

Clinical Trial Protocol

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EudraCT No.:	Not applicable	
BI Trial No.:	1237.30	
BI Investigational Products:	Tiotropium+olodaterol RESPIMAT solution for inhalation.	
Title:	An open-label trial to assess pharmacokinetics and safety of tiotropium + olodaterol fixed-dose combination (5 µg / 5 µg) delivered by the RESPIMAT inhaler after single and multiple dose treatment in Chinese patients with Chronic Obstructive Pulmonary Disease (COPD)	
Brief Title:	Bioavailability of tiotropium + olodaterol fixed-dose combination (5 µg / 5 µg) in Chinese COPD patients	
Clinical Phase:	Ib	
Trial Clinical Monitor:	<div></div>	
Principal Investigator:	<div></div>	
Status:	Final Protocol (Revised Protocol (based on Global Amendment(s)2))	
Version and Date:	Version:	Date:
	3.0	20 Feb 2017
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CLINICAL TRIAL PROTOCOL SYNOPSIS

Name of company: Boehringer Ingelheim			
Name of finished product: Tiotropium+olodaterol RESPIMAT			
Name of active ingredient: Tiotropium+olodaterol RESPIMAT solution for inhalation.			
Protocol date: 19 Nov 2015	Trial number: 1237.30		Revision date: 20 Feb 2017
Title of trial:	An open-label trial to assess pharmacokinetics and safety of tiotropium + olodaterol fixed-dose combination (5 µg/ 5 µg) delivered by the RESPIMAT inhaler after single and multiple dose treatment in Chinese patients with Chronic Obstructive Pulmonary Disease (COPD)		
Principal Investigator			
Trial site:			
Clinical phase:	Ib		
Objective:	The primary objective of this study is to assess the pharmacokinetics of tiotropium + olodaterol fixed-dose combination (5 µg / 5 µg) delivered by the RESPIMAT inhaler after single dose and at steady state in Chinese patients with COPD.		
Methodology:	Open-label design		
No. of patients:			
total entered:	16 (at least 12 completed)		
each treatment:	16 (at least 12 completed)		
Diagnosis :	Chronic Obstructive Pulmonary Disease (COPD)		
Main criteria for inclusion:	Male and Female Chinese outpatients, aged ≥40 years with a diagnosis of COPD; smoking history >10 pack years, post-bronchodilator FEV1 ≥30% and <80% predicted, post-bronchodilator FEV1/FVC <70%.		
Test product:	Tiotropium + olodaterol FDC solution for inhalation - RESPIMAT		
dose:	5 µg tiotropium + 5 µg olodaterol		
mode of administration:	Oral inhalation		
Comparator products:	Not applicable		
dose:	Not applicable		

Name of company: Boehringer Ingelheim			
Name of finished product: Tiotropium+olodaterol RESPIMAT			
Name of active ingredient: Tiotropium+olodaterol RESPIMAT solution for inhalation.			
Protocol date: 19 Nov 2015	Trial number: 1237.30		Revision date: 20 Feb 2017
mode of administration:		Not applicable	
Duration of treatment:		3 weeks	
Endpoints		Pharmacokinetics: PK parameters of tiotropium and olodaterol: Primary endpoints : After a single dosing: C_{max} , t_{max} , AUC_{0-6} After multiple dosing: $C_{max,ss}$, $t_{max,ss}$, $AUC_{0-6,ss}$, $AUC_{\tau,ss}$, $C_{pre,ss}$, Accumulation ratio based on C_{max} and AUC_{0-6} Secondary endpoints: The number (%) of subjects with drug related Adverse Events <div></div>	
Safety criteria:		Adverse events (including physical examination), vital signs, laboratory evaluations, 12-lead ECG	
Statistical methods:		Safety and pharmacokinetic parameters will be summarised by using descriptive statistics. Attainment of steady state will be explored by using repeated-measurement ANOVA.	

FLOW CHART

Trial periods	Screening		Treatment period			Follow-up
Visit	0	1 ⁶	2 ⁸	3 ¹⁵	4 EOT	5
Week	-	-2	0	0-2	3	+3
Day	-	-14	1	2-20	21	+21
Time window (days)		-14			+7	+7
Informed consent ¹	X					
Demographic		X				
Medical history		X				
COPD/patient characteristics		X				
Smoking status		X				
In-/Exclusion criteria		X				
Physical examination		X	X		X ¹¹	X ¹²
Patient allocation			X ¹⁴			
Administration of trial medication in clinic			X ¹³	X ^{9,11}	X ^{10, 11}	
Training in use of RESPIMAT (placebo) inhalation in clinic		X	X			
PFT (FEV ₁ and FVC)		X ⁷				
Vital sign (BP, PR) ²		X	X ¹³		X ^{10, 11}	X ¹²
12-lead ECG		X	X		X	X ¹²
Laboratory tests		X	X ¹³		X ^{10, 11}	X ¹²
Pregnancy test ⁴		X	X ¹³		X ^{10, 11}	X
PK sampling (blood/ urine)			X ¹³	X ^{9,11}	X ^{10, 11}	
Adverse events/Concomitant therapy		X	X	X ¹¹	X ¹¹	X
Dispense trial medication			X ³			
Collect trial medication					X ¹¹	
Dispense rescue medication ⁵	X	X	X	X ¹¹	X ¹¹	
Collect rescue medication						X
Dispense patient medication worksheet			X			
Collect patient medication worksheet					X ¹¹	
Review patient medication worksheet				X	X ¹¹	
Med washout compliance check		X				
Termination of trial medication					X ¹¹	
Trial completion						X
Meal in clinic			X	X ⁹	X ¹⁰	

EOT: End of treatment

1. All patients must sign an informed consent consistent with GCP guidelines prior to participation in the trial, which includes medication washout and restrictions.
2. After 5 minutes rest in supine position.
3. The drug will be marked by subject number when collected, while the same drug will be dispensed to subjects correspondingly for multiple dose period.

4. To be completed on all women of childbearing potential. A serum HCG will be performed at Visit 1. A urine pregnancy test will be performed prior to trial medication administration at Visits 2, 4 and 5
5. Additional salbutamol MDI will be only issued if needed from Visit 1 to Visit 3.
6. Visit 1 will be scheduled within 28 days after signing informed consent. Note: patient who takes Spiriva (RESPIMAT or HANDIHALER) need at least 3 weeks wash-out before Visit 2 and 1 week wash out before visit 1.
7. PFTs before and after inhalation of salbutamol MDI (See [Section 10.4](#)).
8. The screening period (i.e. period between Visits 1 and Visit 2) may be extended by 2 weeks (total up to 4 weeks) for administrative reasons.
9. For details, see flow chart "[timing of procedure at Visit 3](#)".
10. For details, see flow chart "[timing of procedure at Visit 4](#)".
11. Assessments to be completed by all patients including patients who discontinue early. For patients who discontinue early, whether PK sampling will be obtained or not will be determined by discussion between investigator and sponsor.
12. To be performed only if relevant findings at Visit 4.
13. For details, see flow chart "[timing of procedure at Visit 2](#)".
14. Assignment of patients to medication numbers will be according to the order of their attendance to the study site.
15. Patients should at least arrive at site for PK sampling at days 7, 14 and stay at site from day 18 to visit 4. If the investigator agrees, the patients could discharge at day 2-6, 8-13, 15-17 in visit 3.

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TIMING OF PROCEDURE at Visit 2

[illegible]

1. Meal could be taken after completing laboratory test, and should not impact other procedure.
2. After urine pregnancy test, site personnel dispense one urine sample for laboratory test. Site personnel add citric acid solution before dispensing 3 urine samples for PK blank. Patient should be instructed to empty the bladder prior to the trial medication administration.
3. Trial medications to be administered after all assessments are completed.
4. Intervals (related to drug administration) for urine PK after drug administration: 0 to 2, 2 to 4, 4 to 6 h.
5. PK samples should be taken before drug administration.

TIMING OF PROCEDURE at Visit 3

Day2-Day20 (counting from day1 in visit 2)	Timing (relate to first drug administration) (HH:MM)														
	143:45	144:00	144:20	311:45	312:00	312:20	407:45	408:00	408:20	431:45	432:00	432:20	455:45	456:00	456:20
Administration of trial medication ¹		X			X			X			X			X	
Blood sampling for PK (from iv line)	X ²		X	X ²		X	X ²		X	X ²		X	X ²		X

1. Administration of trial medication should be within **± 5 minutes** of the administration time at Visit 2.
2. PK blood samples should be taken before drug administration.

TIMING OF PROCEDURE at Visit 4

	Visit 4 Timing (relative to trial medication inhalation time)(HH:MM)																	
	Before -0:30	-0:30	-0:15	0:00	0:02	0:05	0:07	0:10	0:20	0:30	0:40	1:00	2:00	3:00	4:00	6:00	12:00	24:00
		± 5	± 5															
Administration of trial medication ¹				X														
Vital signs (supine)		X						X										
Laboratory tests for safety assessment	X																	
ECG																		X ⁵
Standardised meal in clinic ²										X								
Urine pregnancy test	X																	
Blood sampling for PK (from iv line)			X ⁴		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine sampling for PK ³				<div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> </div>														

1. Administration of trial medication should be within **± 5 minutes** of the administration time at Visit 2 .
2. Meal could be taken after completing laboratory test, and should not impact other procedure.
3. Patient should be instructed to empty the bladder prior to inhalation of trial medication administration. For PK urine sampling, all urine voided during the periods from 0 to 2, 2 to 4, 4 to 6, 6 to 12, 12 to 24 h will be collected.
4. PK blood samples should be taken before drug administration. The ECG should be performed after completing the PK sampling

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ABBREVIATIONS

AE	Adverse Event
AESI	Adverse Event of Special Interest
[REDACTED]	[REDACTED]
AP	Alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATS	American Thoracic Society
AUC	area under the plasma concentration-time curve
AUC _{τ,ss}	area under the plasma concentration-time curve at steady state over a uniform dosing interval τ
[REDACTED]	[REDACTED]
AUC _{t1-t2,ss}	area under the concentration time curve in plasma over the time interval t_1 to t_2 at steady state
BAC	benzalkonium chloride
BI	Boehringer Ingelheim
b.i.d.	bis in die (twice daily dosing)
BIRDS	Boehringer Ingelheim Regulatory Documents for Submission
BLQ	below limit of quantification
BP	blood pressure
CCDS	Company Core Data Sheet
CI	Confidence Interval
CK	creatine kinase
CK-MB	creatine kinase-MB
[REDACTED]	[REDACTED]
C _{max}	maximum measured concentration in plasma
C _{max,ss}	maximum measured concentration in plasma at steady state
CML	Local Clinical Monitor
CRA	Clinical Research Associate
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
COPD	chronic obstructive pulmonary disease
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
DMC	Data Monitoring Committee
DILI	drug induced liver injury
DNA	deoxyribonucleic acid
ECG	electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
ePRO	Electronic Patient Reported Outcome
EudraCT	European Clinical Trials Database
FAS	Full Analysis Set
[REDACTED]	[REDACTED]
FEV ₁	forced expiratory volume in one second
FVC	forced vital capacity
FC	Flow Chart
gCV	geometric coefficient of variation
gMean	geometric mean

GOLD	Global Initiative for Chronic Obstructive Lung Disease
GCP	Good Clinical Practice
h	hours
HB	hepatitis B
HbsAg	hepatitis B surface antigen
HCG	human chorionic gonadotropin
HCV	hepatitis C virus
HEV	hepatitis E virus
HPLC	high performance liquid chromatography
HPC	Human Pharmacology Center
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
ICS	inhaled corticosteroid
IEC	Independent Ethics Committee
Ig G	immunoglobulin G
Ig M	immunoglobulin M
INR	internal normalised ratio
IR	incidence rate
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISF	Investigator Site File
IU	international units
L	litres
LABA	long-acting beta-adrenoceptor agonist
LAMA	long acting muscarinic antagonist
LDH	lactate dehydrogenase
log	logarithmic
i.v.	intravenous
IVRS	Interactive Voice Response System
IWRS	Interactive Web-based Response System
LoEE	List of Essential Element
MedDRA	Medical Dictionary for Drug Regulatory Activities
MST	Medical Sub team
max	maximal
MDI	metered dose inhaler
mg	milligram
min	minute
mL	millilitres
MS/MS	tandem mass spectrometry
NA	not applicable
NBI	Nippon Boehringer Ingelheim, Co., Ltd.
NC	not calculated
NDA	new drug application
No.	number
NOA	not analysed
NOAEL	no observed adverse effects level
NOR	no valid result
NOS	no sample
OPU	Operative Unit
PD	Pharmacodynamics
PFT	pulmonary function test
PK	Pharmacokinetics
p.o.	per os (oral)
PCC	Protocol Challenge Committee

PMDA	Pharmaceuticals and medical devices agency
PR	pulse rate
PT	prothrombin time
PRN	as occasion requires
q.d.	quaque die (once a day)
QT interval	time in seconds from onset of QRS complex to end of T wave
QTc	heart rate corrected QT interval
QTcF	heart rate corrected QT interval (using the Fridericia adjustment)
RA	rheumatoid arthritis
RDC	remote data capture
RNA	ribo nucleic acid
REP	Residual effect period, after the last dose of medication with measureable drug levels or pharmacodynamic effects still likely to be present
SABA	short-acting beta-adrenergic
SAE	Serious Adverse Event
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SOP	Standard Operating Procedure
ss	(at) steady state
SUSAR	suspected unexpected serious adverse reaction
s.c.	subcutaneous
SPC	Summary of Product Characteristics
TBL	total bilirubin
TCM	Trial Clinical Monitor
TDMAP	Trial Data Management and Analysis Plan
t.i.d.	ter in die (3 times a day)
TMF	Trial Master File
TMW	Trial Medical Writer
TLC	tal lung capacity
TSAP	Trial Statistical Analysis Plan
T, t	time
TdP	Torsades de Pointes
t _{max}	time from dosing to the maximum concentration in plasma
t _{max,ss}	time from dosing to the maximum concentration in plasma at steady state
ULN	upper limit of normal

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

Treatment guidelines (ERS, ATS and GOLD) all 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 antagonist (LAMAs)), [[P04-07409](#)].

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 or more convenient administration regimen with the development of fixed dose combinations within the same inhaler device. Fixed dose combinations of a short-acting β_2 -agonist and a short-acting anticholinergic have been developed and have been shown to be safe, efficacious and convenient for the patient (e.g: Combivent[®]: salbutamol + ipratropium bromide; [[P94-01346](#)]). The recent interest in the development of LABAs and LAMAs with a once daily posology has presented the opportunity for the development of LABA/LAMA fixed dose combinations with a once daily posology.

1.2 DRUG PROFILE

Tiotropium

Tiotropium is a non-chiral, long-acting, inhaled anticholinergic bronchodilator, with a superior muscarinic receptor subtype selectivity profile and duration of action compared with ipratropium. Complete details of the currently available information regarding the pharmacological, pharmacokinetic, toxicological and clinical profile of tiotropium as mono-product are available in the respective Investigator's Brochure ([U06-3029](#)).

Olodaterol

Olodaterol has an optimised inhaled LABA profile of topical lung selectivity, high β_2 -selectivity, almost full intrinsic activity at β_2 -adrenoceptors and low intrinsic activity at β_1 -adrenoceptors. Complete details of the currently available information regarding the pharmacological, pharmacokinetic, toxicological and clinical profile of olodaterol as monoproduct are available in the respective Investigator's Brochure ([U06-3029](#)).

Tiotropium + olodaterol combination

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

In the pivotal studies (1237.5/6) tiotropium + olodaterol FDC showed statistically significant improvements in Forced Expiratory Volume in one second (FEV₁) Area Under the Curve (AUC_{0-3h}) response and trough FEV₁ response after 24 weeks compared to the mono-components and these improvements were maintained up to 52 weeks. Tiotropium + olodaterol FDC showed statistically significant improvements in health-related quality of life St. George's Respiratory Questionnaire (SGRQ) and dyspnea experienced during everyday activities Transitional Dyspnea Index (TDI) after 24 weeks compared to the mono-components. More patients treated with the combination had an improvement in SGRQ total score and TDI greater than the Minimal Clinically Important Difference (MCID). Treatment with tiotropium + olodaterol FDC also resulted in reductions in both daytime and night time rescue bronchodilator use compared to the mono-components.

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

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

RESPIMAT Inhaler

Boehringer Ingelheim's Respimat[®] Inhaler will be used for administration of tiotropium + olodaterol FDC and olodaterol. The Respimat[®] Inhaler is a novel device which creates a soft mist aerosol without the use of propellants. The medication is provided as an aqueous solution in a cartridge, which is inserted into the device prior to first use. The Respimat[®] Inhaler generates a soft mist which is released over a period of approximately 1.5 seconds. The fraction of fine particles accessible to 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 plus 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. The use of the Respimat[®] Inhaler in phase III trials has been shown to be safe with regards to paradoxical bronchoconstriction during chronic use in patients with COPD ([P05-08465](#)).

2. RATIONALE, OBJECTIVES, AND BENEFIT - RISK ASSESSMENT

2.1 RATIONALE FOR PERFORMING THE TRIAL

In a dedicated PK interaction study in caucasian COPD patients (1237.3) the 90% confidence intervals for the ratios of $C_{\max,ss}$, $AUC_{0-1,ss}$, $AUC_{0-2,ss}$, and $Ae_{0-24,ss}$ for olodaterol when administered in combination with tiotropium compared with administration as monotherapy were generally completely located within the accepted bioequivalence limits of 80 to 125%, suggesting no relevant effect of tiotropium on the systemic exposure to olodaterol; the time point of the maximum olodaterol plasma concentration ($t_{\max,ss}$) was identical after both treatments. Similarly, the 90% confidence intervals for the ratio of $Ae_{0-24,ss}$ and $C_{\max,ss}$ for tiotropium when administered in combination with olodaterol compared with administration as monotherapy were all completely located within the generally accepted bioequivalence limits of 80 to 125%, suggesting no relevant effect of olodaterol on the systemic exposure to tiotropium; the time point of the maximum tiotropium plasma concentration ($t_{\max,ss}$) was identical after both treatments.

The trial 1237.30 is designed to characterize the PK of tiotropium and olodaterol following the administration of the fixed dose combination of tiotropium+olodaterol (5 µg/5 µg) in Chinese patients with COPD. China Food and Drug Administration (CFDA) requested to obtain the PK data with the fixed dose combination of tiotropium+olodaterol (5 µg/5 µg) in Chinese patients with COPD.

2.2 TRIAL OBJECTIVES

The primary objective of this study is to assess the pharmacokinetics of tiotropium + olodaterol FDC (5 µg/ 5 µg) delivered by the RESPIMAT inhaler after single dose and at steady state in Chinese patients with COPD.

The secondary objective is to assess the safety of tiotropium + olodaterol FDC (5 µg/ 5 µg) delivered by the RESPIMAT inhaler after 3 weeks once daily treatment in Chinese patients with COPD.

2.3 BENEFIT - RISK ASSESSMENT

The clinical trials conducted to date have shown tiotropium + olodaterol 5/5 µg to be a safe, well tolerated and efficacious combination therapy according to treatment guidelines in a moderate to very severe COPD patient population that included patients with concomitant cardiovascular diseases.

The observed incremental bronchodilator response for tiotropium + olodaterol 5/5 µg compared to the individual components translated into benefits that were meaningful to the patient, with improvements in several patient centred outcomes. As such, tiotropium + olodaterol 5/5 µg will be a valuable additional therapeutic option for patients with COPD, offering increased treatment benefit compared to the monotherapies with a comparable safety profile.

Based on the overall assessment of benefit to risk, the application for marketing authorization for tiotropium + olodaterol FDC was submitted in the EU and the US in May 2014, and then subsequently in several other countries, including Canada.

The trial design requires that all eligible patients complete a 3 to 4 week screening period in which LABAs and LAMAs are withdrawn prior to treatment. Site will provide open-label salbutamol (albuterol) as needed (PRN) rescue medication for all patients who have signed Informed Consent.

All patients will receive active treatment with tiotropium + olodaterol FDC (5 µg / 5 µg) during the treatment periods. 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 the same equivalent dose and regimen during the study. The only medications that are excluded during the treatment period are anticholinergic and long-acting β-adrenergic other than the study drugs.

Safety will be monitored (as described in [section 5.2](#)) at site visits and withdrawal criteria is provided for investigators' consideration (as listed in [section 3.3.4.1](#)). Women of childbearing potential may be included in clinical trials for tiotropium + olodaterol 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 (including the 3 weeks follow-up period) [[R10-5669](#)].

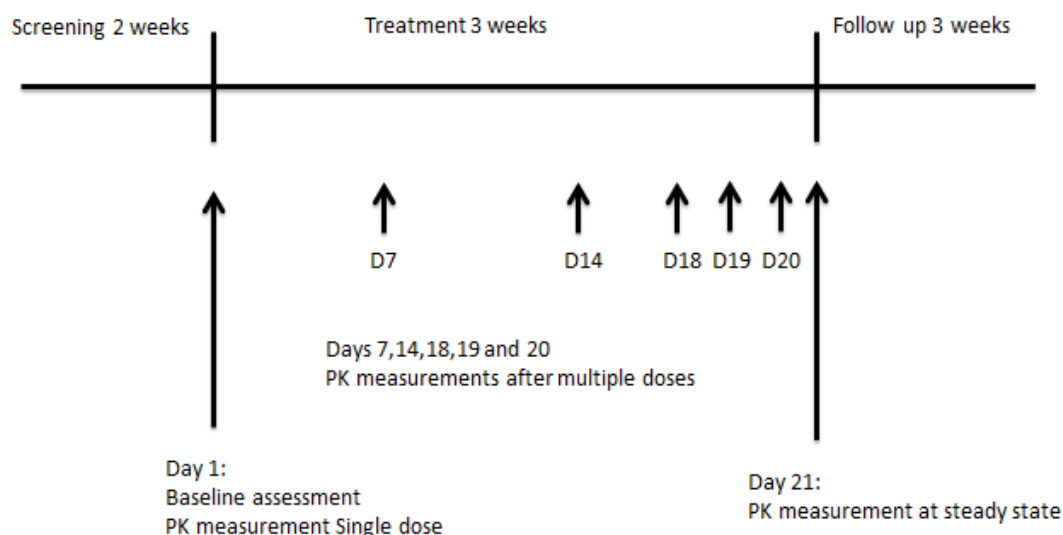
Safety will be monitored including adverse events, physical examination, vital signs, laboratory tests, pregnancy tests, , 12-lead ECG (as described in Section 5.2) at site visits.

Potential benefits for participating patients in this trial are associated with the bronchodilating effects of the active treatments during the treatment period. Careful monitoring of safety is planned at site to decrease risks. This trial is designed to provide data for evaluating the pharmacokinetic characteristics of tiotropium + olodaterol FDC at the planned registration dose in Chinese patients with COPD. The potential benefits for patients outweigh potential risks.

Although rare, a potential for drug-induced liver injury is under constant surveillance by sponsors and regulators. Therefore, this trial requires timely detection, evaluation, and follow-up of laboratory alterations in selected liver laboratory parameters to ensure patients' safety, see also [section 5.3.6.1](#).

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN



This is an open-label trial to assess PK and safety of tiotropium + olodaterol FDC (5 µg/ 5 µg) delivered by the RESPIMAT inhaler after single dose and at steady state in Chinese patients with COPD.

Following an initial screening visit, patients enter a 2-week screening period to ensure clinical stability (i.e. no exacerbations). Patients who successfully complete this phase will be allocated into the 3-week open-label treatment period. PK profiles will be determined at Visit 2 (1st dose administration), during the 3 week treatment period at Visit 3 and at Visit 4 (the end of the 3-week treatment period). At Visit 2 and Visit 4, blood and urine samples for PK measurement will be collected prior to administration and for a 6 hour period and a 24-hour period post dose of allocated treatment, respectively. At visit 3, a pre-dose sample and a sample at 20 minutes after the drug administration will be collected at days 7,14,18,19 and 20. Safety measurements will be conducted such as adverse events, vital signs, laboratory tests, 12-lead ECG recording and physical examination. All patients (including patients who discontinue early) will be evaluated for an additional 3-week following the final dose of study medication.

Adverse events will be tracked throughout the 8 weeks study period. Analysis of clinical laboratory samples will be performed at the trial site.

3.1.1 Administrative structure of the trial

The trial is sponsored by Boehringer Ingelheim.

BI will appoint a Trial Clinical Monitor (TCM), responsible for coordinating the activities required in order to manage the trial in accordance with applicable regulations and internal standard operating procedures (SOPs), directing the clinical trial team in the preparation, conduct, and reporting of the trial, order the materials as needed for the trial, ensures appropriate training and information of clinical monitors local (CML), clinical research associates (CRAs), and investigators.

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

Tasks and functions assigned in order to organise, manage, and evaluate the trial will be defined according to BI SOPs. A list of responsible persons and relevant local information (as protocol reference if applicable) are in the investigator site file (ISF) and the Trial Master File (TMF) document.

The analyses of tiotropium and olodaterol will be performed at [REDACTED]

The organisation of the trial will be done by the BI with which the responsibilities and tasks have been agreed and a written contract has been filed before initiation of the clinical trial. All contracts and relevant meeting minutes will be stored by BI in the TMF.

A CML will be appointed and will be responsible for coordinating the activities required to manage the trial in accordance with applicable regulations and internal SOPs in China.

Documents on participating investigators, especially their curricula vitae, will be filed in the TMF document.

Details on handling of the trial supplies including responsible institutions are given in [Section 4](#) of this protocol.

The ISF document will be kept in print-out version at the sites as far as required by regulation and BI SOPs. A copy of the ISF documents will be kept as an electronic TMF document according to BI SOPs.

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

A 3-week treatment period is justified because the pharmacokinetic results obtained in healthy volunteers suggested that pharmacokinetic steady state is reached within 3 weeks.

Patients with moderate to severe COPD will be included in this trial. Pharmacotherapy with long-acting bronchodilators (as single-agent therapy or as combination therapy) is the recommended maintenance treatment for these patients according to various international clinical guidelines for the management of this disease [[P01-02794](#), [P04-07409](#)]. Therefore, the systemic exposure in Chinese patients with COPD under maintenance treatment, *i.e.* at pharmacokinetic steady state, is the relevant endpoint for determining the PK of tiotropium and olodaterol in the dose combination to be used in the FDC.

Following once daily inhalation of the tiotropium + olodaterol FDC, the terminal half-life of both tiotropium and olodaterol was about 60 h and pharmacokinetic steady state was reached latest at day 8 to 10 for both compounds [[U08-2169](#)]

3.3 SELECTION OF TRIAL POPULATION

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

3.3.1 Main diagnosis for trial entry

16 patients will be included in the trial to ensure that a minimum of 12 evaluable patients of both sex, 40 years of age or older, and with a diagnosis of COPD complete the study, trial could be ended in case 12 evaluable patients are available. The evaluable patients are defined as the patients who have available blood samples for PK measurement at Visit 2, 3 and 4 as described in Flowchart. Every effort should be made to keep patients in the study until they complete all study procedures and all test days.

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

3.3.2 Inclusion criteria

1. All patients must sign an informed consent consistent with ICH-GCP guidelines and local legislations prior to any study-related procedures, which includes medication washout and restrictions.
2. All patients must have a diagnosis of COPD [[P11-05865](#)] and must meet the following spirometric criteria:

Patients must have relatively stable airway obstruction with a post-bronchodilator FEV₁ ≥30% of predicted normal and <80% of predicted normal (ECSC, [[R94-1408](#)]; and a post-bronchodilator FEV₁/ FVC<70% at Visit 1 (See [Appendix 10.4](#) for ECSC predicted normal equations).

3. Male or female patients, 40 years of age or older.
4. Patients must be current or ex-smokers with a smoking history of more than 10 pack years. (See Appendix 10.4 for calculation).

Patients who have never smoked cigarettes must be excluded.

5. Patients must be able to
 - perform technically acceptable pulmonary function tests,
 - maintain medication worksheet records during the study period,
 - perform all other assessments as required in the protocol.
6. Patients must be able to inhale medication in a competent manner from the RESPIMAT inhaler (See [Appendix 10.2](#)) and from a metered dose inhaler (MDI).
7. Male or female patients. Women of childbearing potential* must be ready and able to use highly effective methods of birth control per ICH M3(R2) that result in a low failure rate of less than 1% per year when used consistently and correctly. A list of contraception methods meeting these criteria is provided in the patient information.

*Women of childbearing potential are defined as:

Any female who has experienced menarche and does not meet the criteria for "women not of childbearing potential" as described below.

Women not of childbearing potential are defined as:

Women who are postmenopausal (12 months with no menses without an alternative medical cause) or who are permanently sterilized (e.g., tubal occlusion, hysterectomy, bilateral oophorectomy or bilateral salpingectomy).

3.3.3 Exclusion criteria

1. Patients with a significant disease other than COPD; a significant disease is defined as a disease which, in the opinion of the investigator, may (i) put the patient at risk because of participation in the study, (ii) influence the results of the study, or (iii) cause concern regarding the patient's ability to participate in the study.
2. Patients with a, in the opinion of the investigator, clinically relevant abnormal baseline haematology, blood chemistry, or urinalysis; all patients with an SGOT > 2 x ULN, SGPT > 2 x ULN, bilirubin > 2 x ULN or creatinine > 2 x ULN will be excluded regardless of clinical condition (a repeat laboratory evaluation will not be conducted in these patients).
3. Patients with a history of asthma. For patients with allergic rhinitis or atopy, source documentation is required to verify that the patient does not have asthma. If a patient has a total blood eosinophil count $\geq 600/\text{mm}^3$, source documentation is required to verify that the increased eosinophil count is related to a non-asthmatic condition.

Patients with any of the following conditions:

4. A diagnosis of thyrotoxicosis (due to the known class side effect profile of 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. Unstable or life-threatening cardiac arrhythmia.
8. Hospitalization for heart failure within the past year.
9. Known active tuberculosis.
10. A malignancy for which patient has undergone resection, radiation therapy or chemotherapy within last five years (patients with treated basal cell carcinoma are allowed).
11. A history of life-threatening pulmonary obstruction.
12. A history of cystic fibrosis.
13. Clinically evident bronchiectasis.
14. A history of significant alcohol or drug abuse.
15. Patients who have undergone thoracotomy with pulmonary resection (patients with a history of thoracotomy for other reasons should be evaluated as per exclusion criterion No. 1).
16. Patients being treated with oral or patch β -adrenergics.
17. Patients being treated with oral corticosteroid medication at unstable doses (i.e., less than six 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.
18. Patients who regularly use daytime oxygen therapy for more than one hour per day and in the investigator's opinion will be unable to abstain from the use of oxygen therapy during clinic visits.
19. Patients who have completed a pulmonary rehabilitation program in the six weeks prior to the screening visit (Visit 1) or patients who are currently in a pulmonary rehabilitation program.

20. Patients who have taken an investigational drug within one month or six half lives or (in case the investigational drug (sub) class is listed in [Table 4.2.2.1:1](#)) within the wash out period specified in Table 4.2.2.1:1 (whichever is greater) prior to screening visit (Visit 1).
21. Patients with known hypersensitivity to β -adrenergics and/or anticholinergic drugs, BAC, EDTA or any other component of the RESPIMAT inhalation solution.
22. Women who are pregnant, nursing, or who plan to become pregnant while in the trial
23. Women of childbearing potential not using two 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.
24. Patients who have previously been allocated in this study or are currently participating in another study.
25. Patients who are unable to comply with pulmonary medication restrictions prior to allocation.

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*
3. Patients with moderate to severe renal impairment (creatinine clearance ≤ 50 mL/min) should be monitored closely by the investigator, as tiotropium is a predominantly renally excreted drug.
4. Beta-blockers do 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.*
5. As an anticholinergic drug, tiotropium may potentially worsen symptoms and signs associated with narrow-angle glaucoma, prostatic hyperplasia or bladder-neck obstruction and should be used with caution in patients with any of these conditions.

* cf prescribing information for registered LABAs (salmeterol/formoterol) and olodaterol

3.3.4 Removal of patients from therapy or assessments

3.3.4.1 Removal of individual patients

An individual patient is to be withdrawn from the trial 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).
4. Decision by Boehringer Ingelheim to discontinue one or all patients (e.g., new toxicological findings or SAEs invalidate the earlier positive benefit–risk assessment).

No patient should be discontinued from the trial for a protocol violation before discussion with the clinical monitor. In the event of a COPD exacerbation, please contact the CML / TCM to discuss the possibilities to re-schedule the clinic visits.

Data of patients who discontinue or withdraw prior to allocation will be entered in the trial database and will be listed. Data of patients who discontinue or withdraw after allocation must be documented with the reason for withdrawal in source document and must be recorded in the electronic case report form (eCRF). The data must be included in the trial database and must be reported.

See [Section 6.2.4](#) for procedures to be followed for patients prematurely terminating the trial.

Pregnancy

If a patient becomes pregnant during the trial the investigational product needs to be stopped and the patient should be followed up until birth or until termination of the pregnancy. The data of the patient will be collected and reported in the CTR until patient's last visit and any events thereafter will be reported in the BI drug safety database. See [Section 5.3.7](#) for detailed information on event reporting in case of pregnancy.

3.3.4.2 Discontinuation of the trial by the sponsor

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

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

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

4. TREATMENTS

4.1 TREATMENTS TO BE ADMINISTERED

Patients will be allocated to the following treatments according to the order they enter the study site, while be assigned to Tiotropium+Olodaterol FDC treatment group:

Tiotropium + olodaterol FDC (5 µg/ 5 µg) solution for inhalation

During the entire 3-week treatment period, the patients inhale 2 puffs from the RESPIMAT inhaler, once a day, in the morning.

The investigational products will be provided by Boehringer Ingelheim.

4.1.1 Identity of BI investigational products and comparator product

Table 4.1.1: 1 Test product:

Substance:	Tiotropium + olodaterol fixed-dose combination
Pharmaceutical formulation:	Solution for inhalation
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Unit strength:	2.5µg/ 2.5µg per actuation (tiotropium/olodaterol)
Posology	2 inhalations once daily (AM dosing)
Route of administration:	Oral inhalation via RESPIMAT inhaler (A5)

4.1.2 Method of assigning patients to treatment groups

Upon signing informed consent, patients will be assigned a unique patient number using the remote data capture (RDC) system.

Patients are allocated to treatment groups at Visit 2. After assessment of all in- and exclusion criteria, each eligible patient will be assigned the lowest available medication number at the time of treatment. The 16 medications, medication number starting from the lowest, contain Tiotropium + olodaterol fixed-dose combination. Note that the medication number is different from the patient number (the latter is assigned at trial entry). Site personnel will enter the medication number on the eCRF. See [Section 4.1.6](#) for details on packaging and labelling.

4.1.3 Selection of doses in the trial

Tiotropium + olodaterol FDC (5 µg/ 5 µg) will be the submitted doses in China. These doses are included in the trial in order to assess PK in Chinese patients with COPD as required by CFDA.

4.1.4 Drug assignment and administration of doses for each patient

Dispensing of trial medication

Trial medication will be dispensed to the patient by the investigator/pharmacist. The amount of trial medication dispensed will be recorded on the drug accountability forms.

Priming of the RESPIMAT inhaler

Each newly assembled RESPIMAT inhaler has to be primed. Priming should **NOT** take place in the same room where the patient is inhaling trial medication nor where samples for PK analyses are drawn or processed (to avoid contamination of the environment). At Visit 2, priming should be performed by site personnel, and not by the patient himself. The inhaler should be primed by actuating it until an aerosol is visible plus three additional actuations. All priming actuations should be directed to the ground. For detailed priming instructions, please see the RESPIMAT inhaler handling instructions in [Appendix 10.2](#).

Once the cartridge is inserted into the Respimat inhaler, the shelf-life of the RESPIMAT with **trial** 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.

Testing of the MDI (rescue medication)

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

Trial medication administration at clinic visits

Detailed written instructions and training for the use of the RESPIMAT inhaler will be given to the patient at Visit 1 and the patient will inhale from the training device. (See [Appendix 10.2](#)). The investigator or qualified study personnel will observe the inhalation procedure and will reinforce a correct inhalation technique. At Visit 2, detailed instructions on the use of the device will be repeated, but the patient will not inhale from the training device. Patients inhale the first dose of trial medication at Visit 2.

The utmost care should be taken to ensure that the study medication is not taken prior to coming to the site at Visit 3 and Visit 4. At Visit 2 (after all assessment completion), Visit 3 and Visit 4 puffs of the study medication from the assigned RESPIMAT inhaler will be self-administered by the patient under the direct supervision of the investigating physician or deputy. Gloves must be worn and discarded immediately after the priming to avoid contamination of the PK samples to be taken and processed subsequently. The patient should not be present while priming takes place. Inhalation should **NOT** take place in the same room where samples for PK analyses are drawn or processed (to avoid contamination of the environment). Patient should inhale his/her medication in an isolated area from other patients (to avoid contamination of the environment).

Trial medication administration at home

Patients will receive two 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.

Each morning except on the days of a clinic visit, *two* puffs of the trial medication from the assigned RESPIMAT inhaler will be self-administered by the patient.

Patients have to be instructed that for the three days proceeding the days with PK sampling, the appropriate dose of study medication must be self-administered within ± 5 min of time of drug administration at Visit 2 AND between 7:00 AM and 10:00 AM in order to avoid influence on the data collected on the Visits 3 and 4.

If the patient forgot to inhale the 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 and make a note of the missed dose in his/her medication worksheet.

RESPIMAT inhaler return

The RESPIMAT inhalers dispensed for the treatment period can be used for approximately 30 days each. All used and unused trial medication must be returned at Visit 4 by the patient. Any RESPIMAT inhaler that has been reported as malfunctioning by a patient or investigator will be returned to the BI for investigation. See the ISF for specific instructions and for details regarding drug accountability requirements. Details of the procedure for the return of malfunctioning inhalers are provided in [Appendix 10.3](#).

4.1.5 Blinding and procedures for unblinding

4.1.5.1 Blinding

Not applicable since this is an open-label trial.

4.1.5.2 Unblinding and breaking the code

Not applicable since this is an open-label trial.

4.1.6 Packaging, labelling, and re-supply

All trial medication will be contained in individual RESPIMAT treatment boxes identified with the trial number and a medication number. The boxes will have a two-part tear-off label. One part of each tear-off label will remain on the box, and the other part will be attached to a special drug dispensing log which will be part of the ISF. Examples of the labels are provided in the ISF.

The investigator or designee should fill out the following information on the medication label prior to dispensing the medication to the patient:

- date of cartridge insertion (RESPIMAT inhaler only; should be entered at time of cartridge insertion)

For details of packaging and the description of the label, see the ISF.

RESPIMAT treatment box

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.

Medication dispensing

Two boxes are packed in one outer box with medication number. The one box should be used for the treatment period and the other box is for reserve.

The one RESPIMAT inhaler will be primed by the site staff (See [Section 4.1.4](#)) used to dose the patient at inhalation at the end of Visit 2, as well as continued to be used at home until Visit 4. The other RESPIMAT for reserve medication is to allow the patient the flexibility of not having to return to the site immediately to replace a lost or malfunctioning RESPIMAT inhaler.

NOTE: The RESPIMAT and drug-filled cartridge that is not yet in use by the patient should NOT be assembled prior to leaving the site. The patient must assemble and prime the reserve device at home if needed (See [Appendix 10.2](#)).

The date of cartridge insertion should be entered (label of RESPIMAT inhaler only) at time of cartridge insertion only, i.e. for the first RESPIMAT inhaler this is entered by site staff (at Visit 2), for the second RESPIMAT inhaler the patient is advised to do so when assembling this device at home during the treatment period.

Supplies other than treatment medication

BI will provide the following open-label supplies:

- RESPIMAT inhalers, placebo cartridges for training purposes. One training device will be used for several patients. 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.
- Salbutamol MDI inhalation aerosol (100 µg per actuation) for use as rescue medication during screening, treatment and follow-up periods (Visit 0 to Visit 4). It will also be used for reversibility testing at Visit 1. Salbutamol will be purchased at site and dispensed to the patient at site visits as needed.
- Ipratropium bromide will be purchased at site and provided to be dispensed at the discretion of the investigator for use by patients on long acting anticholinergics (LAMA) during the 3-week washout period of LAMA preceding Visit 2.

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

4.1.7 Storage conditions

All clinical trial supplies, which will be provided by the sponsor, must be stored in a secure, limited access storage area under the storage conditions defined on the label and may only be dispensed to patients according to protocol. A temperature log must be maintained at the site to make certain that the drug supplies are stored at the correct temperature. If the storage conditions are found to be outside the specified range, immediately contact the CML.

Regarding to the drug which will be used by patient at home, a patient diary will be provided to patient which including the drug storage temperature record.

Further details are provided in the labels, a sample of which will be part of the ISF.

4.1.8 Drug accountability

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

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

The Investigator or Pharmacist or investigational drug storage manager must maintain records of the product's delivery to the trial site, the inventory at the site, the use by each patient, and the return to the Sponsor or alternative disposal of unused products.

These records will include dates, quantities, batch / serial numbers, expiry ('use- by') dates, and the unique code numbers assigned to the investigational product and trial patients. The Investigator / Pharmacist / investigational drug storage manager will maintain records that document adequately that the patients were provided the doses specified by the CTP and reconcile all investigational products received from the Sponsor. At the time of return to the Sponsor or appointed CRO, the Investigator / Pharmacist / investigational drug storage manager must verify that all unused or partially used drug supplies have been returned by the clinical trial patient and that no remaining supplies are in the Investigator's possession.

4.2 CONCOMITANT THERAPY, RESTRICTIONS, AND RESCUE TREATMENT

The investigator must record all medication used by the patient for the three months preceding the Screening Visit (Visit 1) and throughout the trial, on the eCRF. This record will include the name of the medication, the total daily dose, route of administration, dates when medication was started and stopped, and the indication for medication usage.

4.2.1 Rescue medication, emergency procedures, and additional treatments

4.2.1.1 Rescue medication

Administration of rescue medication can occur at any point during the trial as deemed necessary by the patient or the investigator. Open label salbutamol MDI (100 µg per puff) will be provided as rescue medication by Site; the salbutamol MDI purchased at site is allowed for rescue medication use.

4.2.1.2 Emergency procedures

There are no special emergency procedures to be followed.

4.2.1.3 Additional treatments

Medications Allowed to Control Acute Exacerbations as Medically Necessary during the Treatment Period:

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

- Temporary increases in the dose or addition of oral steroids are allowed during the treatment portion of the study. Pulmonary function testing should not occur within seven days of the last administered dose of an increase or addition of oral steroids. Pulmonary function testing may be postponed up to 14 days to meet this restriction. Subsequent visits will be scheduled according to the patient's regular schedule.
- Temporary additions of theophylline preparations are allowed during the treatment portion of the study. Pulmonary function testing should not occur within seven days of the last dose. Pulmonary function testing may be postponed up to 14 days to accommodate this restriction. Subsequent visits will be scheduled according to the patient's regular schedule.
- The use of antibiotics is not restricted and may be prescribed as medically necessary for exacerbations and / or infections. If antibiotics are prescribed for a respiratory infection prior to pulmonary function testing days, the testing will be postponed for at least two days but not more than seven days after the last dose is given. Subsequent visits will be scheduled according to the patient's regular schedule. There are no special emergency procedures to be followed.

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

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

Table 4.2.2.1: 1 Permitted Medications and Medication Restrictions

Drug Class	Sub-class	Prior to study	Study Period		
			Screening Period	Treatment Period	Follow up Period
Corticosteroids⁴	Inhaled corticosteroids (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	Inhaled short-acting β-adrenergics	Permitted ¹	Rescue ¹	Rescue ¹	Permitted
	Inhaled long-acting β-adrenergics (bid) (e.g. formoterol / salmeterol)	Permitted (w.o. 48 hrs prior to V1)	NOT permitted	NOT permitted	Permitted
	Inhaled long-acting β-adrenergics (qd) (e.g. indacaterol, olodaterol)	Permitted (w.o. 1 week prior to V1)	NOT permitted (w.o. 3 wks prior to [visit 2])	Study medication	Permitted
	Oral and patch beta-adrenergics	Permitted (w.o. 4 wks 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

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

Drug Class	Sub-class	Prior to study	Study Period		
			Screening Period	Treatment Period	Follow up Period
Anticholinergics	Short-acting anticholinergics (e.g. inhalation aerosol, nasal spray)	Permitted ¹	Permitted until [visit 2] (w.o. 8 hrs prior to [visit 2])	NOT permitted	Permitted
	Long-acting anticholinergics (bid / qd) (e.g. tiotropium, aclidinium, glycopyrronium, umeclidinium)	Permitted (w.o. 1 week prior to V1)	NOT permitted (w.o. 3 wks prior to [visit 2])	Study medication	Permitted
Combinations	ICS / long-acting β -adrenergics (bid) (switch to ICS mono-product, no change to steroid dose, at least 48 hrs prior to V1)	Permitted ¹	NOT permitted	NOT permitted	Permitted
	ICS / long-acting β -adrenergics (qd) (switch to ICS mono-product, no change to steroid dose + LABA bid, at least 3 weeks prior to V1) (e.g. fluticasone+vilanterol)	Permitted ¹	NOT permitted	NOT permitted	Permitted
	ICS / short-acting β -adrenergics (switch to ICS mono-product, no change of steroid dose, at least 8 hrs prior to V1)	Permitted ¹	NOT permitted	NOT permitted	Permitted
	Short-acting anticholinergic / short-acting β -adrenergics	Permitted (w.o. 8 hrs prior to V1)	NOT permitted	NOT permitted	Permitted
	Long-acting anticholinergics / long-acting β -adrenergics ³ (e.g. glycopyrronium+indacaterol, umeclidinium+vilanterol)	Permitted (w.o. 1 week prior to V1)	NOT permitted (w.o. 3 wks prior to [visit 2])	Study medication	Permitted

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

Drug Class	Sub-class	Prior to study	Study Period		
			Screening Period	Treatment Period	Follow up Period
Miscellaneous	Other investigational drugs (*see exclusion criterion #xx)	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*1	Permitted*1	Permitted*1	Permitted
	Mucolytics (*not containing bronchodilators; stabilized 6 wks prior to V1)	Permitted*	Permitted	Permitted	Permitted
	PDE-4 inhibitors (e.g. roflumilast)	NOT permitted2	NOT permitted	NOT permitted	NOT permitted

w.o.: wash out, V: Visit

1. Refer to [Section 4.2.2.1](#) for washout period prior to PFTs.
Refer to [Section 4.2.1](#) for washout period prior to PFTs in case of treatment of a COPD exacerbation.
2. Patients currently using PDE4-inhibitors (e.g. roflumilast) should not be enrolled and roflumilast should not be withdrawn for the purpose of enrolling in this study.
Patients who were using roflumilast in the past may be included if their last use was a minimum of 3 months prior to Visit 1. In the event a patient with prior use of roflumilast is enrolled, past medical records are required to support and document why and when roflumilast was stopped.
3. Patients may be switched to bid LABA and / or short acting anticholinergic. Refer to Section 4.2.2.1 for washout period prior to PFTs
4. Patients are not allowed to initiate nor change the dose of Inhaled corticosteroids and oral corticosteroids during the trial.

Medication restrictions for pulmonary function testing for reviewing eligibility of patient at Visit 1:

- At least an 8-hour washout of short-acting beta-adrenergic bronchodilators prior to Visit 1.
- At least an 8-hour washout of short-acting anticholinergic bronchodilators prior to Visit 1.
- At least a 1-week washout of long-acting anticholinergic bronchodilators prior to Visit 1.
- At least a 1-week washout of long-acting beta-adrenergic bronchodilators (q.d.) prior to Visit 1.
- At least a 48-hour washout of long-acting beta-adrenergic bronchodilators (b.i.d.) prior to Visit 1.
- The morning dose of inhaled steroids should not be taken in the 1-hour period prior to PFTs.
- At least a 24-hour washout of short-acting (b.i.d. or more frequent administration) theophylline preparations.
- At least a 48-hour washout of long-acting (q.d. administration) theophylline preparation.

4.2.2.2 Restrictions on diet and life style

Restrictions prior to PFT at Visit 1

- Medication washout restrictions should be adhered to as described in [Section 4.2.2.1](#).
- Patients must refrain from strenuous activity for at least 12 hours prior to pulmonary function testing at Visit 1. 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 are not allowed at least 2 hours prior to and during the pulmonary function testing. Decaffeinated beverages are acceptable.
- Smoking should be discouraged for the 12 hours prior to pulmonary function testing and throughout the test day and will not be permitted in the 30-minute period prior to spirometry.

4.3 TREATMENT COMPLIANCE

The patient will complete a patient's medication worksheet confirming that trial medication has been taken each day during treatment periods. The investigator will review these records with the patient at Visits 3, 4 to assess treatment compliance of trial medication. Treatment compliance should be emphasized with a goal of at least 80% compliance rate.

Each patient will be trained on the screening visit, Visit 1 as to the correct inhalation using a training RESPIMAT inhaler containing placebo. On Visit 2, the trial staff should ensure that the patient knows how to inhale from the RESPIMAT inhaler correctly.

5. VARIABLES AND THEIR ASSESSMENT

5.1 TRIAL ENDPOINTS

Pharmacokinetics and safety will be assessed at the time points indicated in the [flow chart](#). In the case of premature withdrawal from the trial, all end of study assessments are to be performed.

5.1.1 Primary Endpoints

The following pharmacokinetic parameters will be determined as primary endpoints:

After a single dose:

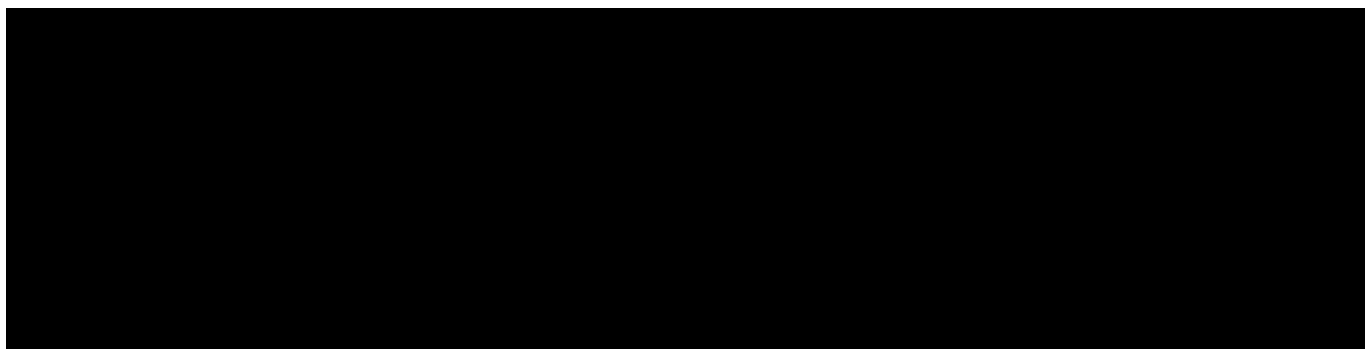
- C_{\max} (maximum measured concentration in plasma).
- t_{\max} (time from dosing to the maximum concentration in plasma).
- AUC_{0-6} (area under the concentration time curve in plasma over the time interval from 0 to 6 hours after drug administration).

After multiple dosing:

- $C_{\max,ss}$ (maximum measured concentration in plasma at steady state).
- $t_{\max,ss}$ (time from dosing to the maximum concentration in plasma at steady state).
- $AUC_{0-6,ss}$ (area under the concentration time curve in plasma over the time interval from 0 to 6 hours at steady state).
- $AUC_{\tau,ss}$ (area under the concentration-time curve in plasma at steady state over a uniform dosing interval τ at steady state).
- $C_{pre,ss}$ (pre-dose concentration in plasma at steady state).
- Accumulation ratios in plasma ($R_{A,C_{\max}} = C_{\max,ss}/C_{\max}$ and $R_{A,AUC} = AUC_{0-6,ss}/AUC_{0-6}$)

5.1.2 Secondary Endpoints

The number (%) of subjects with drug related Adverse Events will be determined as secondary endpoint to assess safety and tolerability of tiotropium + olodaterol fixed-dose combination (5 µg/ 5 µg).



5.2 ASSESSMENT OF EFFICACY

No efficacy endpoint is defined in this trial.

5.3 ASSESSMENT OF SAFETY

- All adverse events (including physical examination) until the end of study
- Vital signs: pulse rate and blood pressure (supine position)
- Routine blood chemistry, haematology and urinalysis
- 12-lead ECG

5.3.1 Physical examination

Physical examination will be performed according to [Flow Chart](#).

5.3.2 Vital Signs

Pulse rate and blood pressure will be measured and recorded. Measurements will always be obtained with the patient with supine position and rested for a minimum of 5 min. Preferably,

the same person using the same sphygmomanometer on the same (dominant) arm should perform all recordings.

5.3.3 Safety laboratory parameters

Laboratory tests

Clinical laboratory testing will be conducted on all patients at the screening visit (Visit 1), at Visit 2 and at Visit 3& 4(or at the withdrawal visit if the patient does not complete all study visits). Follow-up clinical laboratory testing may be performed at Visit 5 if there are any clinically significant findings at Visit 4. The laboratory tests at Visit 2 will be considered as the baseline measurements. Patients should be instructed not to do any unaccustomed physical exercise 36 hours prior to laboratory testing. Haematology, blood chemistry and urinalysis will be conducted at trial site. Laboratory values will be recorded on the eCRF. In case the investigator indicates a laboratory value to be clinically significant this needs to be entered in eCRF as an AE.

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-GT, SGOT, SGPT, glucose, calcium, inorganic phosphorus, uric acid, urea nitrogen, creatinine, total protein, potassium, sodium, chloride, total bilirubin, creatin phosphokinase.

Urinalysis

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

Pregnancy Testing

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

5.3.4 Electrocardiogram

The ECGs will be recorded for 10 seconds duration after the subjects have rested for at least 5 minutes in a supine position.

Printed paper traces from 12 lead ECGs (I, II, III, aVR, aVL, aVF, V1-V6) will be collected

at screening visit, visit 2 and at the end of the trial for all subjects. In the event of any cardiac symptoms (i.e. suspicion of heart rhythm disorders or cardiac ischemia), an additional ECG will be recorded. All ECGs will be evaluated, (signed, dated and commented upon) by the treating physician/investigator and stored locally. Any clinically relevant changes in the ECG will be reported as AEs and followed up and/or treated locally until normal or stable condition.

For those subjects experiencing clinically relevant changes in the ECG classified as an AE, the ECG abnormalities will be carefully monitored and if necessary the subject will be removed from the trial and medically treated. All ECGs recorded during trial conduct including the baseline ECG will be stored at a site with other source documents.

5.3.5 Other safety parameters

Not applicable

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 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 RDCs. These events should always be reported as SAEs as described in [section 5.3.7](#).

Adverse events of special interest (AESIs)

The term AESI relates to any specific AE that has been identified at the project level as being of particular concern for prospective safety monitoring and safety assessment within this trial, e.g. the potential for AEs based on knowledge from other compounds in the same class. AESI need to be reported to the Sponsor’s Pharmacovigilance Department within the same timeframe that applies to SAE, see Section 5.3.7.

The following are considered as AESIs:

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

These lab findings constitute a hepatic injury alert and the patients showing these lab abnormalities need to be followed up according to the “DILI checklist” provided in the ISF. via the RDC-system.

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. Should the results meet the criteria of hepatic injury alert, the procedures described in the DILI checklist should be followed.

Intensity of AEs

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

- | | |
|-----------|--|
| Mild: | Awareness of signs or symptoms that is/are easily tolerated |
| Moderate: | Enough discomfort to cause interference with usual activity |
| Severe: | Incapacitating or causing inability to work or to perform usual activities |

Causal relationship of AEs

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

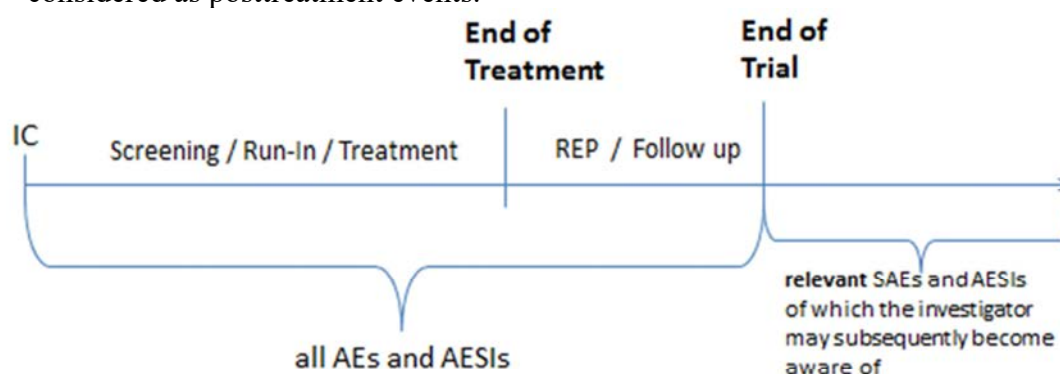
- | | |
|------|---|
| Yes: | There is a reasonable causal relationship between the investigational product administered and the AE. |
| No: | There is no reasonable causal relationship between the investigational product administered and the AE. |

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 last trial medication application. All AEs which occurred through the treatment phase 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 posttreatment 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 (country specific contact details will be provided in the ISF). The same timeline applies if follow-up information becomes available. In specific occasions the Investigator could inform the Sponsor upfront via telephone. This does not replace the requirement to complete and fax the BI SAE form.

Information required

For each AE, the Investigator should provide the information requested on the appropriate (e)CRF 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 a Non-Investigational Medicinal Product (NIMP).

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

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

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

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

Pregnancy

In rare cases, pregnancy might occur in a study. Once a subject, has been enrolled into the clinical trial after having taken trial medication the investigator must report any drug exposure during pregnancy which occurred in a female subject or in a partner to a male subject to the Sponsor immediately (within 24 hours) by means of Part A of the Pregnancy Monitoring Form to the Sponsor's unique entry point.

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

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

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

5.4 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

5.4.1 Assessment of Pharmacokinetics

As far as feasible, the following pharmacokinetic parameters will be determined for tiotropium and olodaterol, after a single dose at Visit 2 (day 1) and after multiple dosing at

Visit 4 (3 weeks after 1st drug administration). Single dose:

- C_{\max} (maximum measured concentration in plasma).
- t_{\max} (time from dosing to the maximum concentration in plasma).
- $AUC_{t_1-t_2}$ (area under the concentration time curve in plasma over the time interval t_1 to t_2).

[REDACTED]

Multiple dosing

(If steady state can be reasonably assumed, the parameters will be denoted with 'ss' as shown; otherwise, they will be denoted with the dose number of the last dose):

- $C_{\max,ss}$ (maximum measured concentration in plasma at steady state).
- $t_{\max,ss}$ (time from dosing to the maximum concentration in plasma at steady state).
- $AUC_{t_1-t_2,ss}$ (area under the concentration time curve in plasma over the time interval t_1 to t_2 at steady state).

[REDACTED]

- $AUC_{\tau,ss}$ (area under the concentration-time curve in plasma at steady state over a uniform dosing interval τ at steady state).
- $MRT_{ih,ss}$ (mean residence time in the body after inhalation at steady state)
- $C_{pre,ss}$ (pre-dose concentration in plasma at steady state).

[REDACTED]

In addition, accumulation ratios in plasma ($R_{A,C_{\max}}$ and $R_{A,AUC}$) will be calculated based on $C_{\max,ss}/C_{\max}$ and $AUC_{t_1-t_2,ss}/AUC_{t_1-t_2}$, respectively.

Further pharmacokinetic parameters may be calculated as appropriate. Terminal half-lives and terminal rate constants in plasma at steady state ($t_{1/2,ss}$, $\lambda_{z,ss}$) will be calculated if sufficient data points from the terminal phase are available, i.e. plasma concentrations are quantifiable up to the 24-hour post dose sampling time point.

For investigation of the attainment of steady state, the plasma concentrations prior to dosing and 20 min after dosing will be determined on days 7, 14, 18, 19, and 20 on visit 3.

See [Appendix 10.1](#) for details derivation of pharmacokinetic parameters.

5.4.2 Methods of sample collection

Blood sampling

Date and exact clock time of administration as well as of pharmacokinetic blood sampling have to be recorded. A blank blood sample will be collected prior to drug administration (i.e. at Visit 2, 5min (\pm 5 min) before the trial drug administration). Blood samples shall be drawn as close to the planned time as possible.

The time point zero for pharmacokinetic sampling is defined as end of (last) inhalation. Exact time points of plasma sampling will be documented in the eCRFs by the medical personnel. These actual sampling times will be used for the determination of pharmacokinetic parameters.

For quantification of drug plasma concentrations, about 6 mL of blood will be taken from a forearm vein using a blood collection tube containing potassium EDTA as anticoagulant blood drawing tube at the times indicated in the [Flow chart](#).

After completion of each blood drawing procedure, the indwelling catheter can be filled with up to 0.5 mL of sterile heparinised saline (50 IU heparin/mL 0.9% saline) in order to prevent clotting (per local clinical practice). Prior to every new blood drawing a small blood volume (approximately 0.5 mL) must be aspirated and discarded in order to avoid contamination of blood samples with heparin.

The EDTA-anticoagulated blood samples will be centrifuged as soon as possible after collection (within 40 min). Centrifugation will last for about 10 min (at about 2000 x g to 4000 x g) at room temperature or below. Two aliquots of at least 1 mL EDTA plasma samples will be obtained. One aliquot is intended for analysis of olodaterol, the second aliquot for analysis of tiotropium. Plasma samples will be frozen within 90 min after sampling and stored at the study site at about -20°C or below.

Detailed instructions for shipment of plasma samples are provided in the ISF or lab manual. In order to avoid contamination of plasma samples, study personnel are required to wash their hands with soap prior to collecting the plasma or handling of plasma samples. The RESPIMAT inhalers should be handled with gloves on and these gloves should be changed and discarded as soon as any container for PK samples is touched. As soon as the plasma is

obtained from the blood, gloves should again be changed. Plasma vials should be stored closed and only opened if necessary for the procedure.

The PK procedures should NOT take place in the same room where priming of the RESPIMAT inhaler or drug inhalation takes place.

Urine sampling

In order to enable a sufficient urine flow patients might be asked to drink at least 150 to 200 mL of a non-caffeinated beverage 20 min prior to the end of each urine fraction in order to support a miction in time.

At Visit 2, a blank urine sample will be collected prior to drug administration. 1 mL of a 1 molar citric acid stock solution (21 g citric acid monohydrate in 100 mL water) is added. Two aliquots for PK blank samples retained to check for analytical interference (5 mL per aliquot). All urine voided during the sampling intervals listed in the “[Timing of procedure at Visit 2](#)” will be collected in containers. At Visit 4, all urine voided during the sampling intervals listed in the “[Timing of procedure at Visit 4](#)” will be collected in containers. Urine containers will be stored at room temperature or below between collection time points. For urine collection, the weight of the empty containers has to be determined (e.g. documented on a worksheet and/or the container, eCRF). Then, 10 mL of a 1 molar citric acid stock solution (21 g citric acid monohydrate in 100 mL water) is added to each 2 L container and urine is collected over the collection interval. At the end of the collection interval, patients have to empty their bladder and the weight of the filled urine container will be determined. Urine container weights (i.e. tare and gross) and times of collection will be documented in the eCRFs (weight will be set equal to volume without correction for specific gravity of urine when calculating the urine volume for analysis). Two aliquots of 5 mL urine samples will be obtained. One aliquot is intended for analysis of olodaterol, the second aliquot for analysis of tiotropium. Storage of urine samples at the study site will be at about -20°C or below.

Detailed instructions for shipment of urine samples are provided in the ISF.

Detailed instructions for shipment of urine samples are provided in the ISF.

In order to avoid contamination of urine samples, study personnel are required to wash their hands with soap prior to collecting the urine or handling of urine samples. The RESPIMAT inhalers should be handled with gloves on and these gloves should be changed and discarded as soon as any container for urine samples is touched. Urine containers should only be stored closed and only opened if necessary for collection.

The handling and processing of urine samples should NOT take place in the same room where priming of the RESPIMAT inhaler or drug inhalation takes place.

5.4.3 Analytical determinations

Plasma and urine concentrations of olodaterol and tiotropium will be determined by validated high performance liquid chromatography tandem mass spectrometric (HPLC-MS/MS) assays. The analyses will be performed at [REDACTED]

[REDACTED] and will be described in appendices to the Clinical Trial Report.

5.4.4 Pharmacokinetic – Pharmacodynamic Relationship

Not Applicable

5.5 ASSESSMENT OF EXPLORATORY BIOMARKERS

Not Applicable

5.5.1 Biobanking

Not Applicable

5.6 OTHER ASSESSMENTS

Not applicable

5.7 APPROPRIATENESS OF MEASUREMENTS

All measurements performed during this trial are standard measurements and will be performed in order to monitor safety and tolerability aspects and to measure pharmacokinetic parameters in an appropriate way.

The pharmacokinetic parameters and measurements outlined in [Section 5.4](#) are generally used as measurements to assess drug exposure.

The scheduled measurements are appropriate to see drug induced changes in vital signs, standard laboratory values and ECG. These endpoints are standard and accepted for evaluation of safety and tolerability of the drug, and they are widely used in these kinds of studies.

Therefore, the appropriateness of all measurements applied in this trial is given.

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

Following the screening visit (Visit 1) and the required minimum of 2-week screening period, eligible patients will be entered (at Visit 2) into the 3-week open-label, treatment period (Visits 2–4). PK measurement for single dose will be taken at visit 2 (1st day), then followed by a sparse PK sampling at visit 3 (days 7,14,18,19 and 20). At visit 4 (day 21), PK assessment will be performed for steady state. After completion of treatment period (Visit 4), there will be one post-treatment follow-up visit (Visit 5).

The screening period may be extended by up to 2 weeks (i.e. total up to 4 weeks or 28 days) for administrative reasons. Washout of LAMA must be at least 3 weeks before treatment for patients who used LAMA before participation to the trial. The subsequent treatment period cannot be shorter than 3 weeks. Any deviant rescheduling of visits should be discussed with the CML and will have to be documented. See the [flow chart](#) for time windows for the visits. Patients should make every attempt to complete the protocol as specified. Investigators should encourage patient treatment compliance and adherence to other protocol specific activities.

Rescheduling prior to rtreatment

- The 2-week screening period (between Visit 1 and Visit 2) may be extended by 2 weeks (i.e. total up to 4 weeks or 28 days) for administrative reasons.
- If the screening period is to be extended more than an additional 2 weeks, i.e. it exceeds 4 weeks in total, the sponsor (i.e.CML) should be contacted.

Rescheduling of Visit 4

- If the patient did not take their trial medication for the 3 days preceding Visit 4, this visit must be rescheduled after at least 10 days continual administration.

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

6.2.1 Screening and run-in period

Informed consent visit (Visit 0)

- Informed consent will be obtained prior to patient participation in the trial, which includes any medication washout procedures or restrictions. Upon obtaining informed consent, the patient will be instructed on the medication washout and other restrictions

for the screening pulmonary function test at Visit 1.

- Patients taking LAMA should discontinue the treatment more than 3 weeks prior to Visit 2. Alternative bronchodilator medications may be introduced at the investigator's discretion (See [Section 4.2.2](#)).
- The patient will receive directions on the as needed use of the salbutamol MDI (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.
- Upon obtaining Informed Consent, the patient will receive a trial identification card and a patient appointment card (visit schedule), templates will be provided by the sponsor.

Observations and procedures at Visit 1

- Visit 1 will be scheduled within 28 days after signing informed consent (the period of time between signing informed consent and Visit 1 will depend on medication washout requirements).
 - Blood samples will be collected for haematology, serum chemistry and pregnancy testing (if applicable). Blood samples need to be taken prior to the salbutamol dosing.
 - Pulmonary function testing with the CHEST spirometer will be conducted between 7:00 AM and 10:00 AM, 10 min prior to the inhalation and between 10 to 15 min after the inhalation of 4 puffs of salbutamol, (reversibility testing).
 - Patients qualified to enter the 2-week (up to 4-week) screening period of the trial will be issued additional rescue medication, if needed.
 - Patients will receive training and instructions on
 - the use of the RESPIMAT inhaler in using the training RESPIMAT inhaler containing placebo
 - the use of rescue medication (salbutamol MDI)
 - medication restrictions (i.e. washout of LAMA) for the screening period and subsequent visits
 - returning all issued medication and the patient medication work sheet to the site on all subsequent visits.

Screening Period

If there is any indication during the screening period that the patient is not stable enough to complete the trial or that the patient will be non-compliant with the trial medication or restrictions, the patient should not be treated. This evaluation should take place by the

investigator.

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

6.2.2 Treatment periods

6.2.2.1 Visit 2

- 12-lead ECG will be measured before test drug administration..
- Trial medications must be administered in an area isolated from PK sampling and from other patients' administration in order to prevent any environmental contamination.
- Urine pregnancy test and laboratory test sampling should be done before dispensing urine for blank PK samples.
- The patient should be instructed to empty the bladder prior to dosing. .
- Urine sampling for PK measurement: Post-dosing urine sampling will be performed as indicated in the "[Timing of procedure at Visit 2](#)".
- Blood sampling for PK measurement: Blood sampling will be performed 5min (\pm 5 min) before the trial drug administration and post-dose at indicated in the "Timing of procedure at Visit 2".
- Before dosing with trial medication, site personnel should ensure that the patient knows how to use and inhale properly from the RESPIMAT inhaler. A training inhalation with placebo will be performed as indicated in the "Timing of procedure at Visit 2"
- The patient will be issued a patient medication worksheet to record their trial medication use, the time of administration of trial medication as of 3 days before Visit 3 and other concomitant therapy used between Visit 2 and 4 date. Patients will be instructed to return to the site with the medication worksheet at the Visit 4, so that the medication worksheet can be collected and reviewed.

6.2.2.2 Visit 3

- Trial medications must be administered in an area isolated from PK sampling and from other patients' administration in order to prevent any environmental contamination.

- Blood sampling for PK measurement: Blood sampling will be performed 15 min prior to trial medication administration and post-dose at indicated in the “Timing of procedure at Visit 3”
- Three days prior to the clinic visits on days 7, 14 and 18, a telephone contact will be made to each patient in order to remind him/ her of the medication restrictions, the use of the medication worksheet and to bring their trial medication to the site at Visit 3. From day 18 up to the end of Visit 4, the patient will stay in the clinic.

6.2.2.3 Visit 4

- Drug administration time should be within ± 5 min of the time of drug inhalation at Visit 2.
- Trial medications must be administered in an area isolated from PK sampling and from other patients’ administration in order to prevent any environmental contamination.
- Urine pregnancy test and laboratory test sampling should be done before inhalation of trial medication.
- Urine sampling for PK measurement: The patient should be asked to empty the bladder prior to dosing. Post-dosing urine sampling will be performed as indicated in the [“Timing of procedure at Visit 4”](#).
- Blood sampling for PK measurement: Blood sampling will be performed 15 min prior to trial medication administration and post-dose as indicated in the “Timing of procedure at Visit 4”.
- 12-lead ECG will be measured after last PK sampling.

Note:

If the patient did not take one of the trial medication for the 3 days preceding day 18, this visit must be re-scheduled after at least 10 days continual administration.

6.2.3 Follow Up Period and Trial Completion

Following the treatment phase of the trial, i.e. following the end of 3-week treatment period, patients will be followed up for an additional 3 weeks period. Patients may return to their regular medication after completion of Visit 4. They will be seen at the end of this period (Visit 5) and their AEs, concomitant therapies will be reviewed and recorded. A urine

pregnancy test will be performed where applicable. Dispensed rescue medication (as needed) must be returned. If the physical examination, vital signs or laboratory tests performed at Visit 4 yield abnormal values representing clinically significant changes from baseline, they (for 12-lead ECG) will be repeated at the follow-up visit (Visit 5). Any persistently abnormal test must be fully explained by the investigator and follow-up evaluation performed, if necessary. Additionally, all (S)AEs that occur within 21 days after a patient terminates trial medication must be reported.

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

6.2.4 Premature withdrawal

The physical examination (including vital signs), clinical laboratory test, PK sampling and one 12-lead ECG will be performed following any premature withdrawal in a withdrawal visit at the earliest convenience. For patients who discontinue early, whether PK sampling will be obtained or not will be determined by discussion between investigator and TCM. Any AEs and changes in concomitant therapies will be recorded. The current patient medication worksheet is to be collected. Patients should be converted to their regular medication upon premature withdrawal. The investigator should make every effort to perform a follow-up visit; 3 weeks after the withdrawal visit (please see [flow chart](#)). During follow-up period, rescue medication is dispensed as needed. If the physical examination, vital signs, 12-lead ECG, or laboratory tests performed at the withdrawal visit yield abnormal values representing clinically significant changes from baseline, they will be repeated at the follow-up visit (Visit 5).

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

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 STATISTICAL DESIGN - MODEL

Design

This is an open-label trial in which 3 weeks of treatment are preceded by a 2-week screening period and followed by a 3-week follow-up period.

Objectives

The objectives of this trial is to assess the pharmacokinetics and safety of tiotropium + olodaterol FDC (5 µg/5 µg) delivered by the RESPIMAT inhaler after single dose and at steady state in Chinese patients with COPD.

Endpoints

No efficacy endpoint is defined in this trial. For safety and pharmacokinetic endpoints, see [Sections 5.3](#) and [5.4.1](#), respectively.

Baseline

In general, baseline value will be defined as the last measurement before the first trial drug intake at Visit 2.

7.2 NULL AND ALTERNATIVE HYPOTHESES

No efficacy endpoint is defined in the trial. It is not planned to test any statistical hypothesis with regard to pharmacokinetic and safety endpoints.

7.3 PLANNED ANALYSES

7.3.1 Primary endpoint analyses

See [Sections 7.3.5](#) for pharmacokinetic analyses which are the primary objectives of this trial.

7.3.2 Secondary endpoint analyses

See [Sections 7.3.4](#) for safety analyses which are the secondary objectives of this trial.

7.3.4 Safety analyses

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

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

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

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

Laboratory data will be analysed both quantitatively as well as qualitatively. The latter will be done via comparison of laboratory data to their reference ranges. Values outside the reference range as well as values defined as clinically relevant will be highlighted in the listings.

Vital signs, physical examinations, or other safety-relevant data observed at screening, baseline, during the course of the trial and at the end-of-trial evaluation will be assessed with regard to possible changes compared to findings before start of treatment.

7.3.5 Pharmacokinetic analyses

Concentrations will be used for graphs and calculations in the format that is reported in the bioanalytical report. Only concentrations within the validated concentration range will be used for the calculation of PK parameters.

Plasma concentrations will be plotted graphically versus time for all subjects as listed in the

drug plasma concentration-time tables. For the presentation of the mean profiles the arithmetic mean and the planned blood sampling times will be used.

The following descriptive statistics will be calculated for plasma concentrations as well as for all PK parameters: N, arithmetic mean, standard deviation, minimum, median, maximum, arithmetic coefficient of variation, geometric mean, and geometric coefficient of variation. The descriptive statistics of PK parameters will be calculated using the individual values with the number of decimal places as provided by the evaluation program. Then the individual values as well as the descriptive statistics will be reported with three significant digits in the CTR.

Time to attainment of steady-state will be explored by repeated-measurement ANOVA model through pairwise comparing trough concentrations and concentrations at 20 min after drug administration on days 1, 7, 14, 18-21. The model will be on logarithm scale including “subject” as a fixed effect and “time” as a repeated effect.

7.4 INTERIM ANALYSES

No interim analyse is planned.

7.5 HANDLING OF MISSING DATA

7.5.1 Plasma concentration - time profiles

Concentration data identified with NOS (no sample), NOR (no valid result), NOA (not analysed), BLQ (below the limit of quantification) will be ignored and not replaced by zero at any time point (applies also to the lag phase including the pre-dose value). Descriptive statistics of concentrations at specific time points will be calculated only when at least 2/3 of the individuals have concentrations within the validated concentration range. The overall sample size to decide whether the “2/3 rule” is fulfilled will be based on the total number of samples intended to be drawn for that time point (i.e. BLQ, NOR, NOS, NOA are included). Every effort will be made to include all concentration data in an analysis. If not possible a case by case decision is required whether the value should only be excluded from half-life estimation or the complete analysis.

- If a concentration is only excluded from half life determination, it will be used for all other calculations (e.g. descriptive statistics) and for graphical presentation.

- If a concentration value is excluded from all calculations, it will not be presented graphically or used for the calculation of descriptive statistics and parameter determination. However, the excluded concentration itself will be listed in the tables in the CTR associated with an appropriate flag.

7.5.2 Pharmacokinetic parameters

In the non-compartmental analysis concentration data identified with NOS, NOR, and NOA will not be considered. BLQ values in the lag-phase will be set to zero. The lag phase is defined as the period between time zero and the first time point with a concentration above the quantification limit. All other BLQ values of the profile will be ignored.

Descriptive statistics of parameters are calculated only when at least 2/3 of the individual parameter estimates of a certain parameter are available. If the actual sampling time will not be recorded or will be missing for a certain time point, the planned time will generally be used for this time point instead. Pharmacokinetic parameters which cannot be determined will be identified by "not calculated" (NC).

7.5.3 Safety

It is not planned to impute missing values for safety data, except for missing or incomplete AE dates. Missing or incomplete AE dates will be imputed according to BI standards.

7.6 RANDOMISATION

Not applicable

7.7 DETERMINATION OF SAMPLE SIZE

The sample size is not determined based on formal calculation since this is a study for assessing PK and safety. The size of 12 patients is commonly used in multiple dose Phase I trial of this type. Assuming a dropout rate of 25%, 4 more patients will be needed. Thus, at least 16 patients are planned to be entered into the trial. Should the drop-out rate raise over 25%, additional patients will be entered to reach the target of 12 evaluable patients.

8. INFORMED CONSENT, DATA PROTECTION, TRIAL RECORDS

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

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

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

The certificate of insurance cover is made available to the Investigator and the patients, and is stored in the ISF (Investigator Site File)."

8.1 TRIAL APPROVAL, PATIENT INFORMATION, AND INFORMED CONSENT

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

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

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

The Investigator must sign (or place a seal on) and date the informed consent form. If a trial collaborator has given a supplementary explanation, the trial collaborator also signs (or places a seal on) and dates the informed consent.

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

This trial will be conducted in accordance with the ICH-GCP guidelines, local regulations and BI SOPs.

In order to achieve a high level of standardised processes, data collection of PK will be coordinated centrally.

A laboratory at site will be used to collect, analyse and report the results of all blood samples and cultures. The site laboratory need to be certified.

Training will be provided to all investigators, coordinators and CRAs to ensure consistency and accuracy of the data. The data will be source verified by the CRAs.

The data management procedures to ensure the quality of the data are described in detail in the trial data management and analysis plan (TDMAP) available in the TMF.

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

8.3 RECORDS

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

8.3.1 Source documents

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 CRF 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 eCRFs all data must be derived from source documents.

8.3.2 Direct access to source data and documents

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

The trial site must retain the source documents and essential documents for a period defined by the 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 5 µg tiotropium inhalation solution this is the current version of the Investigator's Brochure [[U06-3029](#)]. For the 5 µg olodaterol inhalation solution this is the current version of the Investigator's Brochure [U06-3029]. For the FDC of tiotropium and olodaterol this is the current version of the Investigator's Brochure [U06-3029]. For the non-investigational medicinal product salbutamol the reference document is the US-PI (Proair HFA) and for the non-investigational medicinal product ipratropium bromide, the reference document is the UK-SPC (Atrovent Inhaler CFC-Free). The current versions of these reference documents

are to be provided in the ISF. No AEs are classified as listed for matching placebo (for training purposes only), study design, or invasive procedures.

8.4.2 Expedited reporting to health authorities and IEC / IRB

Expedited reporting of serious adverse events, e.g. suspected unexpected serious adverse reactions (SUSAR) to health authorities and IEC / IRB, will be done according to local regulatory requirements.

8.5 STATEMENT OF CONFIDENTIALITY

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

8.6 END OF TRIAL

The end of the trial is defined as all subjects finished visit 5 or follow the agreement between sponsor and investigator.

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.

9. REFERENCES

9.1 PUBLISHED REFERENCES

- P94-01346 Bone R, et al. In chronic obstructive pulmonary disease, a combination of ipratropium and albuterol is more effective than either agent alone: an 85-day multicenter trial. *Chest* 105 (5), 1411-1419 (1994).
- P01-02794 Pauwels RA, Buist AS, Calverley PMA, Jenkins CR, Hurd SS. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: NHLBI/WHO Global Initiative for Chronic Obstructive Lung Disease (GOLD) workshop summary. *Am J. Respir Crit Care Med* 2001;163 (5):1256-1276
- P04-07409 Celli BR, MacNee W. Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. *Eur Respir J* 23(6), 932-946 (2004).
- P05-08465 Hodder R, Pavia D, Dewberry H, Alexander K, Iacono P, Ponitz H, Beck E. Low incidence of paradoxical bronchoconstriction in asthma and COPD patients during chronic use of Respimat Soft Mist inhaler. *Respir Med* 2005; 99:1087-1095.
- P05-12782 Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al. Standardisation of spirometry. *Eur Respir J* 2005;26(2):319-338.
- P11-05865 Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: updated 2010. Website: goldcopd.com.
- R94-1408 Quanjer PH, Tammeling GJ, Cotes JE, Pedersen OF, Peslin R, Yernault JC. Lung volumes and forced ventilatory flows. Report Working Party Standardization of Lung Function Tests, European Community for Steel and Coal. Official Statement of the European Respiratory Society. *Eur Respir J* 1993; 6(Suppl 16):5-40.

- R04-4303 Foradil Aerolizer (Schering) (formoterol fumarate inhalation powder), Rx only (rev. June 2003). Website: pdrel.thomsonhc.com; In: PDR Electronic Library. Thomson; 2004.
- R04-4304 Rote Liste Win 2003/II, Version 3.2, Editio Cantor, Freigabedatum: 01.07.2003; 2003.
- R04-4305 Rote Liste Win 2003/II, Version 3.2, Editio Cantor, Freigabedatum: 01.07.2003; 2003
- R10-5669 ICH harmonised tripartite guideline: maintenance of the ICH guideline on non-clinical safety studies for the conduct of human clinical trials for pharmaceuticals M3 (R2) (Current step 4 version, 11 June 2009)

9.2 UNPUBLISHED REFERENCES

- U06-3029 [REDACTED] Investigator's Brochure 1237.P1 07-Aug-2012
- U08-2169 [REDACTED] Clinical trial report: Safety, tolerability, pharmacokinetics and pharmacodynamics of multiple rising inhalative doses (2 mcg/5 mcg, 10 mcg/5 mcg, and 40 mcg/10 mcg) of BI 1744 CL in fixed dose combination with Tiotropium Bromide for 14 days in healthy male volunteers (double-blind, randomised, placebo controlled [at each dose level] study 1237.2 18 November 2008
- U08-1543 [REDACTED] A double-blind, randomised, placebo controlled, six-way crossover study including an open-label positive control (moxifloxacin) to assess the influence of via Respimat inhaled BI 1744 CL (single doses of 10 µg, 20 µg, 30 µg and 50 µg) on the QT/QTc interval of the ECG in healthy male and female volunteers. (1222.8) 03 June 2008. Revised 08 December 2010.

10. APPENDICES

10.1 PHARMACOKINETIC METHODS

Concentrations will be used for calculations in the format that is reported in the bioanalytical report. The data format for descriptive statistics of concentrations will be identical with the data format of the respective concentrations. For the calculation of PK parameters, only concentrations within the validated concentration range will be used. The descriptive statistics of PK parameters will be calculated using the individual values with the number of decimal places as provided by the evaluation program. Then the individual values as well as the descriptive statistics will be reported with three significant digits in the CTR. The actual sampling times will be used. For pre-dose samples, the actual sampling time will be set to zero. Noncompartmental PK parameters will be determined using WinNonlin or another validated program.

Analyte plasma concentrations will be plotted graphically versus time for all subjects as listed in the analyte plasma concentration-time tables. For the presentation of the mean profiles, the arithmetic mean and the planned blood sampling times will be used.

Individual $C_{\max(ss)}$ and $t_{\max(ss)}$ values will be directly determined from the plasma concentration time profiles of each subject. If the same $C_{\max(ss)}$ concentration occurs at different time points, $t_{\max(ss)}$ is assigned to the first occurrence of $C_{\max(ss)}$.

AUC: The area under the curve will be calculated using the linear up/log down algorithm. If an analyte concentration is equal to or higher than the preceding concentration, the linear trapezoidal method will be used. If the analyte concentration is smaller than the preceding concentration, the logarithmic method will be used.

Linear trapezoidal rule ($t_2 > t_1$ and $C_{t_2} \geq C_{t_1}$):

The area of the trapezoid between the two data points (t_1, C_{t_1}) and (t_2, C_{t_2}) will be computed by:

$$AUC_{t_1-t_2} = 0.5 \times (t_2 - t_1) \times (C_{t_1} + C_{t_2})$$

Logarithmic trapezoid rule ($t_2 > t_1$ and $C_{t_2} < C_{t_1}$):

The area of the trapezoid between the two data points (t_1, C_{t_1}) and (t_2, C_{t_2}) will be computed by:

$$AUC_{t_1-t_2} = \frac{(t_2 - t_1) \times (C_{t_2} - C_{t_1})}{\ln(C_{t_2}/C_{t_1})}$$

$MRT_{ih,ss}$: $MRT_{ih,ss}$ calculation in the steady state will be performed according to the

following equation:

$$MRT_{ih,ss} = \frac{AUMC_{ss}}{AUC_{r,ss}}$$

$AUMC_{ss}$ is the area under the first moment curve at steady state.

[REDACTED]

$R_{A,Cmax}$ and $R_{A,AUC}$: Accumulation ratios are derived as follows for the respective doses:

$$R_{A,Cmax} = \frac{C_{max,ss}}{C_{max}}$$

$$R_{A,AUC} = \frac{AUC_{t1-t2,ss}}{AUC_{t1-t2}}$$

gMean, gCV: The geometric mean (gMean) and coefficient of variation, gCV (given in %), will be calculated by the formulae:

$$gMean = \exp \left[\frac{1}{n} \sum_{i=1}^n \ln(x_i) \right] = \exp \left[\overline{\ln(x_i)} \right]$$

$$gCV(\%) = 100 \cdot \sqrt{\exp[\text{Var}(\ln(\bar{x}))] - 1}$$

where

$$\text{Var}(\ln(x_i)) = \frac{1}{n-1} \sum_{i=1}^n \left[\ln(x_i) - \overline{\ln(x_i)} \right]^2$$

10.2 THE RESPIMAT INHALER

Instructions for Use

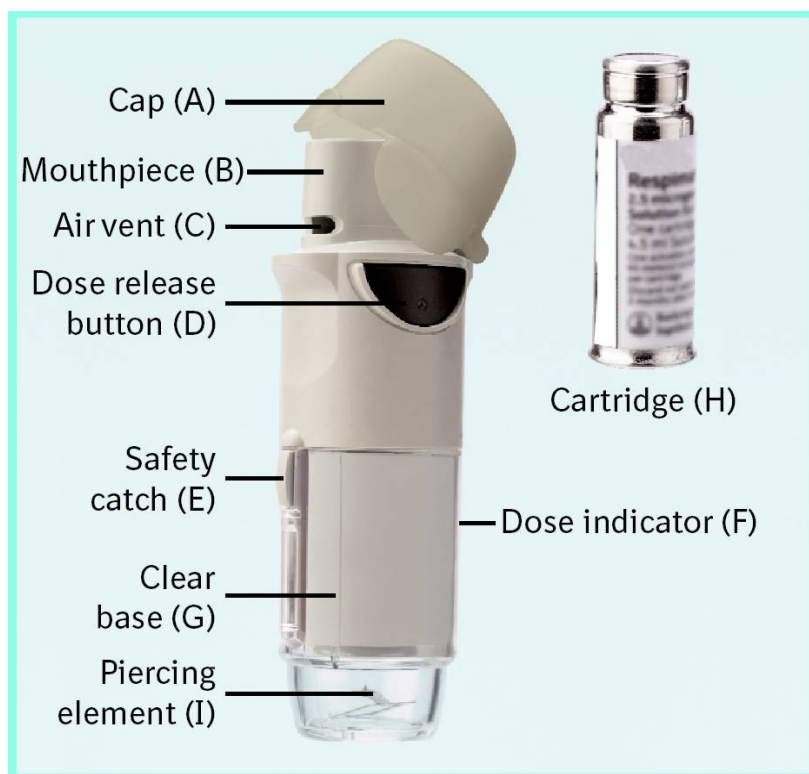
RESPIMAT inhaler

How to use your RESPIMAT[®] inhaler

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

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



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





RESPIMAT[®] inhaler and the RESPIMAT[®] cartridge




Inserting the cartridge and preparation for use

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

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

 <p>2b</p>	
 <p>3</p>	<p>3 Replace the clear base (G).</p> <p>Do not remove the clear base again.</p>


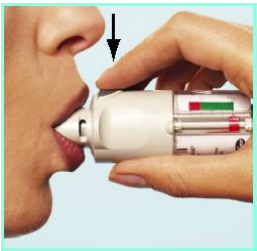
To prepare the RESPIMAT[®] inhaler for first-time use

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


Using the RESPIMAT[®] inhaler

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

Each time you use it take 2 PUFFS.

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

When to get a new RESPIMAT[®] inhaler

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

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

How to care for your inhaler

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

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

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

Further information

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

Do not touch the piercing element inside the base.

Keep out of the reach and sight of children.

Do not freeze.

Boehringer Ingelheim Pharma GmbH & Co. KG

D - 55216 Ingelheim, Germany



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

10.3 RETURN OF INHALERS/CARTRIDGES

Return of Malfunctioning RESPIMAT inhalers

RESPIMAT inhalers, with the used cartridge in situ, that appeared to malfunction, will be returned to Boehringer Ingelheim Int'l Trading (Shanghai) Co., Ltd by responsible CRA as soon as possible.

The following information should be included in malfunction report form when the inhaler is returned:

- a) Medication number
- b) Visit number
- c) Date of malfunction
- d) Description of malfunction and cause of malfunction (if known)
- e) Person identifying malfunction
- f) Trial number

Investigator's name/center number

The original version of the Returned Inhaler Form should be included with the returned inhaler. A copy should be filed in Section 4 of ISF.

All inhalers and cartridges should be wrapped in bubble wrap or a similar packing material, placed in a secure shipping box (not a packing envelope) and shipped. Any questions regarding shipping and handling should be directed to the CML.

10.4 ADDITIONAL INFORMATION REGARDING IN/ EX CRITERIA

FEV₁ and FVC - Pulmonary Function Testing

The qualifying pulmonary function tests (FEV₁ and FVC) will be conducted at the screening visit (Visit 1) for reviewing eligibility of the patient.

Spirometers and their use, including daily calibration, must meet ATS/ERS criteria [[P05-12782](#)]. Spirometry will be conducted with the patient in a seated position and it is preferable that the same trained individual performs the PFTs for a given patient. At each time point, spirometric maneuvers will be conducted in triplicate. The highest FEV₁ and FVC from an acceptable maneuver will be recorded regardless of whether they come from different spirometric maneuvers or from the same maneuver. The 24-hour clock time of the **first** maneuver for each PFT time point will be recorded.

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

At the screening visit (Visit 1), following the completion of 3 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 1 breath to total lung capacity (TLC). The breath is then held for 5-10 s before the subject exhales. Four separate doses (total dose 400 µg) are delivered at approximately 30-s intervals (this dose ensures that the response is high on the salbutamol dose-response curve). Three additional, acceptable post-bronchodilator forced expiratory manoeuvre tests are recorded ≥ 10 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: $FEV_1 \text{ predicted (L)} = 4.30 \times [\text{height (inches)} / 39.37] - 0.029 \times [\text{age (yrs)}] - 2.49$

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

For height measured in meters

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

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

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

Calculation of number of pack years

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

11. DESCRIPTION OF GLOBAL AMENDMENT

Number of global amendment		1
Date of CTP revision		13 Jul 2016
EudraCT number		NA
BI Trial number		1237.30
BI Investigational Products		Tiotropium+olodaterol RESPIMAT solution for inhalation. Olodaterol RESPIMAT solution for inhalation
Title of protocol		An open-label trial to assess pharmacokinetics and safety of tiotropium + olodaterol fixed-dose combination (5 µg/ 5 µg) and olodaterol 5µg delivered by the RESPIMAT inhaler after single and multiple dose treatment in Chinese patients with Chronic Obstructive Pulmonary Disease (COPD)
To be implemented only after approval of the IRB / IEC / Competent Authorities		<input type="checkbox"/>
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		<input type="checkbox"/>
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		<input checked="" type="checkbox"/>
Section to be changed		Synopsis
Description of change		<div style="background-color: black; width: 100%; height: 50px; margin-bottom: 5px;"></div> Was changed to : <div style="background-color: black; width: 100%; height: 50px; margin-top: 5px;"></div>
Rationale for change		Site was changed

Section to be changed		Synopsis and section 3.3.1 Main diagnosis for trial entry
Description of change		‘approximately sex ratio: 1:1’ was changed to ‘at least 1/3 of each gender’
Rationale for change		To meet the lowest criteria of CFDA

Section to be changed		4.1.2 Method of assigning patients to treatment groups
Description of change		‘Note that the medication number is same with the patient number (the latter is assigned at trial entry)’ was changed to ‘Note that the medication number is different from the patient number (the latter is assigned at trial entry)’
Rationale for change		As in patients trial eCRF will collect screening failure patients data, this process can’t guarantee the patient number and medication number are same

Section to be changed		5.4.2 Methods of sample collection The 4th paragraph
Description of change		‘After completion of each blood drawing procedure, the indwelling catheter can be filled with up to 0.5 mL of sterile heparinised saline (50 IU heparin/mL 0.9% saline) in order to prevent clotting.’ was changed to ‘After completion of each blood drawing procedure, the indwelling catheter maybe filled with up to 0.5 mL of sterile heparinised saline (50 IU heparin/mL 0.9% saline) if necessary to prevent clotting.’
Rationale for change		To maintain flexible for action of prevent clotting.

Number of global amendment		2
Date of CTP revision		20 Feb 2017
EudraCT number		NA
BI Trial number		1237.30
BI Investigational Products		Tiotropium+olodaterol RESPIMAT solution for inhalation. Olodaterol RESPIMAT solution for inhalation
Title of protocol		An open-label trial to assess pharmacokinetics and safety of tiotropium + olodaterol fixed-dose combination (5 µg/ 5 µg) and olodaterol 5µg delivered by the RESPIMAT inhaler after single and multiple dose treatment in Chinese patients with Chronic Obstructive Pulmonary Disease (COPD)
To be implemented only after approval of the IRB / IEC / Competent Authorities		<input type="checkbox"/>
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		<input type="checkbox"/>
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		<input checked="" type="checkbox"/>
Section to be changed		Synopsis and section 3.3.1 Main diagnosis for trial entry
Description of change		‘at least 1/3 of each gender’ was deleted
Rationale for change		According to experience of Japanese Phase II trial and PI , It is almost impossible to recruit 1/3 female patient

Section to be changed		Synopsis,section 1-7
Description of change		‘and olodaterol 5µg ’ was deleted
Rationale for change		Olodaterol 5µg treatment group is unnecessary for NDA application.

Section to be changed		Section 6.2.2.1
Description of change		‘15 min prior to the training administration of placebo’ was changed to ‘5min (\pm 5 min) before the trial drug administration’
Rationale for change		To Keep consistent with Flow Chart and section 5.4.2

Section to be changed		Synopsis, section 3.3.1 and 7.7
Description of change		‘32 (at least 24 completed)’ was changed to ‘16 (at least 12 completed)’ ‘trial could be ended in case 12 evaluable patients are available’
Rationale for change		Olodaterol 5 μ g treatment group is unnecessary for NDA application.

Section to be changed		Flow Chart, Section 3.1 and 4
Description of change		‘The first 16 recruited patients will be assigned to the olodaterol treatment and the other patients will be assigned to tiotropium + olodaterol FDC treatment’ was deleted
Rationale for change		Olodaterol 5 μ g treatment group is unnecessary for NDA application.

Section to be changed		Section 7.4
Description of change		‘To support new drug submission for olodaterol in China and to fulfil the timeline requirement by CFDA, the database will be locked after the last patient in olodaterol treatment group completes/withdraws from the trial. Interim analyses will be performed including all the planned analyses on pharmacokinetic and safety endpoints for patients treated by olodaterol. This will be the basis of the primary clinical trial report

		<p>and submission to regulatory agencies. A final database lock will be done once the last patient treated with tiotropium+olodaterol FDC completes the extended follow-up visit. The final clinical trial report will include analysis results of all patients in both treatment groups.'</p> <p>Was changed to</p> <p>'No interim analyses is planned.'</p>
Rationale for change		<p>Olodaterol 5µg treatment group is unnecessary for NDA application.</p>

APPROVAL / SIGNATURE PAGE**Document Number:** c07779972**Technical Version Number:**3.0**Document Name:** clinical-trial-protocol-version-03

Title: An open-label trial to assess pharmacokinetics and safety of tiotropium + olodaterol fixed-dose combination (5 µg/ 5 µg) delivered by the RESPIMAT inhaler after single and multiple dose treatment in Chinese patients with Chronic Obstructive Pulmonary Disease (COPD)

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Approval-Clinical Pharmacokinetics		20 Feb 2017 09:40 CET
Approval-Team Member Medicine		20 Feb 2017 20:41 CET
Approval-Clinical Monitor		21 Feb 2017 03:17 CET
Approval-Team Member Medicine		21 Feb 2017 05:56 CET
Approval-Biostatistics		21 Feb 2017 14:45 CET

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
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