2 for inclusion. Additional tests will be conducted at Visit 3 and Visit 4/EOT during the treatment period (90 minutes post-dosing). [redacted]

Physical activity assessment for baseline will be performed between Visit 1 and Visit 2. Physical activity assessments during the treatment period will be conducted for approximately 2 weeks prior to Visit 3 and Visits 4/EOT.

Adverse events and concomitant therapies will be documented throughout the trial, i.e. starting with informed consent and ending 21 days after actual last administration of trial medication.

3.1.1 Administrative structure of the trial

Boehringer Ingelheim has appointed a Trial Clinical Monitor, responsible for coordinating all required activities, in order to

- manage the trial in accordance with applicable regulations and internal SOPs,
- direct the clinical trial team in the preparation, conduct, and reporting of the trial,
- order the materials as needed for the trial,
- ensure appropriate training and information of local clinical monitors (CML), Clinical Research Associates (CRAs), and Investigators of participating countries.

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

A list of responsible persons and relevant local information (as protocol reference, if applicable) can be found in the ISF.

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

Boehringer Ingelheim (BI) will be responsible for the monitoring of the study.

Clinical Research Organisation (CRO)
IRT system will be used for randomisation in this trial and for allocation of trial medication to patients throughout the treatment period. The ability to unblind will be available to the investigator via IRT during emergency.

Spirometer, Flowscreen (eRT), which meets ATS/ERS Criteria (P05-12782) will be provided by BI.

All contracts and relevant meeting minutes will be stored by BI in the trial master file (TMF).

A physical activity monitor (Omron healthcare), a mobile pulse oximeter (Fukuda denshi) and a body composition meter (Omron healthcare) are provided by BI.

The following local facilities/equipment are required at the investigational site: body weight scale, height scale, sphygmomanometer, 12-lead ECG device will be used on all patients during the trial. Sites have to be able to perform 6MWT.

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

Since patients may be randomised to a treatment arm that includes both a LABA (olodaterol) and a LAMA (tiotropium), it is necessary to restrict the use of LABA (e.g. salmeterol, formoterol, indacaterol) and LAMA or SAMA (e.g. tiotropium, ipratropium) during the treatment period. Patients will continue to receive treatment with inhaled corticosteroids as required. SABA medication (salbutamol MDI) will be prescribed at the trial site to all patients for rescue use, and appropriate medications will be allowed to control acute exacerbations as medically necessary.

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 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].

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Patients participating in this trial should perform exercise tolerance test for every visit. In order to decrease the burden on patients, medication restrictions such as a longer washout period have not been included in this trial. All participants are treated with tiotropium in both treatment periods, so a washout period for tiotropium before treatment 2 has not been included in this trial. In terms of olodaterol, we set the efficacy endpoints in the 2 weeks prior to Week 6 in order to avoid a carryover effect of olodaterol in the previous period. It is also considered sufficient to evaluate the effects of tiotropium + olodaterol FDC at the efficacy endpoints in the 2 weeks prior to Week 6 because a pharmacodynamic steady state of olodaterol has been reached.

3.3 SELECTION OF TRIAL POPULATION

A sufficient number of patients will be enrolled (sign informed consent) to ensure that at least 180 patients (90 patients per each treatment sequence) of either sex, aged ≥ 40 years with a diagnosis of COPD are randomised into the study.

Enrolment will be competitive. Additional sites may be initiated may be closed to ensure sponsor's timelines.

Patients who treated with LABA/LAMA combination (both fixed-dose and free-dose) at Visit 0, at the time of informed consent, and are able to be switched their medication to LAMA or LABA monotherapy (one of component of their used LABA/LAMA) as judged by investigators can be switched to monotherapy.

Patients will be required to perform 6MWT on several occasions during the trial. 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.

Patients can only be randomised if their COPD has been clinically stable for screening phase.

All log of 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 are eligible for inclusion if they fulfil all the inclusion criteria (Section 3.3.2) and do not present with any of the exclusion criteria (Section 3.3.3). Please refer to Section 8.3.1 (Source Documents) for the documentation requirements regarding to the in- and exclusion criteria.

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3.3.2 Inclusion criteria

1. All patients must sign an informed consent consistent with ICH-GCP guidelines prior to participation in the trial, which includes medication washout and restrictions.
2. All patients must have a diagnosis of chronic obstructive pulmonary disease (P11-05865) and must meet the following spirometric criteria:
   Patients must have relatively stable airway obstruction with a post-bronchodilator FEV_1 < 80% of predicted normal (ECSC [R94-1408]); GOLD grade II-IV (P11-05865) and post-bronchodilator FEV_1/FVC < 70% at Visit 1 (see Appendix 10.5 for ECSC predicted normal equations).
3. Male or female patients, aged ≥ 40 years.
4. Patients must be current or ex-smokers with a smoking history of more than 10 pack-years (see Appendix 10.5 for calculations). Patients who have never smoked cigarettes must be excluded.
5. Patients with score on the modified Medical Research Council (mMRC) ≥ 1.
6. Patients who walk < 400 meters of 6MWT and have a score on the modified Borg ≥ 4 at the end of 6MWT at Visit 2.
7. Patients must be able to perform technically acceptable pulmonary function tests (spirometry), to use the physical activity monitor and must be able to complete 6MWT during the study period as required in the protocol.
8. Patients must be able to inhale medication in a competent manner from the RESPIMAT Inhaler (Appendix 10.1) and from a metered dose inhaler (MDI).

3.3.3 Exclusion criteria

1. Patients with a significant disease other than COPD; a significant disease is defined as a disease which, in the opinion of the investigator, may:
   - put the patient at risk because of participation in the study
   - influence the results of the study
   - cause concern regarding the patient's ability to participate in the study.
2. Patients with clinically relevant abnormal baseline haematology, blood chemistry, urinalysis or creatinine > x2 ULN will be excluded regardless of clinical condition (a repeat laboratory evaluation can be conducted if deemed necessary by the investigator).
3. Patients with a current documented diagnosis of asthma. For patients with allergic rhinitis or atopy, source documentation is required to verify that the patient does not have asthma.

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Patients with any of the following conditions:

4. A diagnosis of thyrotoxicosis (due to the known class side effect profile of β_2-agonists).

5. A diagnosis of paroxysmal tachycardia (>100 beats per minute) (due to the known class side effect profile of β_2-agonists).

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

7. Life-threatening cardiac arrhythmia as judged by the investigator.

8. Hospitalized for heart failure within the past year.

9. Known active tuberculosis.

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

11. A history of life-threatening pulmonary obstruction and patients with chronic respiratory failure.

12. A history of cystic fibrosis.

13. Clinically evident bronchiectasis as judged by the investigator.

14. Patients with severe emphysema requiring endobronchial interventions within 6 months prior to screening visit (Visit 1).

15. A history of significant alcohol or drug abuse as judged by the investigator.

16. Any contraindications for exercise testing as outlined below (see Section 3.3.3.1 below “Contraindications to exercise”).

17. 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).

18. Patients being treated with any oral and patch β-adrenergics.

19. Patients being treated with oral corticosteroid medication at unstable doses (i.e., less than 6 weeks on a stable dose) or at doses in excess of the equivalent of 10 mg of prednisone per day or 20 mg every other day.

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

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21. Patients who have completed a pulmonary rehabilitation program in the 6 weeks prior to the screening visit (Visit 1) or Patients whose pulmonary rehabilitation program is planned to be changed during the trial.

22. Patients who have a limitation of exercise performance as a result of factors other than muscle fatigue or exertional dyspnea, such as arthritis in the leg, angina pectoris or claudication or morbid obesity.

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

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

25. Pregnant or nursing women.

26. Women of childbearing potential not using highly effective methods 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.

27. Patients who have previously been randomised in this study or are currently participating in another study.

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

29. Patient who have dysuria, narrow-angle glaucoma, prostatic hyperplasia or bladder-neck obstruction (contraindications for Tiotropium as an anticholinergic drug, tiotropium may potentially worsen the symptoms and signs)

Note:

1. Extreme caution should be used when including patients:

- with cardiovascular disorders, especially coronary insufficiency and hypertension*

- being treated with monoamine oxidase inhibitors or tricyclic antidepressants.*

2. Caution should be used when including patients on treatment with non-potassium-sparing diuretics.*

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3. Beta-blockers not only block the pulmonary effect of beta-agonists, but may also produce severe bronchospasm in patients with COPD. Therefore, patients should not normally be treated with beta-blockers. However, under certain circumstances, e.g., as prophylaxis after myocardial infarction, there may be no acceptable alternatives to the use of beta-adrenergic blocking agents in patients with COPD. In this setting, cardio selective beta-blockers could be considered, although they should be administered with caution.*

   *cf. prescribing information for registered LABAs

4. As a predominantly renally excreted drug, patients with moderate to severe renal impairment (creatinine clearance ≤ 50 mL/min) treated with tiotropium should be monitored closely.

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 at the investigator's discretion (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

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3.3.4 Removal of patients from therapy or assessments

3.3.4.1 Removal of individual patients

An individual patient may be withdrawn from the trial prior to completion if any of the following criteria apply:

1. The patient withdraws consent, without the need to justify the decision.

2. The patient is no longer able to participate for medical reasons (e.g. pregnancy, surgery, adverse events, or other diseases), or contraindications for exercise testing have occurred.

3. Administrative reasons (protocol violations, persistent non-compliance).

- Investigators must carefully consider withdrawal from the treatment of an individual patient if any of the following criteria apply:
  - At least 3 courses (or increases) of systemic (oral, i.v.) corticosteroids are required to treat a COPD exacerbation.
  - When, during trial participation, a second hospital admission (at least 2 overnight stays) for a COPD exacerbation occurs.
  - Clinical deterioration requiring maintenance treatment not allowed per protocol.

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

Data of patients who discontinue or withdraw prior to randomisation will be entered in the trial database and will be listed. Data of patients who discontinue or withdraw after randomisation must be documented and the reason for withdrawal must be recorded in the eCRF. The data must be included in the trial database and must be reported.

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

Pregnancy
If a patient becomes pregnant during the trial the investigational product needs to be stopped and follow to pregnancy of Section 5.3.7

3.3.4.2 Discontinuation of the trial by the sponsor

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

1. Failure to meet expected enrolment goals overall or at a particular trial site

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2. Emergence of any efficacy/safety information invalidating the earlier positive benefit-risk-assessment that could significantly affect the continuation of the trial
3. Violation of GCP, the CTP, or the contract disturbing the appropriate conduct of the trial

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

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4. TREATMENTS

4.1 TREATMENTS TO BE ADMINISTERED

The trial medication will be provided from Nippon Boehringer ingelheim.

Patients will receive both of the following treatments in random order:

- tiotropium + olodaterol FDCinhalation solution (2.5 µg/2.5 µg per actuation)
- tiotropium inhalation solution (2.5 µg per actuation)

During the 12-week treatment period (2-period, 6-week) patients will inhale two puffs from the RESPIMAT inhaler, once a day, in the morning.

4.1.1 Identity of BI investigational product(s) and comparator product(s)

Table 4.1.1: 1 Investigational product (Test)

- Substance (INN):	- Tiotropium + olodaterol fixed dose combination
- Pharmaceutical form:	- Inhalation solution
- Unit strength:	- 2.5/2.5 µg per actuation
- Total daily dose Route of administration:	- 5/5 µg q.d.. oral inhalation via RESPIMAT Inhaler
- Dose regimen:	- 2 inhalations once daily (a.m. dosing)

Table 4.1.1: 2 Investigational product (Reference)

- Substance (INN):	- Tiotropium
- Pharmaceutical form:	- Inhalation solution
- Unit strength:	- 2.5 µg per actuation
- Total daily dose Route of administration:	- 2.5 µg q.d.. oral inhalation via RESPIMAT Inhaler
- Dose regimen:	- 2 inhalations once daily (a.m. dosing)

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4.1.2 Method of assigning patients to treatment groups

When a patient is qualified for entry into randomised treatment periods, the treatment sequence assignment will be performed by IRT at Visit 2. To facilitate the use of the IRT, the investigator will receive all necessary instructions.
Patient assignment to the treatment sequences will be determined by a computer generated random sequence. Access to the randomisation code will be controlled and documented – for further details please see Sections 4.1.5.1 and 4.1.5.2.
The assigned medication number which will be assigned via IRT will be entered in eCRF, and the corresponding medication kit should be given to the patient. Using this procedure, all relevant parties will be blinded to the treatment group assignment.

4.1.3 Selection of doses in the trial

The doses of Tiotropium + olodaterol FDC or Tiotropium are based on the marketed dose in Japan. These doses were selected based on the results from previous dose finding studies and pivotal studies for submission for registration (please refer to the current version of the IB).

4.1.4 Drug assignment and administration of doses for each patient

Dispensing of medication
Trial medication will be dispensed to the patient by the investigator/pharmacist. At Visit 2 eligible patients will be randomised to one of two double-blinded treatment sequences (1:1 ratio) by the IRT. At Visit 2 and Visit 3, the IRT will assign 3 boxes of a RESPIMAT treatment box to each patient and each RESPIMAT treatment box will have a unique number.

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

Priming of the RESPIMAT Inhaler
Each newly assembled RESPIMAT Inhaler needs to be primed prior to first time use. The inhaler should be primed by actuating it until an aerosol is visible plus three additional actuations. All priming actuations should be directed to the ground. Priming should NOT take place in the same room where the patient is inhaling trial medication. For detailed priming instructions please refer to the RESPIMAT Inhaler handling instructions in Appendix 10.1.
Once assembled, the shelf-life of the RESPIMAT with study medication is 3 months. Once assembled, the shelf-life of the RESPIMAT with training medication is also 3 months. Therefore it is important to ALWAYS enter the date of the cartridge insertion on the medication label of the RESPIMAT immediately after the cartridge is inserted.

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Note: At Visit 2 and Visit 3, patients will receive 3 medication boxes; only one RESPIMAT Inhaler should be ready for use (= cartridge inserted and primed). Once a cartridge is inserted in a RESPIMAT Inhaler, the shelf-life is limited.

Testing of the rescue medication (salbutamol prescribed at sites)
Before using for the first time, one actuation should be released into the air to make sure the device is working.

Instructing the patient
Detailed written instructions and training for the use of the RESPIMAT Inhaler will be given to the patient at Visit 1 (see Appendix 10.1). At Visits 2 and 3, detailed instructions on the use of the device will be repeated, but patients should **not** inhale from the training device on those visit days. The investigator or qualified study personnel will observe the inhalation procedure and will reinforce a correct inhalation technique.

Study medication administration at clinic visits
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 Visit 2 the study medication will be self-administered after all necessary measurement until 12:00 pm (noon). Oral inhalation of two puffs of the study medication from the assigned RESPIMAT Inhaler will be self-administered by the patient in a seated position under the direct supervision of the investigating physician or study personnel.
At Visits 3 and Visit 4/EOT, the RESPIMAT Inhaler that is in current use, must be bring to the site and used for administration of the study medication at that visit. Study medication will be self-administered within ± 30 min of administration time of next day at Visit 2 and between 7:00 a.m. and 10:00 a.m. The clock time of the start of inhalation of test medication will be captured on the source documents and in the eCRF.

At Visit 2, site personnel should discuss with the patient about the preferred regular time of day that the patient will be taking the morning dose of study medication at home.

Study medication administration at home
Each morning between clinic visits, oral inhalation of two puffs of the study medication from the assigned RESPIMAT Inhaler will be self-administered by the patient in a seated position. The doses of study medication will be self-administered preferably within ±30 minutes of time of administration next day of Visit 2 AND between 7:00 a.m. and 10:00 a.m. throughout the trial. If the patient forgot to take study medication within the specified time window, the patient is allowed to administer the dose until 12:00 pm (noon). After 12:00 pm the patient should skip the dose and take the next dose at the next scheduled time the following day. Medication accountability will be done using the counter on the RESPIMAT device.

RESPIMAT Inhaler return
The RESPIMAT Inhalers dispensed during the treatment period will contain sufficient medication for 30 days of treatment. All used and unused test medication will be returned to the medication boxes and must be brought to each clinic visit by the patient.

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

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

However, due to the requirements to report suspected serious unexpected adverse reactions (SUSARs), it may be necessary for a representative from BI's drug safety group to access the randomisation code for individual patients during study conduct. In such cases, access to the code will only be permitted by authorised drug safety representatives. Access to the code will be via the IRT.

The randomisation code will be kept secret by Clinical Trial Support up to database lock. Please see Section 4.1.5.2 for the rules regarding breaking the code for an individual or for all patients in emergency situations.

4.1.5.2 Unblinding and breaking the code

In this blinded trial, an emergency code break will be available to the investigator via the IRT system. This code break may only be accessed in emergency situations when the identity of the trial drug must be known to the investigator in order to provide appropriate medical treatment or if required to assure the safety of trial participants. Each site receives a manual from the IRT provider that contains instructions on how to unblind the treatment of a patient via the IRT (via 24-hour Emergency helpline). If the code break for a patient is accessed, the Sponsor must be informed immediately. The reason for accessing the code break, together with the date, must be documented on the appropriate eCRF page. In case third party needs to break the code, however, when the investigator cannot be reached, the code can be opened by calling emergency code manager (see Emergency Code Break Manual) in the ISF.

4.1.6 Packaging, labelling, and re-supply

Boehringer Ingelheim will provide study supplies including blinded study medication and RESPIMAT inhaler training kits.

Open-label supplies= Auxiliary Medicinal Products (AMPs)

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- Training RESPIMAT inhaler and placebo cartridges for training purposes are supplied. The training RESPIMAT can be used until 3 months after first insertion of the cartridge or until the device is empty. The date of the cartridge insertion should be entered on the medication label of the RESPIMAT immediately after the cartridge is inserted.

  RESPIMAT inhaler for training purposes will be provided by IRT along with the initial supply order.

Blinded study medication= Investigational Medicinal Product (IMP)

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

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

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

!" #$%&&'(
Each site will receive a first supply at or after the initiation visit and will be resupplied upon demand by IRT.

4.1.7 Storage conditions

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

If the storage conditions are found to be outside the specified range, CML (as provided in the list of contacts) must be contacted immediately."

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4.1.8 Drug accountability

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

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

The investigational drug storage manager must maintain records of:

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

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

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

RESPIMAT inhaler:

- dates (dispense and return),
- dispenser's initials
- batch/serial numbers,
- expiry dates,
- the unique RESPIMAT treatment box number assigned by IRT
- trial patient number assigned by the RDC system.

See Section 4.1.2 for the randomisation. It is important to enter the date of priming on the medication label of the RESPIMAT.

Rescue medication **(salbutamol MDI prescribed at sites)** and training RESPIMAT:

AMP accountability form for each will be provided to the trial site. This record will include:

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

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

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

4.2 CONCOMITANT THERAPY, RESTRICTIONS, AND RESCUE TREATMENT

4.2.1 Rescue medication, emergency procedures, and additional treatment(s)

4.2.1.1 Rescue Medication

Administration of rescue medication can occur at any point during the trial as deemed necessary by the patient or the investigator. Salbutamol will be prescribed as rescue medication in the trial site; only the salbutamol prescribed in the trial site is allowed for rescue medication use. If the patient requires rescue medication during the pulmonary function test (PFT) days (Visits 1, 2, 3, and 4), the PFTs will be discontinued. The visit 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.

4.2.1.2 Emergency procedures

There are no special emergency procedures to be followed.

4.2.1.3 Additional treatments

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

- Salbutamol inhalation aerosol from MDI for p.r.n. use

- Temporary increases in the dose or addition of oral steroids are allowed during the treatment portion of the study. PFT should not occur within 7 days of the last administered dose of an increase or addition of oral steroids. These tests 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. PFT should not occur within seven days of the last dose. These tests may be postponed up to 14 days to accommodate this restriction. Subsequent visits will be scheduled according to the patient's regular schedule.

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- 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 PFT, these tests will be postponed for at least 2 days but not more than 7 days after the last dose is given. Subsequent visits will be scheduled according to the patient's regular schedule.

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

- The following Table 4.2.2.1:1 provides an overview of permitted and restricted medication.

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Table 4.2.2.1: 1 Permitted Medications and Medication Restrictions

Drug Class	Sub-class	**Prior to study**	**Study Period**		
			Run-in Period	**Treatment Period**	**Follow up Period**
Corticosteroids	**Inhaled corticosteroids (ICS)** (stabilized 6 wks. prior to V1)	Permitted	Permitted	Permitted	Permitted
	Oral corticosteroids [≤10 mg prednisone per day or ≤20 mg prednisone every other day (or equivalent); stabilized 6 wks. prior to V1]	Permitted	Permitted	Permitted	Permitted
	Injected corticosteroids – local administration (for treatment of e.g. bursitis)	Permitted	Permitted	Permitted	Permitted
β-adrenergics	**SABA(e.g. sulbtamol)**	Permitted	Rescue[1]	Rescue[1]	Permitted
	LABA (bid, qd)[2] (e.g. formoterol / salmeterol / indacaterol)	Permitted as monotherapy[3]	Permitted as monotherapy[3]	**NOT permitted**	Permitted
	Oral and patch beta-adrenergics	**Not Permitted (w.o. 4wks. prior to V1)**	**Not Permitted**	**NOT permitted**	Permitted
	Beta blockers (cautionary statement, Section 3.3.3; stabilized 6 wks. prior to V1)	Permitted	Permitted	Permitted	Permitted

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

Drug Class	Sub-class	**Prior to study**	**Study Period**		
			Screening Period	**Treatment Period**	**Follow up Period**
Anticholinergics	**SAMA** (e.g. inhalation aerosol, nasal spray)	Permitted[4]	Permitted[4]	**NOT permitted**	Permitted
	LAMA (bid, qd)[2] (e.g. tiotropium, aclidinium, glycopyronnium, umeclidinium)	Permitted as monotherapy[3]	Permitted as monotherapy[3]	**Study medication**	Permitted
Combinations	**ICS/LABA (bid, qd)** (Switch to ICS mono-product at the same dose or equivalent dose)	Permitted	**NOT permitted**	**NOT permitted**	Permitted
	ICS/SABA (Switch to ICS mono-product at the same dose or equivalent dose)	Permitted	**NOT permitted**	**NOT permitted**	Permitted
	LABA[3] (i.e. tiotropium+olodaterol, glycopyrronium+indacaterol, umeclidinium+vilanterol)	**Not Permitted (w.o. 3 wks prior to V1)**	**NOT permitted (w.o. 5 wks prior to V2)**	**Study medication**	Permitted
Antibiotics	**Any infection**	Permitted (w.o 4 wks prior to V1)	Permitted	Permitted	Permitted

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

Drug Class	Sub-class	Prior to study	Study Period		
			Screening Period	Treatment Period	Follow up Period
Miscellaneous	**Other investigational drugs** (see exclusion criterion)	**NOT permitted**	**NOT permitted**	**NOT permitted**	**NOT permitted**
	Cromolyn sodium / nedocromil sodium (if prescribed for non-asthma condition)	Permitted	Permitted	Permitted	Permitted
	Antihistamines, antileukotrienes (if prescribed for non-asthma condition)	Permitted	Permitted	Permitted	Permitted
	Methylxanthines/Theophyllines (if prescribed for non-asthma condition)	Permitted	Permitted	Permitted[1]	Permitted
	Mucolytics (not containing bronchodilators; stabilized 6 wks prior to V1)	Permitted	Permitted	Permitted	Permitted

1. Use rescue medication (salbutamol) delivered by each visit.
2. Commercial long-acting bronchodilators will be discontinued prior to Visit 2 in accordance with drug restriction for PFTs.
3. Patients on LAMA/LABA combination therapy (FDC or free dose combination) should be treated with either LAMA or LABA at Visit 0. Patients treated with LAMA or LABA monotherapy for at least 3 weeks are proceeded to Visit 1 and Visit 2.
4. SAMA is allowed to be used in patients who do not use any LAMA from Visit 0 until Visit 2.

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Medication restrictions for pulmonary function testing

- At least an 8-hour washout of SABA bronchodilators.
- At least an 8-hour washout of SAMA bronchodilators prior to Visit 1 and 2 (Not allowed during treatment periods).
- At least a 48-hour washout of LABA (BID or QD) prior to Visit 1 and Visit 2 (Not allowed during treatment periods).
- At least a 48-hour washout of LAMA (BID or QD) prior to Visit 1 and Visit 2 (Not allowed during treatment periods).
- The morning dose of ICS 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 (Study medication should be taken on previous day of the visit)
- A patient visit may be re-scheduled twice due to lack of medication washout compliance.
- 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.

4.2.2.2 Restrictions on diet and life style

Medication washout restrictions should be adhered to as described in Table 4.2.2.1:1.

Patients must remain in the building where the PFT is performed and must return to the laboratory at least 10 minutes prior to the start of each test.

On PFT days (including the Screening Visit), patients must refrain from strenuous activity for at least 2-3 days prior to PFT and throughout the testing period. Patients should also avoid cold temperatures, environmental smoke, dust or areas with strong odours (e.g. perfumes).

Coffee, tea, chocolate, cola and other caffeine-containing beverages and foods, and ice-cold beverages should be avoided the morning of or during the PFT period. Decaffeinated beverages are acceptable.

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 PFT.

4.3 TREATMENT COMPLIANCE

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

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correct use of the RESPIMAT Inhaler using the training RESPIMAT Inhaler with inserted placebo cartridge on Visit 1.

The patient will complete a patient Diary confirming that trial medication has been taken and indicating the number of puffs of salbutamol MDI use. Compliance should be emphasised with a goal of within 80% to 120% compliance rate with treatment in the patient Diary. The investigator or designee will review these records with the patient at all visits to assess rescue medication use and treatment compliance in treatment phase. However, randomised patients will not be discontinued for lack of compliance without prior discussion with CML.

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5. VARIABLES AND THEIR ASSESSMENT

5.1 TRIAL ENDPOINTS

5.1.1 Primary Endpoint

Inspirational Capacity (IC) at rest measured at 60 minutes post-dose, after 6 weeks of treatment
This is no safety issue.

5.1.2 Secondary Endpoints

The following secondary endpoints will be assessed:

- 6-minute walk distance (6MWD [m]) after 6 weeks of treatment
- Average number of step per day (step/day) in the 2 weeks prior to Week 6
- Average daily duration (minute) of ≥4 metabolic equivalents (METs) in the 2 weeks prior to Week 6
- Average daily duration (minute) of ≥3 METs in the 2 weeks prior to Week 6
- Average daily duration (minute) of ≥2 METs in the 2 weeks prior to Week 6
- Average daily active strength (METs·minute) of ≥3 METs in the 2 weeks prior to Week 6
- 60 minutes post-dose Slow vital capacity (SVC), after 6 weeks of treatment
- 30 minutes post-dose FEV_1, after 6 weeks of treatment
- 30 minutes post-dose FVC, after 6 weeks of treatment

These are no safety issue.

[redacted]

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[redacted]

5.2 ASSESSMENT OF EFFICACY

5.2.1 Pulmonary Function Testing

These tests will be performed using spirometers (Flowscreen, eResarch Technology GmbH) provided by BI. Spirometers and their use, including daily calibration, must meet ATS/ERS criteria (P05-12782). Baseline PFT will be conducted at Visit 2. PFT will also be conducted post-dose and before 6MWT (at Visit 3 and Visit 4). Patient will be in a seated position and it is preferable that the same trained individual performs the pulmonary function tests for a given patient.

Baseline IC and SVC measurement (Visit 2) should be done 30 minutes before 6MWT. IC and SVC measurement (at Visit 3 and Visit 4) should also be done 30 minutes before 6MWT, which is on 60 minutes post-dosing. For IC and SVC at least three reproducible measurements should be obtained with a maximum of 5 measurements to be performed. The resting IC and SVC should be recorded as the mean of the two highest acceptable efforts. For additional details on the IC maneuvers, please refer to Appendix 10.11.

Baseline FEV_1 and FVC measurement (Visit 2) should be done 60 minutes before 6MWT. FEV_1 and FVC measurement (at Visit 3 and Visit 4) should also be done 60 minutes before 6MWT, which is on 30 minutes post-dosing. The best of three efforts will be defined as the highest FEV_1 and the highest FVC each obtained on any of three manoeuvres meeting the ATS criteria (to a maximum of five attempts). The highest FEV_1 and the highest FVC will be selected regardless of whether they come from different spirometric manoeuvres or from the same manoeuvre.

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.

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Reversibility testing (P05-12782) for the qualifying PFT at the Screening Visit (Visit 1): the procedure is described in Appendix 10.5. The post-bronchodilator measurements must meet the inclusion criteria specified in Section 3.3.2.

5.2.2 Six-minute walk test (6MWT)

The test will be conducted according to the methodology described by ATS guideline (R03-0725, R13-4735, R13-2807). At Visit 1, a training for 6MWT before administration of 400 µg salbutamol will be done. At Visit 2, 6MWT for eligibility assessment will be performed before administration of the study medication. The 6MWT will be repeated at Visit 3 and Visit 4, starting 90 minutes (+15 minutes) after inhalation of the study medication.

During 6MWT, oxygen saturation and heart rate are monitored to measure [redacted] and recovery time for SpO_2 (%, see Section 5.1.3) using a mobile pulse oximeter, which is provided by BI.

During 6MWT and at the end of 6MWT, the intensity of breathing discomfort and leg discomfort will be assessed (modified Borg Scale as outlined in Appendix 10.7) by the patients. The outline of 6MWT is described in Appendix 10.6.

5.2.3 Activity monitoring

A physical activity monitor (HJA-750C, OMRON) is an accelerometer that is used to measure the overall movement of a patient and provided by BI.

Patients will wear the physical activity monitor every day for 2 weeks and 3 times repeat during the trial i.e. in the 2 weeks prior to Visit 2, Visits 3 and Visit 4. The device will not be worn during bathing or water sport activities. Activities that may hamper proper functioning of the equipment are limited and not likely to happen in the population studied, but should be discussed with the investigator and eventually avoided. (e.g. high impact sports).

Muscle amount (% in BW) will be measured before activity monitor measurement at Visit 1.

[redacted]

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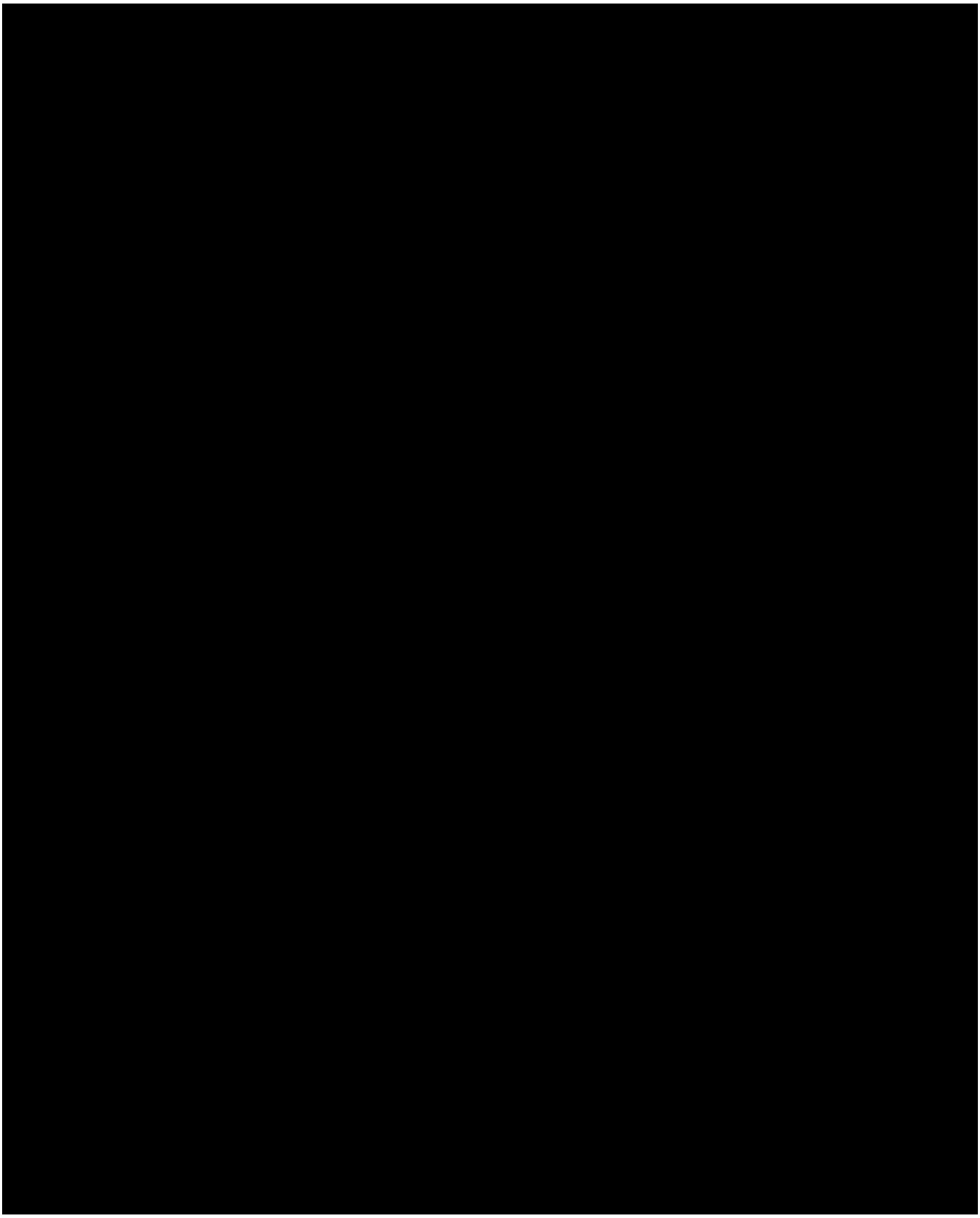

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[redacted]

5.2.8 Patient diary

Patient daily will be used to collect and the study medication (salbutamol) and rescue medication, steps, and weather throughout trail.

5.3 ASSESSMENT OF SAFETY

The safety endpoints will be assessed:

- All adverse events (including physical examination) until the end of the study
- Heart rate and SpO_2 in conjunction with 6MWT

5.3.1 Physical examination

At start of screening (Visit 1), Visit 2, Visit 3 and Visit 4/EOT, a complete physical examination (including cardiac, neurological, dermatological, pulmonological) will be performed by the investigator. Documentation of, and findings from the physical examination, must be part of the source documents available at the site. Follow-up examination will be performed at Visit 5 if there are any clinically significant findings at Visit 4/EOT.

5.3.2 Vital Signs

Measurements of heart rate and blood pressure will be obtained prior to 6MWT and spirometry measurement, with the patient seated and rested for a minimum of 5 minutes.

5.3.3 Safety laboratory parameters

Laboratory tests

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Safety laboratory testing will be conducted (non-fasting) on all patients at the screening visit (Visit 1), and at Visit 4/EOT. Follow-up clinical laboratory testing will be performed at Visit 5 if there are any clinically significant findings at Visit 4/EOT. 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, urinalysis will be analysed by the local laboratory.

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, LDH, Gamma- glutamyl transferase (GT), aspartate aminotransaminase AST (SGOT), alanine aminotransaminase ALT (SGPT), glucose, calcium, inorganic phosphorus, uric acid, urea nitrogen, creatinine, total protein, potassium, sodium, chloride, total bilirubin, creatine kinase.

Urinalysis

Specific gravity, pH, glucose, protein, occult blood.

Pregnancy Testing

Pregnancy tests to be performed at Visit 1 and Visit 4/EOT. If a patient discontinues early, a pregnancy test will also be conducted.

Local laboratory will be used and the laboratory data will not be collected or captured in the eCRF. All laboratory values will be evaluated, (signed, dated and commented upon) by the investigator and stored locally. Any clinically relevant changes in the laboratory values will be reported as AEs (see Section 5.3.6) and followed up and/or treated locally until returning to normal or stable condition.

Any laboratory abnormalities will be carefully monitored and if necessary the patient will be removed from the trial and medically treated.

5.3.4 Electrocardiogram

A standard 12-lead electrocardiogram (ECG) at rest will be performed on all patients at Visit 1, Visit 2, Visit 3 and Visit 4/EOT. An ECG will be repeated at Visit 5 in case of any findings at Visit 4/EOT.

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The purpose of the screening ECG (Visit 1) is to obtain information about the patient's baseline conditions. Therefore, any significant findings from the examination are recorded on the baseline condition page. In case of indication of a disease listed under the exclusion criteria, the patient should not be randomised for treatment.

ECG will be completed using site´s own equipment and ECG data will not be collected or captured in the eCRF. All ECGs will be evaluated, (signed, dated and commented upon) by the investigator and stored locally. Any clinically relevant changes in the ECG will be reported as AEs (see Section 5.3.6) and followed up and/or treated locally until returning to normal or stable condition.

Any ECG abnormalities will be carefully monitored and if necessary the patient will be removed from the trial and medically treated.

5.3.5 Other safety parameters

Other safety parameters
Heart Rate Monitoring and Oxygen Saturation (SpO_2): A mobile pulse oximeter will be provided by sponsor for use during the 6MWT. Both heart rate and SpO_2 will be monitored during 6MWT.

5.3.6 Assessment of adverse events

5.3.6.1 Definitions of AEs

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

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

Serious adverse event
A serious adverse event (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

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require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions.

Life-threatening in this context refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if more severe.

Every new occurrence of cancer must be reported as a serious event regardless of the duration between discontinuation of the drug and the occurrence of the cancer.

The following events will be handled as "deemed serious for any other reason". An AE which possibly leads to disability will be reported as an SAE.

AEs considered "Always Serious"
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 system. These events should always be reported as SAEs as described in Section 5.3.7.

Adverse events of special interest (AESIs)
There are no AESIs in this study.

Hepatic injury
A hepatic injury is defined by the following alterations of hepatic laboratory parameters:
- an elevation of AST and/or ALT >3 fold ULN combined with an elevation of total bilirubin >2 fold ULN measured in the same blood draw sample, and/or
- marked peak aminotransferase (ALT, and/or AST) elevations ≥10 fold ULN

In case of clinical symptoms of hepatic injury (icterus, unexplained encephalopathy, unexplained coagulopathy, right upper quadrant abdominal pain, etc.) without lab results (ALT, AST, total bilirubin) available, the investigator should make sure these parameters are analysed, if necessary in an unscheduled blood test.

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

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Causal relationship of AEs
Medical judgment should be used to determine the relationship, considering all relevant factors, including pattern of reaction, temporal relationship, de-challenge or re-challenge, confounding factors such as concomitant medication, concomitant diseases and relevant history. Assessment of causal relationship should be recorded in the eCRFs. The reason for the decision on causal relationship for unlisted AEs needs to be provided in the eCRF.

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

5.3.7 Adverse event collection and reporting

AE Collection
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) and all AESIs.

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

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

AE reporting to sponsor and timelines
The Investigator must report SAEs, AESIs, and non-serious AEs which are relevant for the reported SAE or AESI, on the BI SAE form via fax immediately (within 24 hours) to the Sponsor's unique entry point (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.

All SAEs and AESIs must be reported immediately to the head of the trial site.
With receipt of any further information to these events, a follow-up SAE form has to be provided. For follow-up information the same rules and timeline apply as for initial information.

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Information required
For each AE, the Investigator should provide the information requested on the appropriate eCRF pages and the BI SAE form, e.g. onset, end date, intensity, treatment required, outcome, seriousness, and action taken with the investigational drugs. The Investigator should determine the causal relationship to the trial medication, and any possible interactions between the investigational drugs and AMPs.

The following should also be recorded as an (S)AE 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 the rare case that a female subject participating in this clinical trial becomes pregnant after having taken trial medication, the investigator must report immediately (within 24 hours) the drug exposure during pregnancy (DEDP) to the sponsor's unique entry point (specific contact details will be provided the ISF). 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/AESI, only the Pregnancy Monitoring Form for Clinical Trials and not the SAE form is to be completed. If there is an SAE/AESI associated with the pregnancy, then the SAE/AESI 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 Assessment of Pharmacokinetics

Not Applicable

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5.4.2 Methods of sample collection

Not Applicable

5.4.3 Analytical determinations

Not Applicable

5.4.4 Pharmacokinetic – Pharmacodynamic Relationship

Not Applicable

5.5 ASSESSMENT OF EXPLORATORY BIOMARKER(S)

Not Applicable

5.5.1 Biobanking

Not Applicable

5.6 OTHER ASSESSMENTS

Not applicable in this trials

5.7 APPROPRIATENESS OF MEASUREMENTS

Six-Minute Walk Test

6MWT is a standard test to assess treatment changes in patients with COPD (R03-0725, R13-4735, R13-2807).

Activity monitoring

HJA-750C provided by BI will be used as physical activity monitor in this trial. This is an electronic device used to measure physical activity levels of the patient. The devices are standard method to assess various output parameters (i.e. steps, METs, etc.) of activity in patients during the trial.

Spirometry

PFT are a validated and well established measurement tool for lung function testing. PFT will be conducted at clinic visits using the equipment which meets ATS/ERS criteria (P05-12782) provided by BI. FEV_1, FVC, SVC and IC are standard measurements for the assessment of lung function.

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6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

This trial consists of a screening period, two period 6-week treatment periods, and a 3-week follow-up period. Following the screening visit (Visit 1) and 2-week screening period, patients will be randomised into the first of double-blind treatment period (Visit 2). Additional clinic visits will be scheduled after 6 weeks of treatment (Visits 3 and Visit 4/EOT) and once 3 weeks post-treatment (Visit 5).
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 Flow chart for time windows for the visits.

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

If rescheduling of visits after randomisation is necessary, the total daily doses of the RESPIMAT inhaler 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 local clinical monitor.

Refer to Section 4.2.1 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 washout 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 period

Visit 0 (Informed Consent Visit)

- Informed consent will be obtained prior to patient participation in the trial, which includes any medication washout procedures or restrictions (e.g., for exercise testing

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or lung function testing). Upon obtaining consent, the patient will be instructed on the medication washout and other restrictions for the screening PFT and 6MWT (Visit 1). Rescue medication will be dispensed.

- The patient will receive directions on the as needed use of the salbutamol (as rescue medication) that will be dispensed at this visit.
- A preliminary check of in-/exclusion criteria is recommended at Visit 0 to avoid unnecessary washout procedures in non-eligible patients.

Visit 1 (Screening visit)

- Medication washout compliance will be verified as described in Section 4.2.
- mMRC questionnaire will be completed in the order noted prior to all other procedures.
- Demographic data (gender, race, year of birth, height, weight, muscle amount, duration of COPD, pack years, and smoking status) will be recorded.
- COPD background characteristics will be recorded.
- All adverse events experienced since signed informed consent will be reviewed and recorded.
- In/Exclusion criteria will be reviewed
- Any change of concomitant therapy since signed informed consent will be reviewed and recorded.
- A relevant medical history, and physical examination including vital signs (blood pressure and pulse rate) and 12-lead ECG will be conducted. The vital signs (seated) and ECG should be conducted following 5 minutes rest and prior to blood sampling.
- Blood and urine samples will be collected. A pregnancy test will be performed for women of child-bearing potential. Blood samples need to be taken prior to the salbutamol dosing.
- 6MWT should be performed as mentioned in Flow chart and respective protocol sections.
- [redacted]
- PFT will be conducted both immediately prior to within 10 min. and 10 - 15 min. after the inhalation of 4 puffs of salbutamol between 7:00 a.m.-10:00 a.m..
- Patients qualified to enter the 2-week screening period of the trial will be issued additional rescue medication if needed.
- Patient takes current concomitant medication after post-dosing PFT until noon.

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- Patients will receive training and instructions on
  - the use of rescue medication (salbutamol)
  - the use of the RESPIMAT Inhaler using the training kit
  - medication restrictions and washout requirements for the screening period and subsequent visits
  - the use of patient diary
  - the use of activity monitor and starting physical activity measurement
- Patients will be asked to return all issued medication, diary, activity monitor, etc. to the clinic on all subsequent visits.

Visit 2 (Baseline visit and randomisation)

- Medication washout compliance will be verified as described in Section 4.2.
- [redacted]
- All adverse events experienced since the last visit will be reviewed and recorded.
- In/Exclusion criteria will be reviewed
- Any change of concomitant therapy since the last visit will be reviewed and recorded.
- Physical examination, vital signs (blood pressure and pulse rate) followed by 12-lead ECG will be measured before start of PFT and with the patient seated and rested for at least five minutes.
- PFT should be performed as mentioned in Flow chart and respective protocol sections
- 6MWT should be performed as mentioned in Flow chart and respective protocol sections.
- [redacted]
- Patients will be instructed to return a trail medication, a rescue medication, a diary and an activity monitor to the clinic on the next scheduled visit.

Randmisation

- Patients will receive instructions on restrictions for the treatment period and subsequent visits. Patients will be instructed to bring all study-related treatments to the clinic at the next visit.
- Trial medication will be dispensed to the patient by IRT.
- Dispense/collect rescue medication as needed.

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- The patient will be instructed in the use of the RESPIMAT, but patient should not inhale from the training inhaler at this visit.

6.2.2 Treatment periods

Clinic visits after 6 weeks of each treatment period (Visits 3 and 4):

Telephone Visit

The investigator or a designated site staff member will telephone the patients 15 days and 8 days prior to the next planned Visit and remind them to wear physical activity monitor every day. An assessment of adverse events including concomitant therapy should be performed from the last assessment.The investigator should ask the patient to visit the clinic, if determined by the investigator as concerning the patient's safety.

Observations / procedures:

Patients will be contacted prior to each of the visits to remind the patient of medication washout times, exercise test restrictions and to bring back all study medication at their next visit.

- Medication washout compliance will be verified at every visit as described in Section 4.2.
- [redacted]
- Patient's smoking status will be recorded only at Visit 4/EOT.
- All adverse events experienced since the last visit will be reviewed and recorded.
- Any change of concomitant therapy since the last visit will be reviewed and recorded.
- A complete physical examination including vital signs (blood pressure and pulse rate) and 12-lead ECG will be conducted. The vital signs and ECG should be conducted following 5 minutes rest and prior to blood sampling.
- Blood and urine samples will be collected (only Visit 4/EOT). A pregnancy test will be performed for women of child-bearing potential.
- Study medication will be self-administered within ± 30 minutes of time of administration next day of Visit 2 and between 7:00 a.m. and 10:00 a.m.; start-time of inhalation will be recorded. Administration of trial medication during these visits will be done using medication that was dispensed at the beginning of the treatment period.
- PFT should be performed as mentioned in Flow chart and respective protocol sections.
- 6MWT should be performed as mentioned in Flow chart and respective protocol sections.

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- [redacted]
- All trial medications should be collected at Visit 3 and Visit 4/EOT. At Visit 3, new trail medications for the patients should be dispensed via IRT.

6.2.3 Follow Up Period and Trial Completion

Following the end of final treatment period, patients will be followed up for an additional 21 days. They will be seen at the end of this period (Visit 5) and their adverse events and concomitant therapies will be reviewed and recorded (see Flow chart). If the physical examination, clinical laboratory tests, Pregnancy test (if applicable) or ECG performed at Visit 4/EOT yield abnormal values representing clinically significant changes from baseline, they will be repeated at the follow-up visit (Visit 5). Any persistently abnormal test must be fully explained by the investigator and follow-up evaluation performed, if necessary.

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

Observations and procedures in case of premature withdrawal:

The following procedures of Visit 4/EOT should be performed after any premature withdrawal of patients
that took at least one dose of trial medication.

- Physical examination including 12-lead ECG and vital signs (blood pressure and pulse rate) will be conducted.
- Adverse events and changes in concomitant therapies will be recorded. Any ongoing (serious) adverse events should be followed until the event is resolved or there is a mutual agreement between the investigator and CML that follow-up is sufficient.
- Smoking status will be assessed.
- Laboratory testing
- Pregnancy test in women of child-bearing potential
- Study and rescue medication (used and unused), activity monitor and patient diary will be collected.
- If possible, a spirometry will be performed.

The investigator should make every effort to perform a follow-up visit 21 days after the last dose of study medication in patients that withdrew prematurely, as described earlier in this section.

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7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 STATISTICAL DESIGN - MODEL

The primary objective of this trial is to confirm that bronchodilator FDC therapy (LABA/LAMA FDC) will improve Inspiratory Capacity (i.e., IC) at rest as compared to bronchodilator monotherapy (LAMA) in patients with COPD.

The secondary objective of this trial is to evaluate the effect on two domains of physical activity: (1) amount of physical activity as measured with the activity monitor described in Section 5.1.2.; (2) perceived difficulties associated with physical activity as measured by some questionnaires described in Section 5.1.3.

A mixed effects model repeated measures (MMRM) approach with treatment and period as fixed effects, study baseline as a covariate and patient as a random effect will be used for the primary analysis. Study baseline was defined as the measurement at the baseline (Visit 2).

7.2 NULL AND ALTERNATIVE HYPOTHESES

The following hypothesis (two-sided $\alpha = 0.05$) will be tested for the primary endpoint - IC at rest measured at 60 minutes post-dose - after 6 weeks of treatment:

H_0: Mean IC for Tiotropium + Olodaterol (5 µg/5 µg) = Mean IC for Tiotropium (5 µg) vs.
H_1: Mean IC for Tiotropium + Olodaterol (5 µg/5 µg) $\neq$ Mean IC for Tiotropium (5 µg)

7.3 PLANNED ANALYSES

Details will be described in the Trial Statistical Analysis Plan(TSAP).

7.3.1 Primary endpoint analyses

Primary analysis will be performed in all patients who signed informed consent, are randomised (RS) and are documented to have taken any dose of study medication (TS), and have non-missing baseline at Visit 2 and non-missing post-dose baseline measurements of IC at rest for primary endpoint. This set is called Full Analysis set (FAS) and assignment to the FAS will be done after implementation of any data handling rules which set measurements to missing.

The primary analysis will be conducted using MMRM including treatment and period as categorical fixed effects, study baseline as a covariate and patient as a random effect treatment. 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

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treatment contrasts will be presented together with the 95% confidence intervals (CI) and p-values.

After blinded review of the magnitude and potential impact of any serious protocol violations, a subset of the data corresponding to those patients without serious deviations from the protocol will be created. This will be called the Per–Protocol Set (PPS). If the number of patients in PPS is less than 90% of the number of patients in FAS, the primary analyses will also be performed on PPS. These will be supportive analyses to assess the robustness of the primary analysis using FAS.

7.3.2 Secondary and further endpoint analyses

All secondary and further endpoints (described in Section 5.1.2 and Section 5.1.3) will be analysed using a similar MMRM model as for the primary endpoint. Descriptive statistics will be provided for each of the two treatment groups.

7.3.3 Safety analyses

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

Adverse events will be coded using the Medical Dictionary for regulatory Activities (MedDRA) coding dictionary. The number of patients with adverse events during the treatment period will be summarized. Standard BI summary tables and listings will be produced to compare the incidence of adverse events across the treatment groups. All events with an onset after the first dose of trial medication up to a period of 21 days after the last dose of trial medication will be assigned to the treatment period for evaluation. AEs before the treatment period will be assigned to screening. AEs after 21 days from the last study drug intake up to and including trial completion date will be assigned to post-treatment. AEs after trial completion date will be assigned to post-study.

Frequency, severity, and causal relationship of adverse events will be tabulated by system organ class and preferred term after coding 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 for this trial.

7.4 INTERIM ANALYSES

No interim analysis is planned for this trial.

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7.5 HANDLING OF MISSING DATA

Every effort should be made to collect complete data on each test day, except if the patient has used rescue medication. Missing data at a given visit will be imputed by the available data based on BI standard approaches. Completely missing visits will be handled through the statistical model described in Section 7.3.1.
Additional details on the imputation of missing data will be specified in the Trial Statistical Analysis Plan (TSAP) prior to unblinding.

7.6 RANDOMISATION

This is a cross-over trial with two treatment groups and two groups. Patients who meet the inclusion criteria and do not violate any exclusion criteria will be randomised in equal ratio to one of the two treatment sequences. Randomisation will not be stratified. BI will arrange for the randomisation, the packaging and labelling of study medication. Patients, investigators and everyone involved in analysing or with an interest in this double-blind study will remain blinded with regard to the randomised treatment assignments until database lock.

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. Access to the codes will be controlled and documented. Practical aspects of the treatment allocation process and methods to carry out blinding are detailed in Sections 4.1.2 and 4.1.5.

7.7 DETERMINATION OF SAMPLE SIZE

For the primary endpoint of IC at rest after Week 6, results from the recent two BI studies (BI no.:1237.13[c02094185] and 1237.14[c02094318]) suggest that the standard deviation is approximately 0.4[L]. However, a little conservative 0.41[L] is deemed more appropriate due to uncertain prediction of drop-outs during tests for physical activities. In addition the IC at rest after Week 6 is estimated at 0.1 L for the difference between tiotropium + Olodaterol (LAMA/LABA FDC) and tiotropium (LAMA). To detect a difference of 0.1 L with the standard deviation of 0.41 L in the IC at rest between the two treatments with 90% power at the 2-sided alpha of 0.05, 180 patients will be required. Nquery Advisor nTerim ver.2.0 (MOT0-1, 1-sample t-test) was used for the sample size calculation.

Table 7.7: 1 Summary of sample size considerations

primary endpoint	⊿ [L]	SD [L]	N (power)
IC at rest[L]	0.1	0.41	180 (90%)
		0.40	171 (90%)

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8. INFORMED CONSENT, DATA PROTECTION, TRIAL RECORDS

The trial will be carried out in compliance with the protocol, the principles laid down in the Declaration of Helsinki in accordance with the ICH Harmonised Tripartite Guideline for Good Clinical Practice (GCP), relevant BI Standard Operating Procedures (SOPs), and the Japanese GCP regulations (Ministry of Health and Welfare Ordinance No. 28, March 27, 1997). 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 study subjects against any immediate hazard, and also of any serious breaches of the protocol/ICH GCP and the Japanese GCP regulations (Ministry of Health and Welfare Ordinance No. 28, March 27, 1997).

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

The certificate of the 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 Institutional Review Board (IRB) and competent authority (CA) according to national and international regulations. The same applies for the implementation of changes introduced by amendments.

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

The Investigator must give a full explanation to trial patients by using the patient information form, which is prepared avoiding the use of technical terms and expressions. The patient is given sufficient time to consider participation in the trial. The investigator obtains written consent of the patient's own free will with the informed consent form after confirming that the patient understands the contents. The investigator must sign and date the informed

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consent form. If a trial collaborator has given a supplementary explanation, the trial collaborator also signs and dates the informed consent.

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

8.2 DATA QUALITY ASSURANCE

A quality assurance audit/inspection of this trial may be conducted by the sponsor, the sponsor's designees, IRBs 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 via remote data capture. See Section 4.1.5.2 for rules about emergency code breaks. For drug accountability, refer to Section 4.1.8.

8.3.1 Source documents

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

Data reported on the eCRF must be consistent with the source data or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the trial; current medical records must also be available.

For eCRF, all data must be derived from source documents.

Additionally, the following source documents must be collected and filed at the investigator's trial site:

- ECG results (original or copies of printouts)
- Physical examinations (original documentation)

8.3.2 Direct access to source data and documents

The Investigator / institution will permit trial-related monitoring, audits, IRB review and regulatory inspection, providing direct access to all related source data / documents. eCRFs and all source documents, including progress notes and copies of laboratory and medical test results must be available at all times for review by the Sponsor's clinical trial monitor, auditor and inspection by health authorities (e.g. FDA). The CRA / on site monitor and

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auditor may review all eCRFs, and written informed consents. The accuracy of the data will be verified by reviewing the documents described in Section 8.3.1.

8.3.3 Storage period of records

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

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

8.4 LISTEDNESS AND EXPEDITED REPORTING OF ADVERSE EVENTS

8.4.1 Listedness

To fulfil the regulatory requirements for expedited safety reporting, the Sponsor evaluates whether a particular adverse event is "listed", i.e. is a known side effect of the drug or not. Therefore, a unique reference document for the evaluation of listedness needs to be provided. For the tiotropium inhalation solution, this is the current version of the IB (c01860006). For the tiotropium + olodaterol FDC inhalation solution, this is the current version of the IB (c01735808). For salbutamol, the reference document is the SmPC. The current versions of these reference documents are provided in the ISF. No AEs are classified as listed for matching placebo, study design, or invasive procedures.

8.4.2 Expedited reporting to health authorities and IRB

Expedited reporting of serious adverse events, e.g. suspected unexpected serious adverse reactions (SUSAR) to health authorities and IRB, will be done according to local regulatory requirements. Further details regarding this reporting procedure are provided in the ISF.

8.5 STATEMENT OF CONFIDENTIALITY

Individual patient medical information obtained as a result of this trial is considered confidential and disclosure to third parties is prohibited with the exceptions noted below. Patient confidentiality will be ensured by using patient identification code numbers. Treatment data may be given to the patient's personal physician or to other appropriate medical personnel responsible for the patient's welfare. Data generated as a result of the trial need to be available for inspection on request by the participating physicians, the Sponsor's representatives, by the IRB and the regulatory authorities.

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8.6 END OF TRIAL

The end of the trial is defined as last patient out.
When the trial is completed, the Investigator should inform the head of the trial site of the completion in writing, and the head of the trial site should promptly inform the IRB and Sponsor of the completion in writing.

8.7 PROTOCOL VIOLATIONS

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

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

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

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c02094318 [redacted]. A randomised, double-blind, 5 treatment arms, 4-period, incomplete cross-over study to determine the effect of 6 weeks treatment of orally inhaled tiotropium + olodaterol fixed dose combination (FDC) (2.5 /5 µg and 5 / 5 µg) (delivered by the Respimat® Inhaler) compared with tiotropium (5 µg), olodaterol (5 µg), and placebo (delivered by the Respimat® Inhaler) on lung hyperinflation and exercise endurance time during constant work rate cycle ergometry in patients with Chronic Obstructive Pulmonary Disease (COPD) [MORACTO™ 2] (1237.14) 07 April 2014.

c01860006 [redacted]. Investigator's Brochure: Tiotropium Bromide, Ba 679 BR. Version 21, 07 October 2014

c01735808 [redacted]. Investigator’s brochure- BI 1744 and tiotropium - 1237.P1 - Version 7, 12 Sept 2014

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10. APPENDICES

10.1 THE RESPIMAT INHALER

Instructions for Use

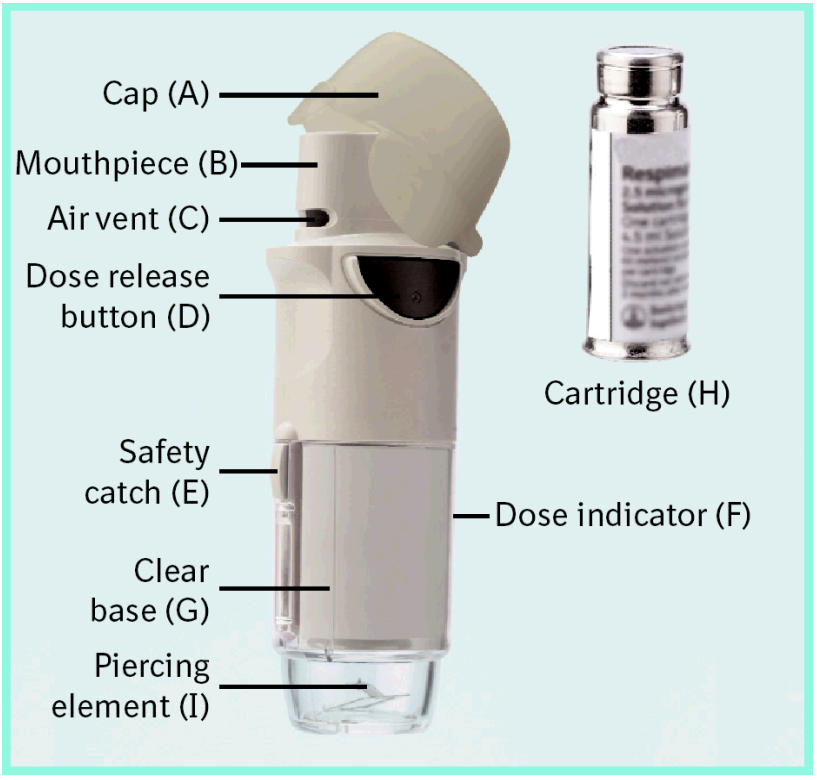
RESPIMAT inhaler

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

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Inserting the cartridge and preparation for use

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

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

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To prepare the RESPIMAT inhaler for first-time use

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

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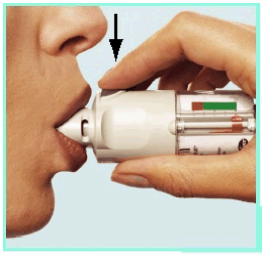
Using the RESPIMAT inhaler

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

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

When to get a new RESPIMAT inhaler

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

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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

CE 0123 **HI-Master-Version-04-BI 1744+tiotropium combination-Respimat-20090831**

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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. Details of the procedures for the return of malfunctioning inhalers are provided in the ISF.

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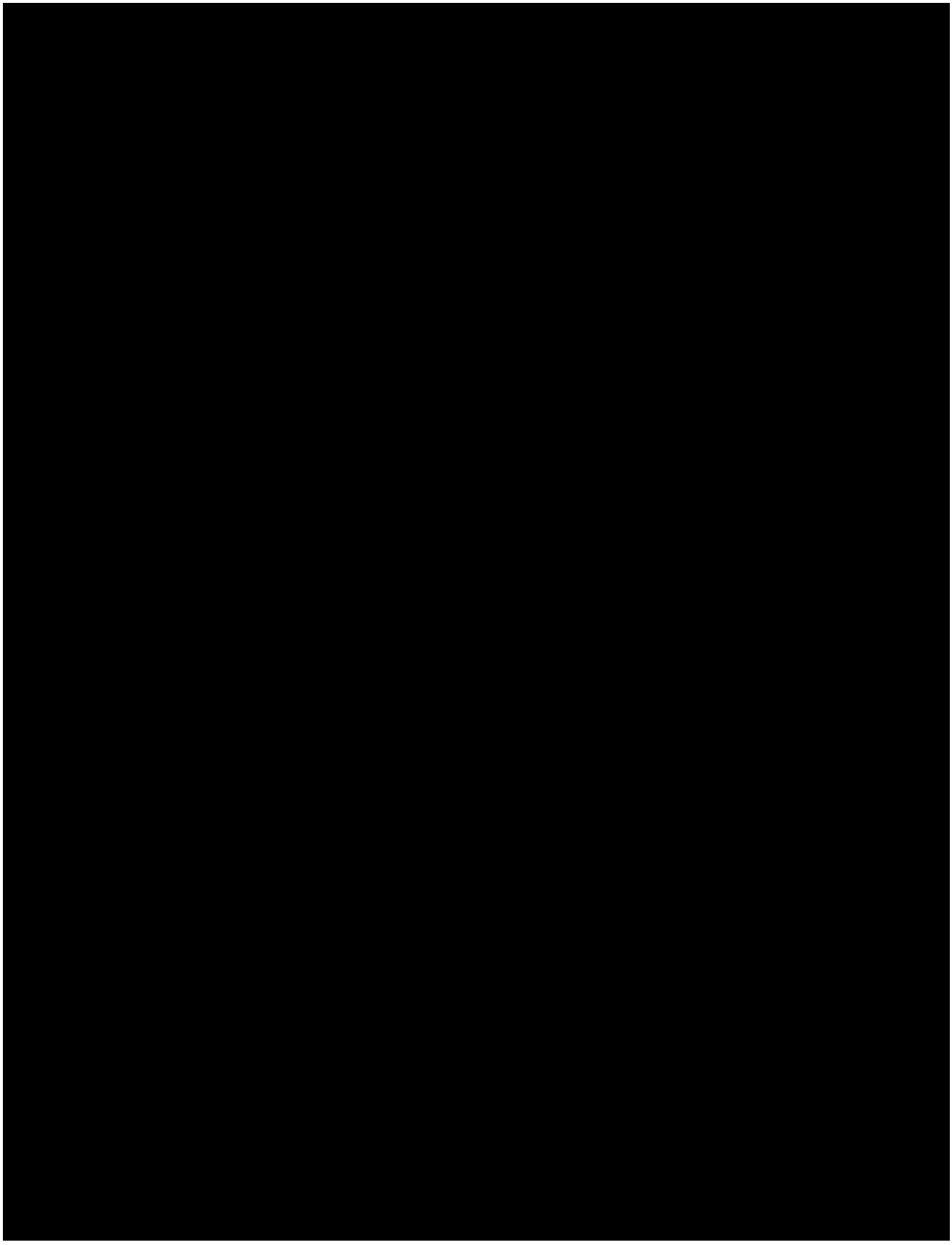

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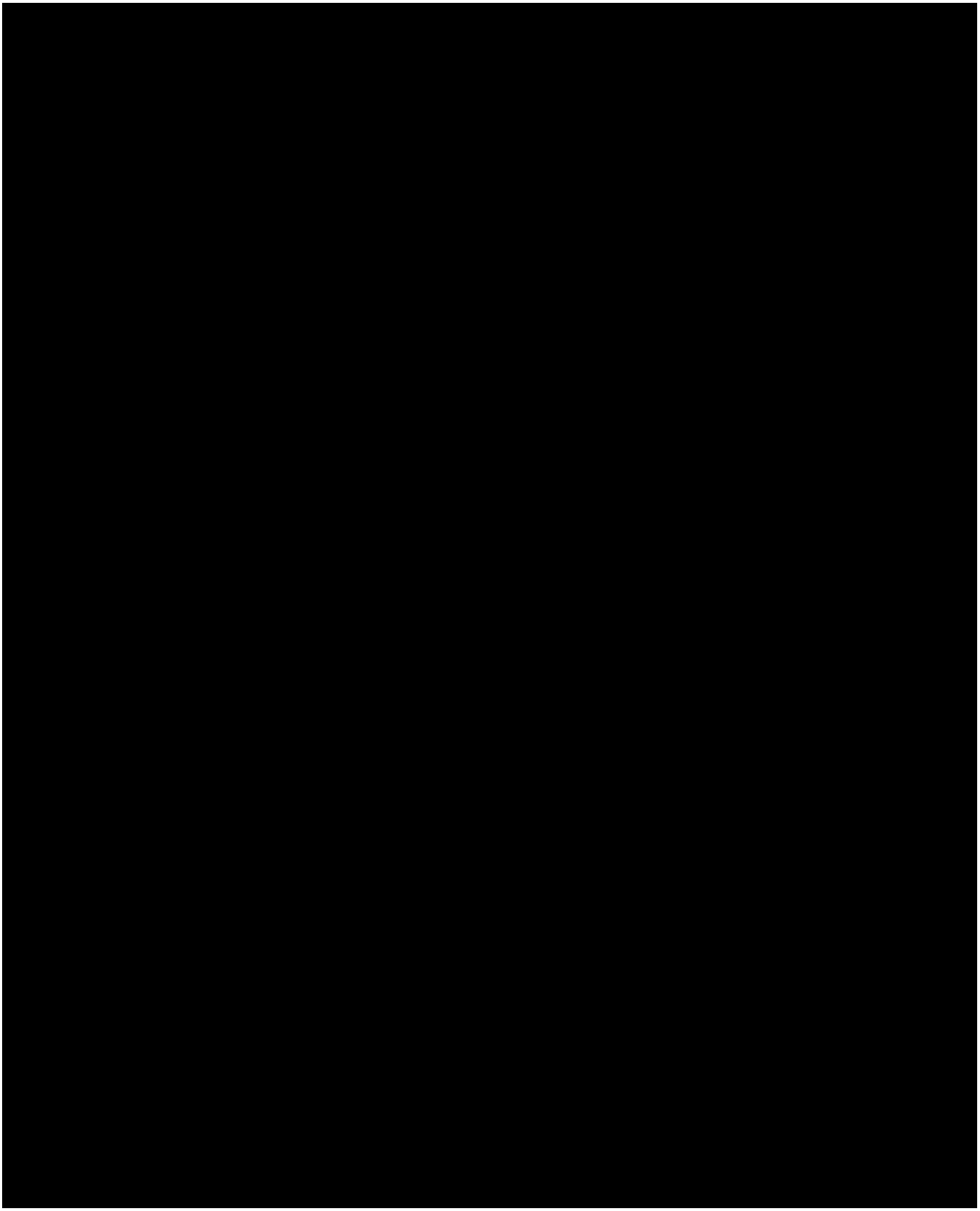

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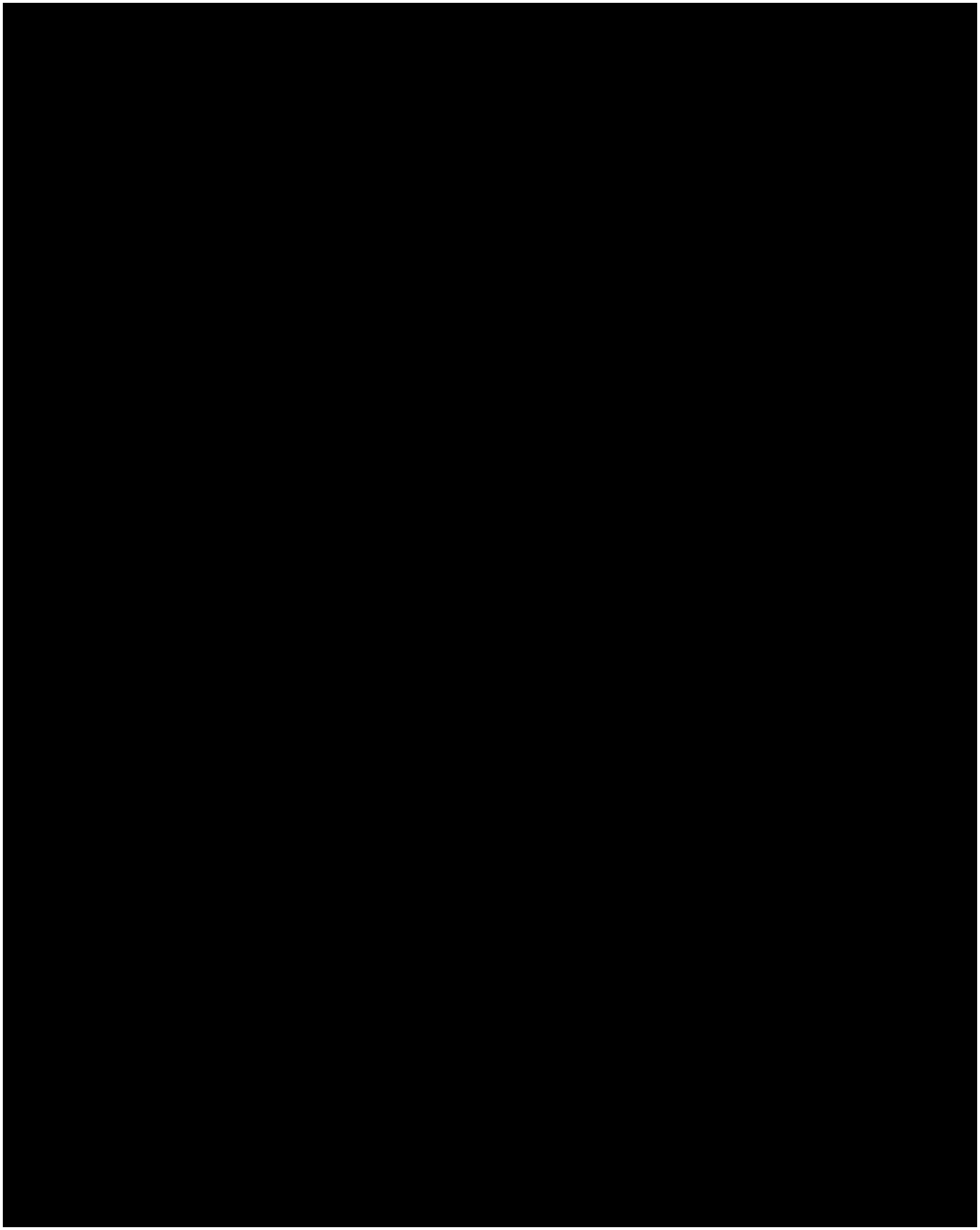

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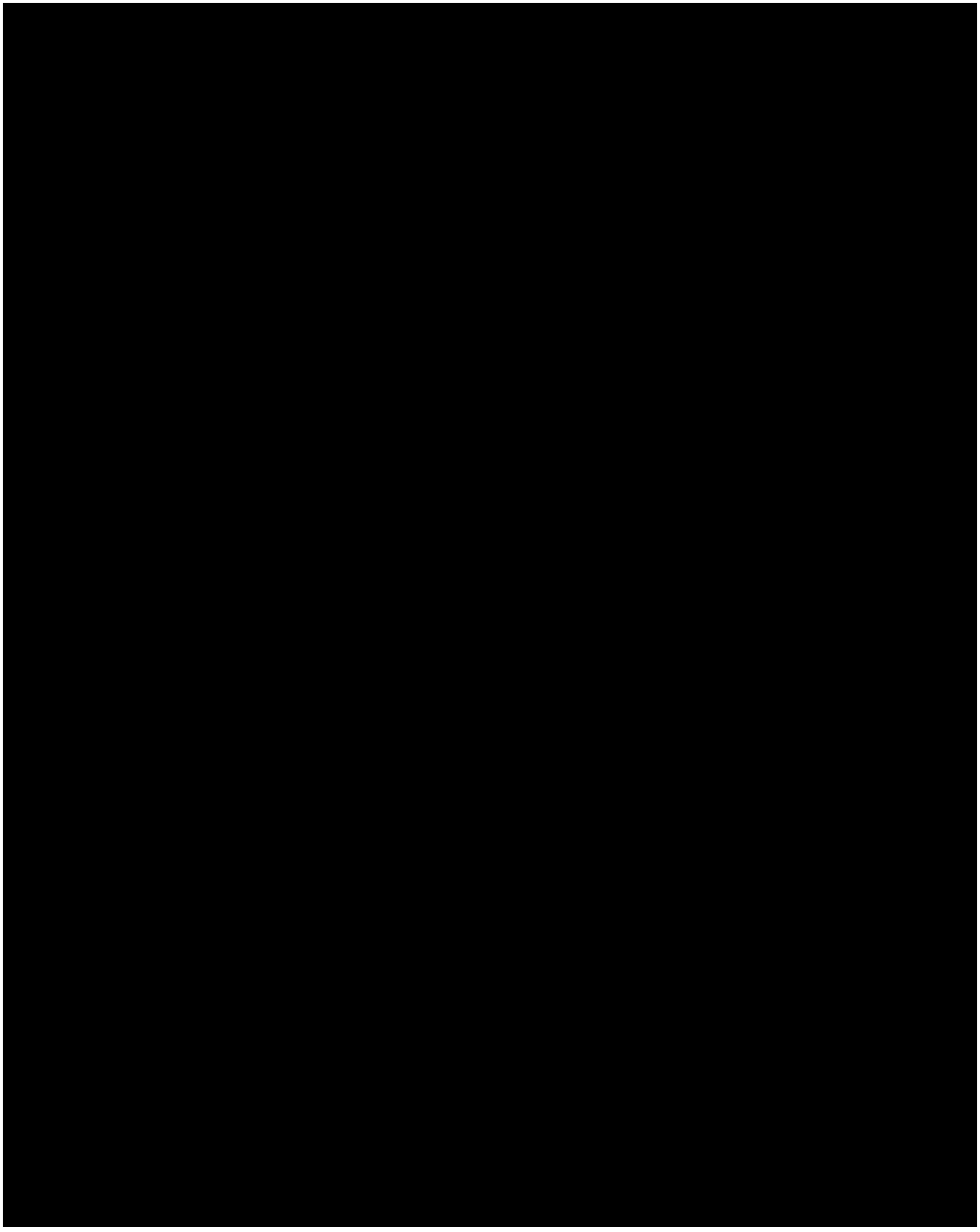

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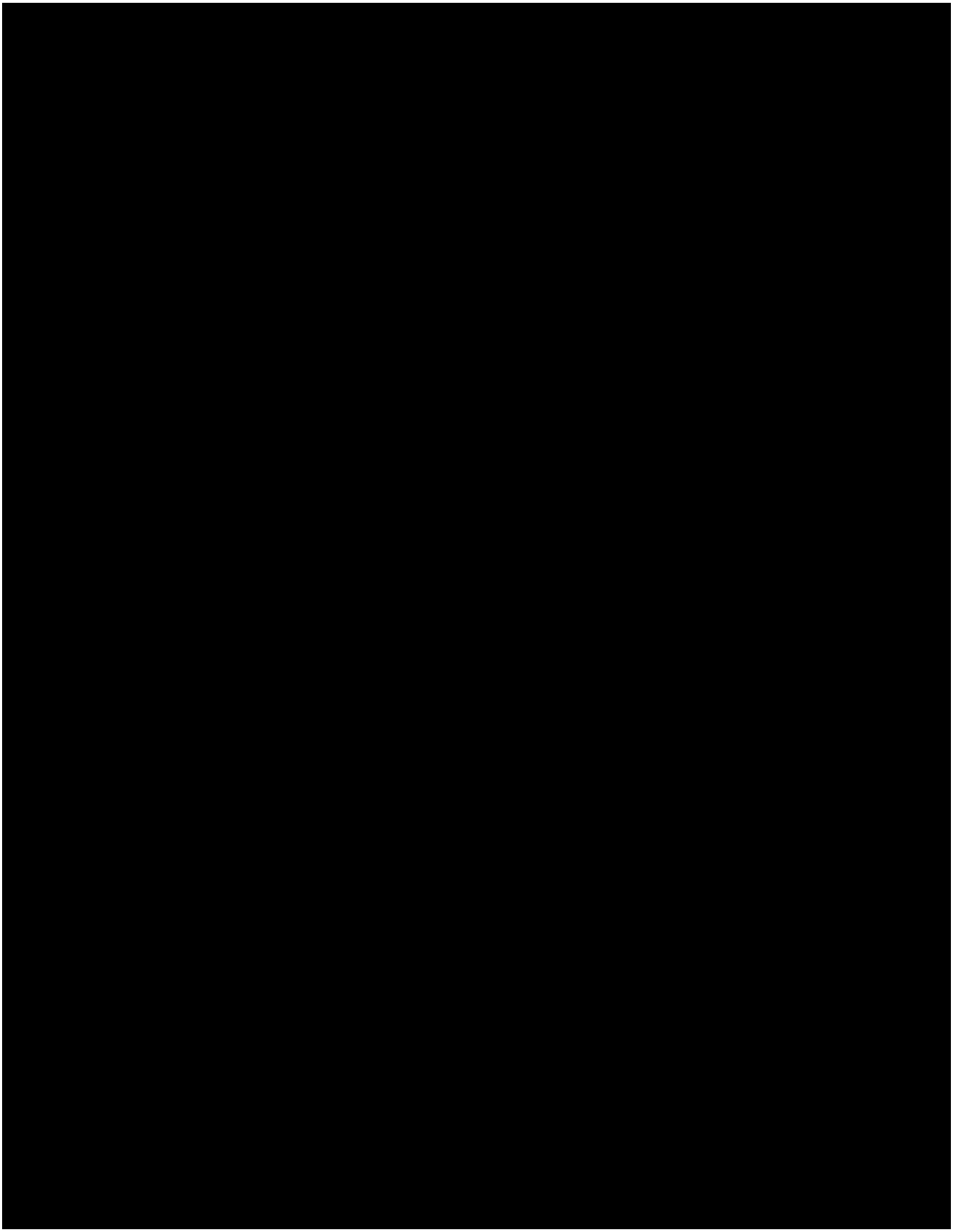

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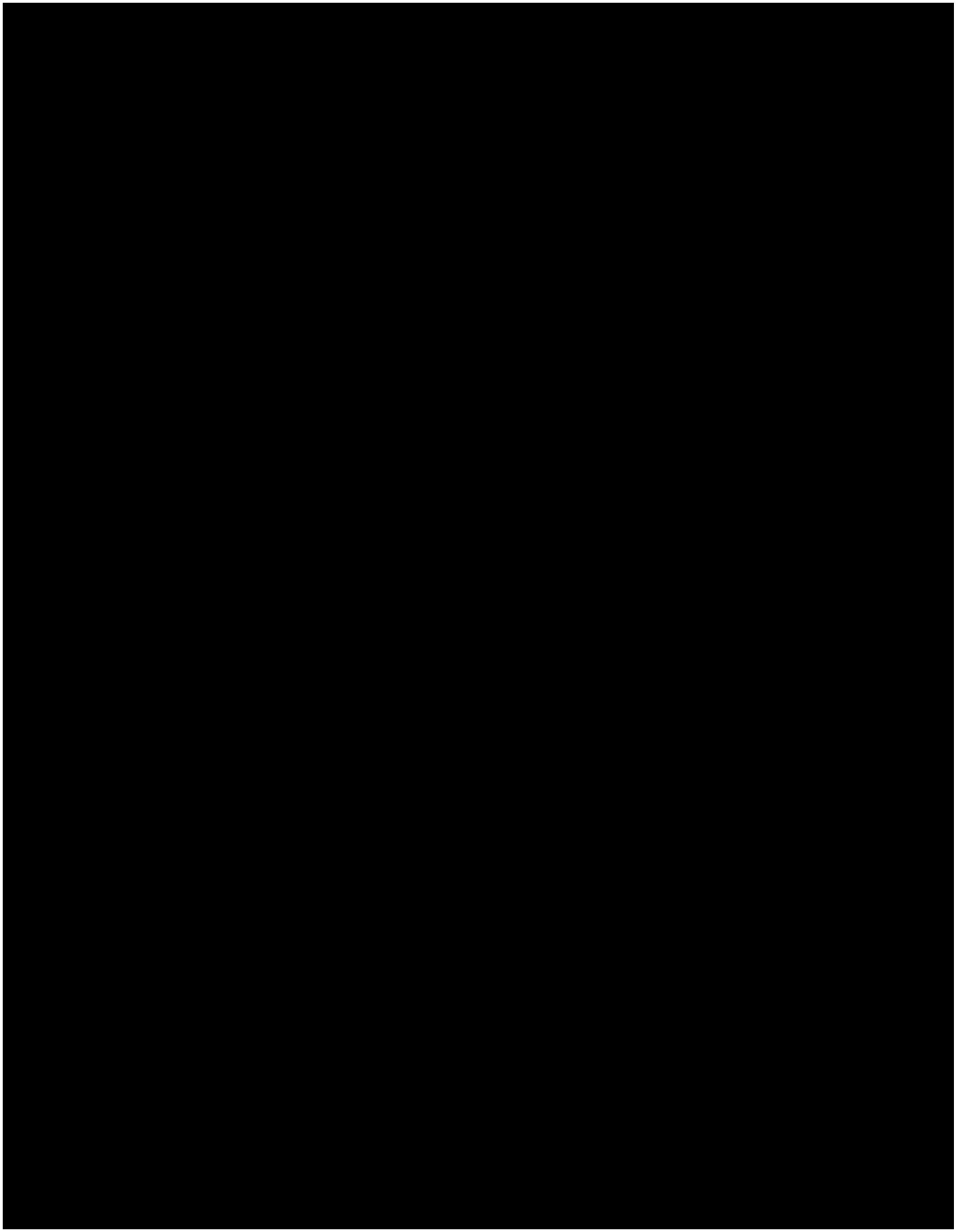

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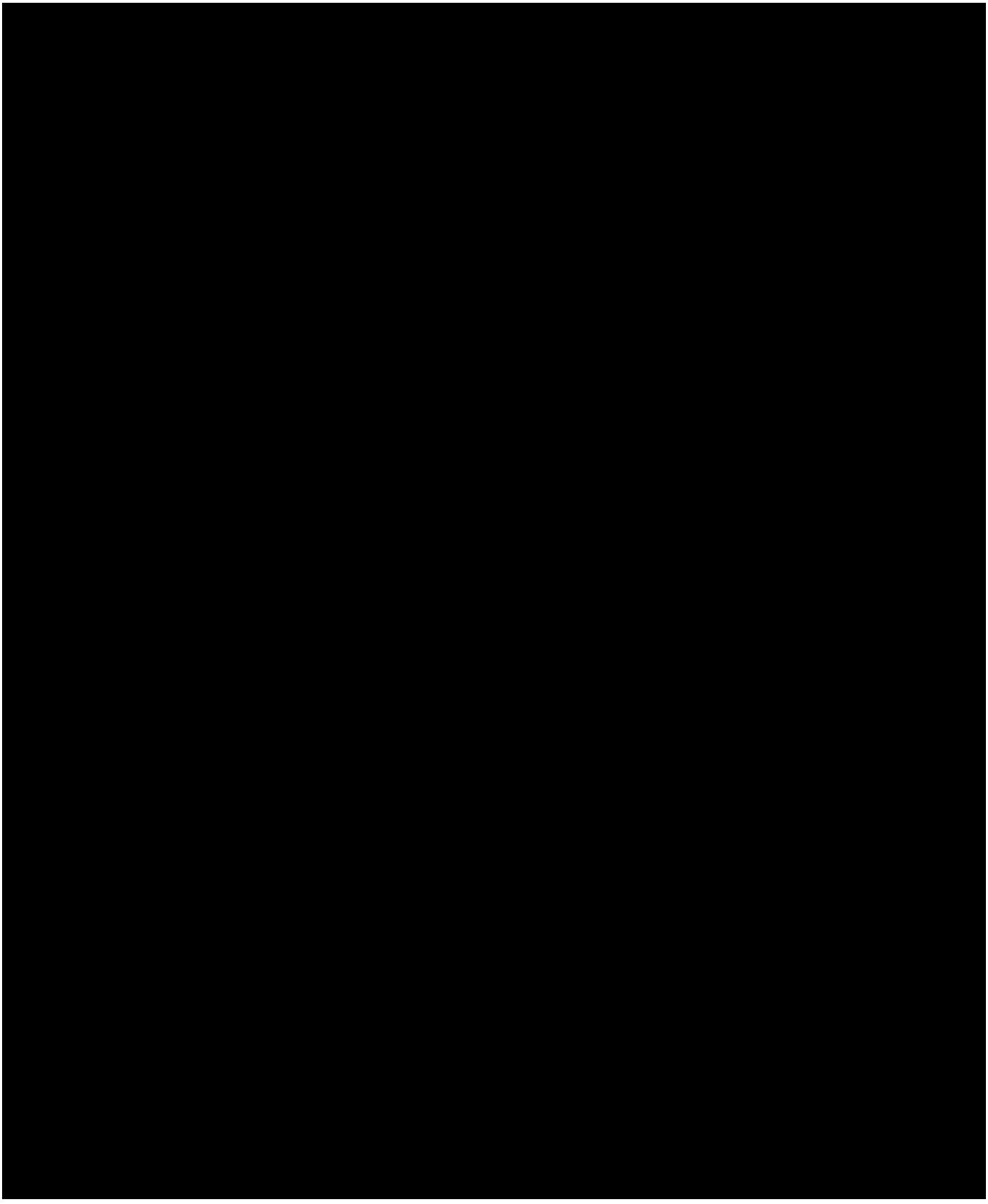

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10.5 ADDITIONAL INFORMATION REGARDING IN/EXCLUSION CRITERIA

Reversibility testing [P05-12782]

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

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

For height measured in inches

Males: FEV_1 predicted (L) = 4.30 x [height (inches)/39.37] - 0.029 x [age (yrs)] - 2.49

Females: FEV_1 predicted (L) = 3.95 x [height (inches)/39.37] - 0.025 x [age (yrs)] - 2.60

For height measured in meters

Males: FEV_1 predicted (L) = 4.30 x [height (m)] - 0.029 x [age (yrs)] - 2.49

Females: FEV_1 predicted (L) = 3.95 x [height (m)] - 0.025 x [age (yrs)] - 2.60

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

Calculation of number of pack years

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

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10.6 SIX-MINUITE WALK DISTANCE

- Testing should be performed at Visits 1 (for training), Visit 2, Visit 3 and Visit 4/EOT in a location where a rapid, appropriate response in the event of an emergency is possible. The appropriate location of a crash cart should be determined by the physician supervising the facility.
- Supplies that must be available include oxygen, sublingual nitroglycerine, aspirin, and salbutamol in metered dose inhaler or nebulizer. A telephone or other means should be in place to enable a call for help.
- Physicians are required to be present for the first test and for subsequent tests as needed.
- During the 6MWT patients will be monitored for both HR and SpO_2 using mobile pulse oximeter.

- If SpO_2 decreases to below 83% at any time after the patients begins walking:

  • The walk should be terminated. Supplemental oxygen should be administered.

  • The patient should then be seated and allowed to rest for 5 minutes. If the resting SpO_2 after 5 minutes is not ≥ 83% then the O_2 flow rate should be increased another 2 L/min and the resting SpO_2 reassessed after 5 minutes. This should be repeated until the resting SpO_2 is ≥ 83 % for 5 minutes.

  Mandatory stopping rules for the 6MWT include the following (ATS guideline):

  • Chest pain

  • Intolerable dyspnea

  • Leg cramps

  • Staggering

  • Diaphoresis

  • Pale or ashen appearance.

- The distance walked will be measured in meters (m) and will be recorded. If the test is stopped prematurely, the distance (m), the duration (min), and the reason for stopping will be recorded.
- Patients will be asked to rate the intensity of breathing discomfort and leg discomfort using the modified Borg Scale (see Section 10.7) prior to exercise (i.e., before the start of walking**), every one minutes during exercise** and at end-exercise.

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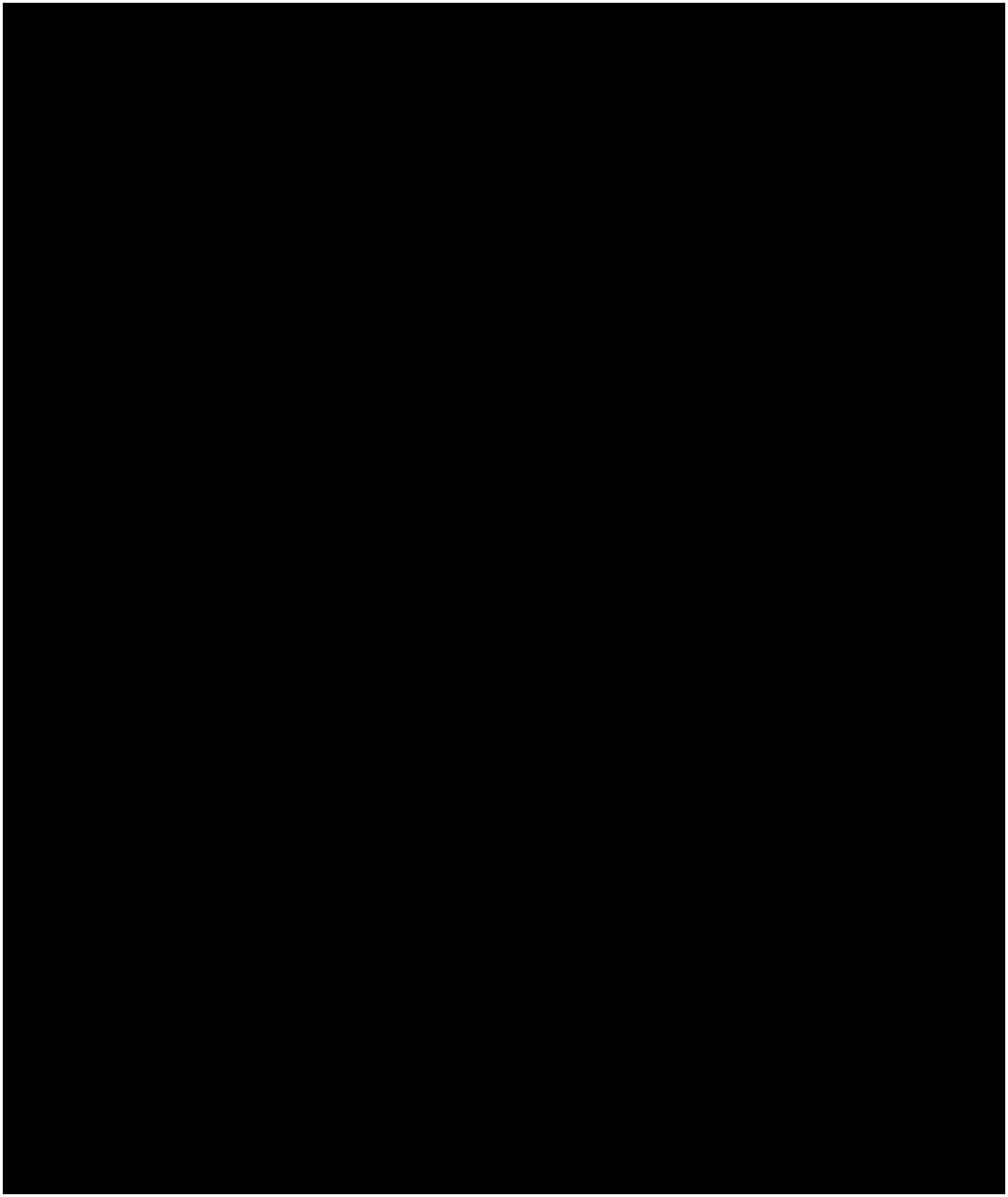

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10.8 MODIFIED MEDICAL RESEARCH COUNCIL (MMRC)

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.

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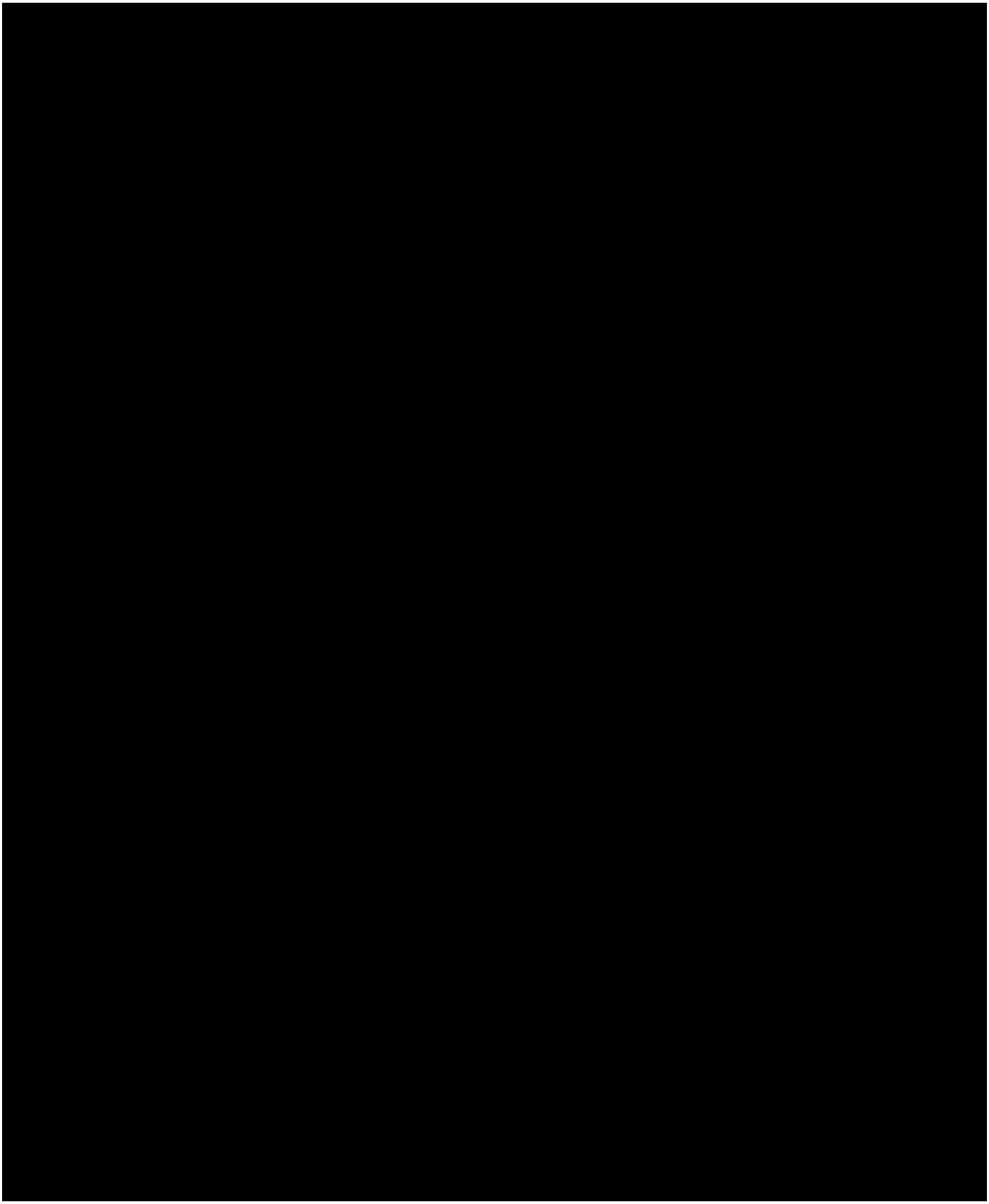

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10.10 INSPIRATORY CAPACITY

In this trial inspiratory capacity measurements will be done at rest in combination with dosing of trial medication. A baseline measurement will be completed at Visit 2 prior to the exercise tests. IC measurements will also be performed 1.0 hours post morning dose on Visits 3 and 4 after measurement of FEV_1 and FVC. 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 breathe through a mouthpiece attached to the spirometer. 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 preforming the next maneuver. At least three reproducible IC measurements should be obtained (i.e., IC s.d. /IC mean values is 0.06 or less than 0.06) with a maximum of 5 measurements to be performed. The resting IC should be recorded as the mean of the two highest acceptable efforts.

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.

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10.11 PATIENT GLOBAL PHYSICAL ACTIVITY RATING AND GLOBAL IMPRESSION OF CHANGE

- Patient Global Rating of physical activity experience (Visit 2; baseline)
- Instruction: This question should be used immediately before the patient completes other visit specific questionnaires. The investigator is to read out the question and response options to the patient. The patient's response should be noted in the eCRF.

- Overall, how would you describe your experience of physical activity in the last week? - By physical activity we mean all activities that require movement of your body. Examples are household activities, walking, going out and about. *(please select one answer)*
☐ Not limited at all ☐ Slightly limited ☐ Quite limited ☐ Severely limited

Patient Global rating of change (Visit 3 and 4/EOT)

- Instruction: This question should be used immediately before the patient completes other visit specific questionnaires. The investigator is to read out the question and response options to the patient. The patient's response should be noted in the e-CRF.
- Rating of change; overall concept
- The comparison to the time at which the patient answered the global rating of severity question (study start/ randomisation) should be emphasised and the patient asked to think about the last week.

- Compared to the start of the study –mention day and month-, how would you describe your overall experience of physical activity in the past week? *(please select one answer)*
☐ Much worse ☐ Worse ☐ Slightly worse ☐ No change ☐ Slightly better ☐ Better ☐ Much better

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- Rating of change; amount domain
- The comparison to the time at which the patient answered the global rating of severity question (study start/ randomisation) should be emphasised and the patient asked to think about the last week.

- Compared to the start of the study –mention day and month-, how physically active have you been in the last week? *(amount) (please select one answer)*
☐ Much less active ☐ Less active ☐ A little less active ☐ No change ☐ A little more active ☐ More active ☐ Much more active

- Rating of change; difficulty domain
- The comparison to the time at which the patient answered the global rating of severity question (study start/ randomisation) should be emphasised and the patient asked to think about the last week.

- Compared to the start of the study, how difficult have you found it to conduct physical activity in the last week: *(difficulty) (please select one answer)*
☐ Much more difficult ☐ More difficult ☐ A little more difficult ☐ No change ☐ A little easier ☐ Easier ☐ Much easier

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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: c03397161 **Technical Version Number:1.0**

Document Name: clinical-trial-protocol

Title: A randomised, double-blinded, active-controlled 2-way cross over trial to assess the effects of 6 weeks treatment of once daily orally inhaled tiotropium + olodaterol fixed dose combination delivered by RESPIMAT Inhaler compared with tiotropium delivered by RESPIMAT Inhaler on lung hyperinflation, exercise capacity and physical activity in Japanese patients with Chronic Obstructive Pulmonary...

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Author-Trial Clinical Monitor	[redacted]	02 Nov 2015 01:37 CET
Author-Trial Statistician		02 Nov 2015 08:40 CET
Approval-Therapeutic Area [redacted]		02 Nov 2015 10:46 CET
Approval-Team Member Medical Affairs		03 Nov 2015 11:10 CET
Verification-Paper Signature Completion		04 Nov 2015 00:21 CET

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed