Clinical Trial Protocol

	Document Number:	**c27526629-04**
EudraCT No.	2019-001719-21	
BI Trial No.	1237-0095	
BI Investigational Medicinal Product	Tiotropium + olodaterol (fixed dose combination) Respimat® or matching placebo	
Title	A randomized, double blind, placebo-controlled, multi-center, parallel group study to compare the efficacy of inhaled tiotropium + olodaterol, fixed dose combination (5µg/5µg) vs. placebo delivered by Respimat inhaler in patients with moderate to severe COPD, stratified by peak inspiratory flow rate [TRONARTO].	
Lay Title	A study to test the combination of tiotropium and olodaterol using the Respimat® inhaler in people with chronic obstructive pulmonary disease (COPD) who have different abilities to inhale.	
Clinical Phase	IV	
Clinical Trial Leader	[redacted] Phone: [redacted] Fax: [redacted]	
Coordinating Investigator	[redacted] Phone: [redacted] Fax: [redacted]	
Status	Final Protocol (Revised Protocol based on Global Amendment 2)	
Version and Date	**Version: 3.0**	**Date: 28 January 2020**

CLINICAL TRIAL PROTOCOL SYNOPSIS

Company name	Boehringer Ingelheim
Protocol date	18 September 2019
Revision date	28 January 2020
BI trial number	1237-0095
Title of trial	A randomized, double blind, placebo-controlled, multi-center, parallel group study to compare the efficacy of inhaled tiotropium + olodaterol, fixed dose combination (5µg/5µg) vs. placebo delivered by Respimat inhaler in patients with moderate to severe COPD, stratified by peak inspiratory flow rate [TRONARTO].
Coordinating Investigator	[redacted] Phone: [redacted] Fax: [redacted]
Trial site(s)	Multi-center, multi-national
Clinical phase	IV
Trial rationale	Despite evidence supporting the efficacy of tiotropium + olodaterol Respimat® in a broad COPD population, data demonstrating the effectiveness of tiotropium + olodaterol Respimat® on pulmonary function in individuals stratified by optimal and sub-optimal peak inspiratory flow rate (PIFR) is lacking.
Trial objective	This study is designed to demonstrate the efficacy of inhaled tiotropium + olodaterol 5ug/5ug via Respimat® on lung function in patients with moderate to severe COPD with optimal and sub-optimal PIFR.
Trial endpoints	**Primary endpoint:** Change from baseline in FEV_1 AUC_{0-3h} at week 4. **Key secondary endpoint:** Change from baseline in trough FEV_1 at week 4.
Trial design	Randomized, double blind, multi-center, parallel group, placebo-controlled trial stratified by PIFR optimal (≥60L/min) and sub-optimal (<60L/min) group.
Total number of patients randomized	Approximately 200
Number of patients on each treatment	100
Diagnosis	Patients diagnosed with moderate to severe COPD (GOLD 2 - 3), based on Global Initiative for Chronic Lung Disease guidelines.
Main inclusion and exclusion criteria	**Inclusion Criteria:** 1. Signed and dated written informed consent in accordance with ICH-GCP and local legislation prior to admission to the trial.

	2. Male or female patients, 40 years of age or older. 3. Diagnosis of chronic obstructive pulmonary disease and must meet the following spirometric criteria: patients with a post-bronchodilator FEV_1 ≥30% and <80% of predicted normal; and a post-bronchodilator FEV_1/FVC <70%, at the screening visit. 4. Patients must be current or ex-smokers with a smoking history of more than 10 pack years (Appendix 10.2). 5. Patients should meet the PIFR criteria (optimal or sub-optimal) at the time of randomization depending on which strata is available for inclusion in the study. 6. Women of childbearing potential must be ready and able to use highly effective methods of birth control. 7. Patients must be able to perform, according to investigator's judgment, all trial related procedures. **Exclusion Criteria** 1. Patients with a significant disease other than COPD 2. Patients who have had a COPD exacerbation that required treatment with antibiotics, systemic steroids (oral or intravenous) or hospitalization in the last 6 weeks prior to visit 1. 3. Patients who experienced two or more moderate COPD exacerbations (exacerbation that required treatment with antibiotics and/or oral corticosteroids), or one or more exacerbation leading to hospitalization within a year prior to the screening visit (visit 1). 4. Patients with a history of asthma. 5. Patients taking inhaled corticosteroids (including combinations, e.g. ICS/LABA) in the 6 months prior to screening 6. Patients being treated with oral corticosteroid medication due to reasons other than COPD exacerbation within 6 weeks prior to visit 1. 7. A history of myocardial infarction within 6 months of the screening visit 8. Hospitalization for heart failure within the past year. 9. Pregnant or nursing women.
Test products	Tiotropium + olodaterol Respimat® fixed dose combination or matching placebo delivered via Respimat® inhaler.
dose	5µg tiotropium + 5µg olodaterol daily (2.5 µg /2.5 µg per actuation administered as 2 actuations once daily)
mode of administration	Oral inhalation (2 inhalations in the morning)
Duration of treatment	4 weeks
Statistical methods	The primary endpoint will be analysed using an ANCOVA model in PIFR optimal and sub-optimal groups seperately. The ANCOVA model will include the fixed, categorical effect of the treatment and the fixed continuous effect of baseline. The key secondary endpoint will be analysed using restricted maximum likelihood (REML) based

	mixed effects model repeated measures (MMRM) approach because data are available at an additional visit. The MMRM model will include the fixed, categorical effect of treatment at each visit, and the fixed continuous effect of baseline at each visit. The primary endpoint will be compared across treatment groups in PIFR subgroups (first optimal and then sub-optimal). Then the key secondary endpoint will be compared across treatment groups in the PIFR subgroups in the same order.The entire hierarchical hypothesis testing strategy for tiotropium + olodaterol FDC (5µg/5µg) versus placebo in PIFR subgroups will be protected at an overall two-sided 0.05 type I error rate.

FLOW CHART

Trial Periods	Screening	Treatment			Follow-up
Visit	**1**[1]	**2**	**3**	**4**[2] **(EOT)**	**5 (Phone call)**
Days	-3 to -14	1	15	29	50
Week	-2	0	2	4	7
Time window for visits	NA	NA	±2 days	±2 days	+ 7 days
Informed consent[3]	X				
Demographics/baseline conditions	X				
Medical history	X				
Physical examination & vital signs[4]	X	X		X	
Register patient in IRT[5]	X	X		X	
Medication washout check[6]		X	X	X	
Pulmonary function tests[7]	X	X	X	X	
Plethysmography[8]	X	X			
Laboratory tests (safety)[9]	X	X		X	
eGFR[10]	X				
Pregnancy test[11]	X	X	X	X	
12 lead-ECG[12]	X	X		X	
Review of in-/exclusion criteria	X	X			
Dispense [redacted] & paper patient diary	X				
[redacted] training[14]	X	X	X		
PIFR measurements at clinic[15]	X	X	X	X	
Dispense rescue medication[16]	X	X	X		
Collect rescue medication		X	X	X	
Training in the use of Respimat®[17]		X	X		
Randomization[18]		X			
Administration of trial medication in clinic		X	X	X	
Dispense trial medication[19]		X			
Collect trial medication				X	
AEs/SAEs*****	X	X	X	X	X
Medication compliance check[20]			X	X	
Concomitant therapy	X	X	X	X	X
Trial completion					X[21]

Footnotes:

1. The interval between visits 1 and 2 (screening period) can be extended for up to 2 weeks for administrative reasons (section 6.2.1).
2. All patients discontinued permanently during the treatment period, should complete EOT visit and the procedures associated with EOT visit. Follow-up visit (via telephone) for discontinued patients should be scheduled 3 weeks after the last dose of trial medication.
3. All patients must sign an informed consent consistent with ICH-GCP guidelines prior to participation in the trial, which includes medication washout and restrictions. Medication washout is not required for screening visit in this study. Patients participating in the optional body plethysmography procedure must sign a separate consent.
4. Please refer to sections 5.2.1 and 5.2.2 for guidance on physical examination and vital signs.

5. Patient should be registered in IRT as an enrolled patient on the day of consent. At visit 2, patient will be randomized and stratified via the IRT. Please refer IRT user manual for details on other transactions with IRT.
6. Medication washout criteria should be checked before initiating any visit procedures. If patient does not meet medication washout requirements, visit should be rescheduled.
7. Pulmonary function tests: visit 1 measurements are to determine patient eligibility. Schedule for serial spirometry measurements at visits 2 and 4 are provided in the table below the footnotes. At visit 3, only trough FEV_1 measurements are done. At visit 2, the PFTs should begin between 07: 00 a.m. and 10:00 a.m. At visits 3 and 4, PFTs should begin within ± 30 minutes of the time it started at visit 2. Pulmonary function tests must be completed before plethysmography in patients participating in the optional trial procedure.
8. Plethysmography to be done only at selected sites on selected patients. Sites should have their own body plethysmography equipment. At the screening visit, an assessment will be completed to see if the patient can perform technically acceptable body plethysmography tests.
9. Fasting is not required for safety labs.
10. eGFR will be derived from serum creatinine values, age, sex and race based on the CKD-EPIcr equation [R12-1392].
11. Women of child-bearing potential: serum pregnancy test is to be completed at visit 1. Urine pregnancy test (dipstick) is to be completed at visits 2, 3, and 4 (see section 5.2.3)
12. If the interval between screening and randomization visits is less than one week, and the ECG recording obtained at the screening visit is normal, ECG will not be repeated at the randomization visit.
13. [redacted] must be dispensed at the screening visit along with the paper diary. Patient must be trained on how the PIFR measurements will be performed and recorded in the diary (see section 6.1). At visits 2 and 3, the diary should be reviewed, and additional training provided to the patient if necessary.
14. Patients should be coached on how PIFR measurements are done and recorded in the patient's diary. Patients should be reminded to bring the diary to all future clinic visits.
15. PIFR measurements using med/low and high resistance in the [redacted] will be collected in the clinic at visits 2, 3, and 4. Measurements made at the screening visit are for training purpose only. For more details, see section 6.1.
16. Rescue medication (salbutamol, also known as albuterol) must be dispensed at the screening visit. Patient should bring the inhaler back to the clinic at all future visits. Investigator should ensure that patient has adequate supply of rescue medication until the next clinic visit. Salbutamol will not be dispensed at EOT. Supply of salbutamol will not be managed via IRT.
17. At the randomization visit, patient must receive adequate training on using the Respimat® device (see section 6.2.2). If necessary, patient must be trained again at visit 3. Study sites will have separate inhalers as training device.
18. PIFR measurement with med/low resistance will be used for stratification of optimal and sub-optimal groups. Measurements will be made in triplicate and the highest value will be used for stratification. PIFR measurements made at the screening visit must not be used for stratification.
19. For unscheduled re-supply of study drug, refer to IRT user manual.
20. Please refer to section 4.3 for treatment compliance.
21. Follow-up visit will be completed by telephone. Investigator will have the discretion to bring the patient to do an in-clinic follow-up visit if any safety issues are identified at EOT.

(*****) After the Follow-up visit (=individual patient's end of the trial) the investigator should report only any cancers of new histology and exacerbations of existing cancer and trial treatment related SAEs of which the investigator may become aware of and only via the BI SAE form, please see section 5.2.6.2.1.

Pulmonary Function Tests: Visits 2 and 4*

	-10 min	0	5 min	15 min	30 min	1 hour	2 hours	3 hours
	-	-	-	±5 min	±5 min	±5 min	±10 min	±10 min
Administer trial medication		X						
Vital signs**	X					X		
Pulmonary Functions Tests (FEV_1, FVC)	X		X	X	X	X	X	X

*At visit 3, PFTs done at 10 mins pre-dose (trough) only, including pre-dose vital signs
**Vital signs (when applicable) should be checked before the PFTs.

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ABBREVIATIONS

AE	Adverse Event
ALCOA	Attributable, Legible, Contemporaneous, Original, Accurate
ATS	American Thoracic Society
AUC	Area under the Curve
BI	Boehringer Ingelheim
CKD-EPIcr	Chronic Kidney Disease Epidemiology Collaboration Equation
COPD	Chronic Obstructive Pulmonary Disease
CRA	Clinical Research Associate
CRO	Contract Research Organization
DPI	Dry Powder Inhaler
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
ECSC	European Coal and Steel Community
eDC	Electronic Data Capture
EELV	End-expiratory Lung Volume
eGFR	Estimated Glomerular Filtration Rate
EOT	End of Treatment
ERS	European Respiratory Society
ERV	Expiratory Reserve Volume
EU	European Union
EudraCT	European Clinical Trials Database
FAS	Full Analysis Set
FDA	Food and Drug Administration
FDC	Fixed Dose Combination
FEV_1	Forced Expiratory Volume in one second
FRC	Functional Residual Capacity
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
GOLD	Global Initiative for Chronic Obstructive Lung Disease
IC	Inspiratory Capacity

ICH	International Council on Harmonisation
ICS	Inhaled Corticosteroids
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISF	Investigator Site File
IVC	Inspiratory Vital Capacity
LABA	Long-Acting β2-agonist
LPLT	Last Patient Last Treatment
MDI	Metered Dose Inhalers
MedDRA	Medical Dictionary for Drug Regulatory Activities
MMRM	Mixed Model with Repeated Measurements
NA	Not Applicable
PFT	Pulmonary Function Test
PIFR	Peak Inspiratory Flow Rate
pMDI	Pressurized metered dose inhaler
REML	Restricted Maximum Likelihood
REP	Residual Effect Period
RV	Residual Volume
SAE	Serious Adverse Event
SD	Standard Deviation
SGOT	Serum Glutamic Oxaloacetic Acid
SGPT	Serum Glutamic Pyruvic Transaminase
SGRQ	St. George's Respiratory Questionnaire
SMI	Soft Mist Inhaler
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reactions
TDI	Transition Dyspnea Index
TLC	Total Lung Capacity
TSAP	Trial Statistical Analysis Plan
USPI	United States Prescribing Information
WHO	World Health Organization

WOCBP	Woman of childbearing potential

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

The complementary modes of action of tiotropium + olodaterol have previously been demonstrated in phase II clinical trials and during the Phase IIIa program that led to the registration of tiotropium + olodaterol combination in the European Union (EU), the United States and several other countries (P15-03349).

In the Phase III program the additional benefits of the tiotropium + olodaterol fixed dose combination (FDC) over its mono-components and placebo have been assessed on lung function, quality of life (St. George's Respiratory Questionnaire -SGRQ), dyspnea (Transition Dyspnea Index-TDI), moderate and severe chronic obstructive pulmonary disease (COPD) exacerbations and exercise endurance time (P15-03349).

Inhaled bronchodilators are a mainstay of therapy for COPD, bronchodilator therapy can be delivered via several modalities including dry powder inhalers (DPIs), soft mist inhalers (SMIs), nebulized solutions, and pressurized metered dose inhalers (pMDIs). Drug delivery via inhalation devices is dependent on the inspiratory flow rate generated by the patient. It is now widely recognised that a successful treatment outcome in COPD depends as much on the inhaler device as it does on the drug (P06-04748).

The majority of patients with COPD present with moderate to severe airflow obstruction at time of diagnosis. In COPD patients expiratory airflow limitation is typically accompanied by decreased inspiratory capacity, hyperinflation and respiratory muscles impairment, which combined, result in reduced inspiratory flow rates, which could diminish lower airway deposition of the drug (P06-04750).

Achieving the correct inhalation flow from any inhalation device is critical in order for the patient to achieve therapeutic benefit from the inhaled drug. Patients with COPD may use sub-optimal inhalation flows as they may not have the energy generated by their inspired breath to achieve the effective inhalation flows that are required for some devices (R15-5362). However, inspiratory flow rates or the patient´s ability to perform the required inhalation maneuver are rarely checked in clinical practice before selecting an inhaler/treatment, increasing the risk of patients not receiving the full clinical benefits of the treatment prescribed.

The Respimat® Soft Mist™ Inhaler actively delivers a metered dose of medication, with minimal inspiratory effort from the patient, as a fine slow moving, long lasting mist, with a high fine particle fraction, resulting in a high lung deposition and lower oropharyngeal deposition (P12-01215, P05-10480, P06-10775). In vitro data has demonstrated that Respimat® Soft Mist™ delivers high lung deposition at low modelled flow rates and across disease severities, and requires only a very low inspiratory effort (P17-06338).

Dry powder inhalers have higher internal resistance than that of SMIs and pMDIs; as a result, the inspiratory force necessary to overcome the internal resistance of DPIs, to optimally

release the medication from the inhaler and deliver into the airways, is greater than what is required for pMDIs and SMIs. The [redacted]) has been introduced as a simple, low cost method of measuring an individual's inspiratory flow rate. It is generally accepted that a PIFR of 60 L/Min (optimal PIFR) is required for adequate drug delivery by a DPI with medium internal resistance. In previous studies of small cohorts, approximately 30-50% of patients are unable to generate the targeted PIFR of 60 L/Min as measured by [redacted] with medium or low resistance. There is also evidence demonstrating that, at the time of discharge from an acute care hospital for treatment of a COPD-related hospitalization, one third of patients had a sub-optimal PIFR with medium or low resistance measured by [redacted]. It has been demonstrated that sub-optimal PIFR is a predictor of 90-day readmission for COPD, days to all-cause readmissions and days to COPD readmission. Multivariate analysis has demonstrated that age, gender, height, forced vital capacity (FVC) % predicted and inspiratory capacity (IC) % predicted are independent predictors of sub-optimal PIFR. This evidence highlights the importance of inspiratory flow rate in the effective delivery of inhaled therapies; yet, the evidence for the benefits provided by currently available inhaled treatments for COPD according to the inspiratory flow rates generated by patients, is scarce.

1.2 DRUG PROFILE

Tiotropium + olodaterol combination

Tiotropium + olodaterol FDC is an aqueous solution of tiotropium + olodaterol contained in a cartridge. It is administered by using the Respimat® inhaler. One cartridge is used per inhaler, which is inserted into the device prior to first use.

In the pivotal studies (c01735218-03, c01735249-03), tiotropium + olodaterol FDC showed statistically significant improvements in Forced Expiratory Volume in first second (FEV_1) Area under the curve (AUC_{0-3h}) response and trough FEV_1 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 (SGRQ) and dyspnea experienced during everyday activities [Transition Dyspnea Index (TDI)] after 24 weeks compared to the mono-components. More patients treated with the combination had an improvement in SGRQ total score and TDI focal score which exceeded the Minimal Clinically Important Difference.

Treatment with tiotropium + olodaterol FDC also resulted in reductions in both daytime and night time rescue bronchodilator use compared to the mono-components. The bronchodilatory profile of the combination was confirmed in a supportive 6-week study (c02093555-02), in which the mean FEV_1 improvements over 24 hours were superior to the monocomponents, with improvements in FVC, inspiratory capacity (IC), and functional residual capacity (FRC), supporting the results for FEV_1.

Tiotropium + olodaterol FDC was shown to be safe and well tolerated over 1 year in a moderate to very severe COPD population. The overall incidence of adverse events (AEs), serious adverse events (SAEs), fatal AEs, frequencies for cardiac events and major adverse

cardiovascular event 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.

Based on these observations, marketing authorization for tiotropium + olodaterol (5µg /5µg) FDC (total daily dose) has been granted in US, Canada, Australia, in all European countries within the decentralized procedure as well as in a number of other countries worldwide.

For a more detailed description of the drug profile refer to the current Summary of Product Characteristics (SmPC) for Spiolto® or the United States Prescribing Information (USPI) for Stiolto® which are included in the Investigator Site File (ISF).

Boehringer Ingelheim's Respimat® inhaler will be used for administration of study drug. The medication is provided as an aqueous solution in a cartridge, which is inserted into the device prior to first use. A propellant-free device, 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 the lungs and airways is very high compared with many metered dose aerosols or dry powder devices. The use of the Respimat® inhaler has been shown to be safe with regards to paradoxical bronchoconstriction during chronic use in patients with COPD (P05-08465). The Residual Effect Period (REP) of tiotropium + olodaterol FDC is 21 days.

Salbutamol used as rescue medication in this trial is a short-acting, selective beta$_2$-adrenergic receptor agonist used in the treatment of asthma and COPD. Salbutamol is a bronchodilator that opens up the airways affected by bronchoconstriction, therefore relieving the wheezing and shortness of breath. Salbutamol can be used as a fast-acting rescue medication that provides quick relief..

1.3 RATIONALE FOR PERFORMING THE TRIAL

Despite evidence supporting the efficacy of tiotropium + olodaterol Respimat® (R19-2073) in a broad COPD population, data demonstrating the effectiveness of tiotropium + olodaterol Respimat® on pulmonary function (trough FEV_1, FEV_1 AUC) in individuals stratified by optimal and sub-optimal PIFR is lacking. Spirometry data from the tiotropium + olodaterol clinical development program include mostly lung function and volumes from an expiratory maneuver, which does not allow to measure PIFR; when an inspiratory maneuver has been performed, it is performed against no resistance from the spirometer, which makes it not possible to measure the PIFR simulating the resistance of an inhaler. Furthermore, since the measurement of PIFR is not routinely performed in daily clinical practice, the effectiveness of tiotropium + olodaterol Respimat® according to the patients´ PIFR from real world use has not been assessed.

Data from this study may facilitate the clinician´s decision when choosing a treatment and delivery system, as it could provide certainty that the treatment selected will be effectively delivered independently of the patient ability to generate sufficient energy through the inhalation effort.

1.4 BENEFIT - RISK ASSESSMENT

1.4.1 Benefits

Clinical trials conducted to date have shown tiotropium + olodaterol (5µg/5µg) fixed dose combination to be a safe, well tolerated and efficacious combination therapy according to treatment guidelines in a moderate to very severe COPD population. The OTEMTO studies, demonstrated improvements in lung function with tiotropium + olodaterol over placebo and tiotropium after 12 weeks of treatment in patients with moderate to severe COPD (P15-08379), the population to be included in this study

1.4.2 Risks

Potential risks associated with administration of the combination of tiotropium + olodaterol include the listed (expected) adverse events for tiotropium / olodaterol (5µg/5µg) fixed dose combination as described in the USPI/EU SmPC.

Women of childbearing potential may be included in clinical trials for tiotropium + olodaterol (5µg/5µg) fixed dose combination provided appropriate precautions are taken to minimize the probability of becoming pregnant. 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.

A placebo group is included in the trial to provide an appropriate control for the assessment of the effects of the tiotropium + olodaterol FDC on lung function (FEV_1) according to the inspiratory flow rate (PIFR) the patients can generate. In order to minimize the risk for the study patients, a number of population and design measures have been put in place, namely:

- The duration of the treatment period including placebo is limited to 4 weeks.
- The population for this study excludes patients with very severe COPD and patients currently treated with inhaled corticosteroids (ICS).
- Patients with a recent exacerbation (6 weeks prior to visit 1) or with a history of frequent exacerbations (two or more exacerbation requiring treatment with systemic glucocorticoids, antibiotics or both, or an exacerbation that required hospitalization within one year prior to visit 1) are also excluded.
- The study does not include a long washout period. In order to shorten the time of placebo treatment; patients will continue to receive their prescribed treatment until three days before randomization.
- Patients will receive salbutamol as rescue medication.
- Within the four-week treatment period, a study visit in the clinic has been added after two weeks of treatment as an opportunity for assessment of the patients' condition by the investigators.

Boehringer Ingelheim will provide open-label salbutamol as rescue medication for all patients during the course of the trial.

1.4.3 Discussion

Tiotropium + olodaterol FDC delivered via the Respimat® device was shown to be effective in improving lung function, quality of life and dyspnea as well as improve exercise tolerance. It has also shown to be safe and well tolerated over 1 year in a moderate to very severe COPD population; however, there is currently no clinical data available from randomized controlled trials or from real world studies to demonstrate whether COPD patients can benefit from tiotropium + olodaterol Respimat® independently of the inspiratory flow they can generate.

Data from this study will provide this evidence and therefore help in the personalization of treatment selection for COPD patients. Considering a placebo arm is included in the study, the treatment and follow-up period has been kept short, and includes a clinic visit after two weeks of treatment to assess the patients' condition. Further measures are in place to minimize the risk for the study population are the exclusion of the most severe COPD population, the population treated with inhaled corticosteroids, those patients with a very recent COPD exacerbation, or with a history of frequent COPD exacerbations and at risk of COPD exacerbations.

2. TRIAL OBJECTIVES AND ENDPOINTS

2.1 MAIN OBJECTIVES, PRIMARY AND SECONDARY ENDPOINTS

2.1.1 Main objectives

This study is designed to demonstrate the efficacy of inhaled tiotropium + olodaterol 5µg/5µg via Respimat® on lung function in patients with moderate to severe COPD with optimal (≥60 L/min) and a sub-optimal (<60 L/min) PIFR. Disease severity (moderate to severe) is based on the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines (GOLD 2 – 3).

2.1.2 Primary endpoints

Change from baseline in FEV_1 $AUC_{0\text{-}3h}$ after 4 weeks of treatment.

Analyses will be performed in PIFR optimal (≥60 L/min) group and PIFR sub-optimal (<60 L/min) group separately.

2.1.3 Key secondary endpoints

Change from baseline in trough FEV_1 after 4 weeks of treatment

Analyses will be performed in PIFR optimal (≥60 L/min) group and PIFR sub-optimal (<60 L/min) group separately.

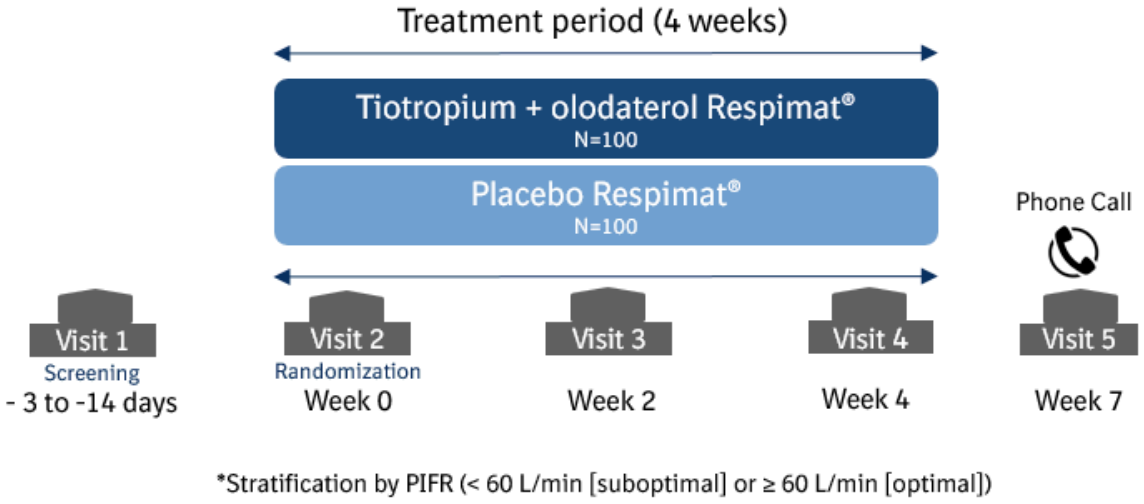
[redacted]

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN

This trial is a randomized, double-blind, placebo-controlled, multicenter, parallel study designed to assess efficacy of tiotropium + olodaterol delivered by Respimat® on FEV_1 $AUC_{0\text{-}3h}$, and trough FEV_1 in patients with moderate to severe COPD, stratified by optimal and sub-optimal PIFR. The study will consist of a screening period of up to 2 weeks, a 4-week randomized treatment period and a three week follow-up period. An overview of the trial design is presented in Figure 3.1: 1.

Figure 3.1: 1 Trial Design



*Stratification by PIFR (< 60 L/min [suboptimal] or ≥ 60 L/min [optimal])

Approximately 200 patients will be randomized (1:1) to either the active arm (tiotropium + olodaterol, FDC) or the placebo arm. The randomization will be stratified by optimal (≥60 L/min) or sub-optimal (< 60 L/min) PIFR as measured with the [redacted] set at med/low resistance. Each strata will be capped to a total of approximately 100 patients. An interactive response technology (IRT) will be used for randomization and stratification.

After signing informed consent and completing the screening visit, patients will enter a screening period of 3 to 14 days. During the screening period, patients will continue to receive their COPD maintenance treatment, except for the medication washout requirements required before the randomization visit (see Table 4.2.3.1: 1). Patients will be randomized into the 4-week treatment period in which they will be randomly assigned to one of two treatments: tiotropium + olodaterol FDC or matching placebo. The randomization visit (visit 2) will be followed by a clinic visit in 2 weeks (visit 3) and end of treatment (EOT) visit (visit 4) will be 4 weeks (28 days) after randomization. A follow-up visit by telephone will be scheduled three weeks after the last dose of study medication. Study procedures to be performed at each clinic visit are presented in the Flow Chart. The timing of the pulmonary function tests with serial spirometry at baseline (visit 2) and at EOT (visit 4) is provided in the table below the Flow Chart.

Patients will be washed out of COPD medications for approximately 72 hours before randomization. Patients will be allowed to use salbutamol as rescue medication during this

washout period. Once randomized, patients will receive either tiotropium + olodaterol FDC via Respimat® inhaler or matching placebo. All patients will receive salbutamol for use as rescue medication, as needed, from screening visit until EOT. At the conclusion of EOT visit, patients can resume taking their regular COPD medications. At the EOT visit, investigator should advise the patients on appropriate care during the follow-up period and after completion of the study. During the follow-up period, patients will not receive study medication. Rescue medication will not be dispensed at EOT visit for use during the follow-up period. Patients on ICS maintenance therapy (monotherapy or combination with bronchodilators) will not be eligible to participate in this study.

Body plethysmography measurements will be an optional trial procedure at visit 2 and will be done only at selected sites on selected patients. Approximately 30 (15%) patients are expected to participate in this procedure. Patients participating in this optional trial procedure will have to sign a separate informed consent. At the screening visit, an assessment will be completed to see if the patient can perform technically acceptable body plethymography measurements.

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

Currently, data on the impact of PIFR on the effectiveness of treatments/inhalers available for COPD is not consistent or not available, and available data on existing treatments/inhalers cannot be extrapolated to the population of interest. A comparison with placebo was considered the best approach to assess the effect of tiotropium + olodaterol FDC in this population.

There is no previous data or knowledge of the treatment effect of tiotropium + olodaterol on spirometric parameters in the two PIFR populations (< 60 L/min and ≥ 60 L/min). Therefore the trial will need to enroll a sufficient number of placebo patients in order to make an assessment of efficacy between treatment and placebo. A 4-week treatment period is considered sufficient to evaluate the effects of tiotropium + olodaterol FDC in patients with COPD (P19-01878).

It is anticipated that with 200 patients randomized 1:1 in the trial and, a duration of 4 weeks, there is adequate statistical power to detect an effect of the treatment vs placebo in each of the PIFR sub populations.

3.3 SELECTION OF TRIAL POPULATION

Recruitment of patients for this trial is competitive, i.e. screening for the trial will stop at all sites once a sufficient number of patients have been screened to randomize 200 patients. Approximately 40 study sites are expected to participate in this study. Approximately 300 patients are expected to be screened. Patients in screening at the time when a decision is made to stop further screening will be allowed to continue and may be randomized in the study if eligible.

A log of all patients enrolled into the trial (i.e. who have signed informed consent) will be maintained in the Investigator Site File (ISF) irrespective of whether they have been treated with investigational drug.

If a patient is enrolled in error (does not meet all inclusion criteria or meets one or more exclusion criteria on the day of enrollment), the sponsor should be contacted immediately. A decision on whether this patient will receive additional study medication and continue in the trial will be made in consultation with the sponsor. The investigator must obtain documented approval from the sponsor to allow the wrongly enrolled patient to continue in the trial.

3.3.1 Main diagnosis for trial entry

Patients diagnosed with moderate to severe COPD (Stage 2 or 3) based on GOLD guidelines (P19-00675).

Refer to section 8.3.1 (Source Documents) for the documentation requirements pertaining to the inclusion and exclusion criteria.

3.3.2 Inclusion criteria

1. Signed and dated written informed consent in accordance with ICH-GCP and local legislation prior to admission to the trial.
2. Male or female patients, 40 years of age or older.
3. All patients must have a diagnosis of COPD and must meet the following spirometric criteria: patients with a post-bronchodilator FEV_1 ≥30% and <80% of predicted normal (ECSC, (R94-1408); and a post-bronchodilator FEV_1/FVC <70%, at the screening visit.
4. Patients must be current or ex-smokers with a smoking history of more than 10 pack years (Appendix 10.2).
5. Patients should meet the PIFR criteria (optimal or sub-optimal) at the time of randomization depending on which strata is available for inclusion in the study.
6. Women of childbearing potential (WOCBP) 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.
7. Patients are expected to be able to perform, according to investigator's judgment, all trial related procedures including:
    a. Technically acceptable pulmonary function tests (spirometry)
    b. Use of [redacted] device to measure PIFR
    c. Inhale medication in a competent manner (in the opinion of the investigator) from the Respimat® device
    d. Perform technically acceptable body plethysmography measurements. This is applicable only to patients who will consent to the optional trial procedure at the selected sites.

3.3.3 Exclusion criteria

1. Patients with a significant disease other than COPD; a significant disease defined as a disease which, in the opinion of the investigator, and referring to the warnings to be observed as quoted in the locally applicable SmPC or prescribing information, could (i) put the patient at risk because of participation in the trial, (ii) influence the results of the trial, or (iii) cause concern regarding the patient's ability to participate in the trial.
2. Patients who have had a COPD exacerbation that required treatment with antibiotics, systemic steroids (oral or intravenous) or hospitalization in the 6 weeks prior to screening visit or during the screening period.
3. Patients who experienced two or more moderate COPD exacerbations (exacerbation that required treatment with antibiotics and/or oral corticosteroids), or one or more exacerbation leading to hospitalization within a year prior to visit 1.
4. 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.
5. Patients taking inhaled corticosteroids (including combinations, e.g. ICS/LABA) in the 6 months prior to screening visit.
6. Patients being treated with oral corticosteroid medication due to reasons other than COPD exacerbation within 6 weeks prior to the screening visit.
7. Patients who have completed a pulmonary rehabilitation program in the 6 weeks prior to screening visit or patients who are currently in a pulmonary rehabilitation program.
8. A history of myocardial infarction within 6 months of the screening visit.
9. Unstable or life-threatening cardiac arrhythmia.
10. Hospitalization for heart failure within 12 months of the screening visit.
11. Known active tuberculosis.
12. A malignancy for which patient has undergone resection, radiation therapy or chemotherapy within last five years (patients with treated basal cell carcinoma are allowed).
13. A history of cystic fibrosis.
14. Clinically evident bronchiectasis.
15. Patients who have taken an investigational drug within one month or 6 half-lives (whichever is greater) prior to screening visit.
16. Pregnant or nursing women.
17. Women of childbearing potential not using a method of birth control classified at least as "acceptable". Female patients will be considered to be of childbearing potential unless surgically sterilized by hysterectomy, bilateral salpingectomy, bilateral oophorectomy, or post-menopausal (defined as no menses for 12 months without an alternative medical cause). Tubal ligation is not a method of permanent sterilization.
18. Patients who have previously been randomized in this study or currently enrolled in another investigational device or drug study. Patients participating in an observational trial will not be excluded.
19. Patients who are unable to comply with medication restrictions prior to randomization, or who are expected to require treatment with a restricted medication during the trial (section 4.2.3.1).

20. Patients with clinically relevant abnormal baseline haematology, blood chemistry.
21. Patients with creatinine >2x upper limit of normal or an estimated glomerular filtration rate (eGFR) determined below 50 ml/min/1.73 m^2 (as derived from CKD-EPIcr equation [R12-1392]).
22. Patients with a hypersensitivity or contraindication to tiotropium and/or olodaterol.
23. Patients with upper respiratory obstruction (i.e. vocal cord dysfunction).
24. A history of significant alcohol or drug abuse based on investigator judgment.

3.3.4 Withdrawal of patients from treatment or assessments

Patients may discontinue trial treatment or withdraw consent for trial participation as a whole ("withdrawal of consent"). Please see sections 3.3.4.1 and 3.3.4.2 below.

Every effort should be made to keep the patients in the trial, if possible on treatment. Measures to control the withdrawal rate include careful patient selection, appropriate explanation of the trial requirements and procedures prior to trial enrollment, as well as the explanation of the procedures if the patient withdraws from the trial. The decision to discontinue trial treatment or withdraw consent to trial participation, and the reason must be documented in the patient files and electronic case report forms (eCRF). If applicable, consider the requirements for adverse event collection and reporting (sections 5.2.6.2.1 and 5.2.6.2).

3.3.4.1 Discontinuation of trial treatment

An individual patient will discontinue trial treatment if:

- The patient wants to discontinue trial treatment, without the need to justify the decision.
- The patient has repeatedly shown to be non-compliant with important trial procedures and, in the opinion of both, the investigator and sponsor representative, is not willing or able to adhere to the trial requirements in the future.
- If a patient experiences a COPD exacerbation (moderate, or severe) during the treatment period, patient will be discontinued from the study (section 6.2.2).
- The patient needs to take concomitant medication that interferes with the investigational medicinal product or other trial treatment (section 4.2.3.1)
- The patient can no longer receive trial treatment for medical reasons (such as surgery, adverse events, other diseases, or pregnancy). In case of a temporary reason, trial treatment should be restarted if medically justified.

In terms of discontinuation of trial treatment, the following criteria must also be taken into account:

- Trial treatment must be stopped immediately if a paradoxical bronchospasm or an allergic reaction of the immediate type occurs.
- If two or more eye symptoms (triggering or aggravation of narrow angle glaucoma, eye pain or discomfort, temporary blurred vision, eye halos or altered color perception associated with reddened eyes due to conjunctival congestion or corneal edema) occur, trial treatment should be discontinued and the patient should consult a specialist immediately.

For safety reasons, the investigator may decide that the patient should discontinue trial treatment.

If new efficacy/safety information becomes available, Boehringer Ingelheim will review the benefit-risk-assessment and, if needed, pause or discontinue the trial treatment for all patients or take any other appropriate action to guarantee the safety of the trial patients.
Even if the trial treatment is discontinued, the patients remain in the trial and, given their agreement, will undergo the procedures for early treatment discontinuation and follow-up as outlined in the Flow Chart and section 6.2.3.

3.3.4.2 Withdrawal of consent to trial participation

Patients may withdraw their consent to trial participation at any time without the need to justify the decision.

If a patient wants to withdraw consent, the investigator should be involved in the discussion with the patient and explain the difference between trial treatment discontinuation and withdrawal of consent to trial participation, as well as explain the options for continued follow-up after trial treatment discontinuation, (section 3.3.4.1).

3.3.4.3 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 enrollment 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. Deviations from Good Clinical Practice (GCP), the trial protocol, or the contract impairing the appropriate conduct of the trial.

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

4. TREATMENTS

4.1 INVESTIGATIONAL TREATMENTS

After screening, eligible patients will be randomly assigned to one of two treatment arms: tiotropium + olodaterol FDC or matching placebo, both delivered by a Respimat® inhaler. Patient will inhale two puffs from the Respimat® inhaler, once daily, in the morning during the 4-week treatment period.

4.1.1 Identity of Investigational Medicinal Products

Table 4.1.1: 1 Test product 1

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

Table 4.1.1: 2 Test product 2

Substance:	Matching placebo
Pharmaceutical formulation:	Inhalation solution
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Unit strength:	NA
Posology	2 inhalations once daily (a.m. dosing)
Route of administration:	Oral inhalation via Respimat® inhaler

4.1.2 Selection of doses in the trial

Tiotropium + olodaterol Respimat® 5µg/5µg once daily is an approved dose regimen for the treatment of COPD in many countries. The clinical trials conducted during the Phase III program for tiotropium + olodaterol FDC 5µg/5µg have shown that this dose is a safe, well tolerated and efficacious combination therapy.

4.1.3 Method of assigning patients to treatment groups

After the assessment of all inclusion and exclusion criteria, each eligible patient will be stratified based on PIFR (optimal vs. sub-optimal) and randomized to one of the two treatment arms: tiotropium + olodaterol FDC or matching placebo in a 1:1 ratio at visit 2 via IRT using each strata. The PIFR will be measured with the [redacted] set at med/low resistance. PIFR measurements with med/low resistance will be done in triplicate the highest PIFR will be used for stratification. Note that the medication number is different from the patient number (the latter is generated during screening via the IRT System).

4.1.4 Drug assignment and administration of doses for each patient

Dispensing trial medication
At visit 2 the IRT will assign two Respimat® kits (one for treatment and one as reserve). At visit 3 the patient will bring in all treatment kits (including the reserve kits) that were dispensed at visit 2. If the reserve kit dispensed at visit 2 was used by the patient, a new reserve kit can be dispensed at visit 3. Each treatment kit will have a unique medication ID number. Trial medication will be dispensed to the patient by the investigator or a qualified site staff at these visits. The amount of trial medication dispensed will be recorded on the drug accountability forms. Patients must return all Respimat® kits at visit 4 which is the end of treatment period

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

At home, if the patient forgets to take the morning dose of trial medication, the patient can take the morning dose up until 12:00 midnight. After 12:00 midnight, the patient should skip the dose for that day and take the next dose the following morning.

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. 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.

Once assembled, the shelf-life of the Respimat® Inhaler with trial medication is 3 months. Therefore, it is important to always enter the date of the cartridge insertion on the medication label of the Respimat® Inhaler immediately after the cartridge is inserted.

Dispensing rescue medication
Salbutamol will be dispensed to all patients when they complete the screening visit, and are eligible to enter the screening period. Patients will receive adequate supply of rescue medication until the end of treatment period. Rescue medication will not be provided for the follow-up period. Before using for the first time, one actuation should be released into the air to ensure the device is working.

4.1.5 Blinding and procedures for unblinding

4.1.5.1 Blinding

Patients, investigators, and everyone involved in trial conduct or analysis or with any other interest in this double-blind trial will remain blinded with regard to the randomized treatment assignments until after database lock. The access to the randomization code will be kept restricted until its release for analysis.

4.1.5.2 Unblinding and breaking the code

Emergency unblinding will be available to the investigator via IRT. It must only be used in an emergency situation when the identity of the trial drug must be known to the investigator in order to provide appropriate medical treatment or otherwise ensure safety of trial participants. The reason for unblinding must be documented in the source documents and/or appropriate eCRF page.

In case the automated unblinding option via the IRT system is malfunctioning, the IRT service provider can be contacted (24 hours a day coverage) and the treatment allocation can be obtained. IRT support has direct access to the database and the treatment information can be manually obtained. Details about this process will be included in the ISF.

Due to the requirements to report Suspected Unexpected Serious Adverse Reactions (SUSARs), it may be necessary for a representative from Boehringer Ingelheim (BI) Pharmacovigilance group to access the randomization code for individual patients during trial conduct. The access to the code will only be given to authorized pharmacovigilance representatives for processing in the pharmacovigilance database system and not be shared further.

4.1.6 Packaging, labelling, and re-supply

The investigational medicinal products will be provided by BI. They will be packaged and labelled in accordance with the principles of Good Manufacturing Practice. Re-supply to the sites will be managed via an IRT system, which will also monitor expiry dates of supplies available at the sites. For details of packaging and the description of the label, refer to the ISF.

4.1.7 Storage conditions

Drug supplies will be kept in their original packaging and in a secure limited access storage area according to the recommended storage conditions on the medication label. A temperature log must be maintained for documentation. If the storage conditions are found to be outside the specified range, the Clinical Research Associate (CRA), as provided in the list of contacts in the ISF, must be contacted immediately.

Further details are provided in the “storage conditions for trial medications” document and on the country-specific labels, a sample of which will be part of the ISF.

Rescue medication (salbutamol) should be stored according to instructions in the local prescribing information.

4.1.8 Drug accountability

The investigator or designee will receive the investigational drugs delivered by the sponsor when the following requirements are fulfilled:

- Approval of the clinical trial protocol by the Institutional Review Board (IRB) / Ethics Committee,
- Availability of a signed and dated clinical trial contract between the sponsor and 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,
- Availability of Food and Drug Administration (FDA) Form 1572 (if applicable).

Investigational drugs are not allowed to be used outside the context of this protocol. They must not be forwarded to other investigators or clinics. Patients should be instructed to return unused investigational drug.

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

These records will include dates, quantities, batch / serial numbers, expiry ('use- by') dates, and the unique code numbers assigned to the investigational medicinal product and trial patients. The investigator or designee will maintain records that document adequately that the patients were provided the doses specified by the Clinical Trial Protocol, and reconcile all investigational medicinal products received from the sponsor. At the time of return to the sponsor or appointed Contract Research Organization (CRO), the investigator or designee 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 OTHER TREATMENTS, EMERGENCY PROCEDURES, RESTRICTIONS

4.2.1 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 (also known as albuterol) will be provided as rescue medication by the sponsor. Only the salbutamol provided by the sponsor should be used during the screening and treatment periods. Patient should return all rescue medication (used and unused) to the study site at visit 4.

If the patient requires rescue medication during the pulmonary function testing, the pulmonary function tests (PFTs) will be discontinued. The medication used, route of administration, and 24-hour clock time will be recorded on the Rescue Medication eCRF page. Patient can continue in the trial.

4.2.2 Emergency procedures

There are no emergency procedures to be followed. Medications to control acute COPD exacerbations are allowed as medically necessary during the patient's participation in the study.

4.2.3 Restrictions

4.2.3.1 Restrictions regarding concomitant treatment

Table 4.2.3.1: 1 Overview of permitted and restricted medication

Drug Class	**Sub-class**	**Prior to study**	**Study Period**		
			Screening Period	**Treatment Period**	**Follow-up Period**
Corticosteroids	Inhaled corticosteroids	Permitted[1]	**NOT** permitted	**NOT** permitted	Permitted
	Oral corticosteroids	Permitted[2]	**NOT** permitted	**NOT** permitted	Permitted
	Injected Corticosteroids – local administration (for treatment of e.g. bursitis)	Permitted	Permitted	Permitted	Permitted
β-adrenergics	Inhaled short-acting β-adrenergics	Permitted	Rescue[3]	Rescue[3]	Permitted
	Inhaled long-acting β-adrenergics (e.g. formoterol / salmeterol)	Permitted	Permitted[4]	**NOT** permitted	Permitted
Anti-cholinergics	Short-acting anticholinergics (inhalation aerosol, nasal spray)	Permitted	Permitted[3]	**NOT** permitted	Permitted
	Long-acting anticholinergics (i.e. tiotropium, aclidinium, glycopryonnium, umeclidinium, tiotropium + olodaterol)	Permitted	Permitted[4]	**NOT** permitted	Permitted
Combinations	ICS/LABA	Permitted[1]	**NOT** permitted	**NOT** permitted	Permitted
	ICS/SABA	Permitted[1]	**NOT** permitted	**NOT** permitted	Permitted

Table 4.2.3.1: 1 Overview of permitted and restricted medications (cont.)

Drug Class	Sub-class	Prior to study	Study Period		
			Screening Period	Treatment Period	Follow-up Period
Combinations	short-acting anticholinergic/ SABA	Permitted	Permitted[3]	**NOT** permitted	Permitted
	Long-acting anticholinergics/long-acting β-adrenergics (e.g. glycopyrronium+indacaterol, umeclidinium+vilanterol)	Permitted	Permitted[4]	**NOT** permitted	Permitted
	ICS, long-acting anticholinergics, long-acting β-adrenergics, (e.g. fluticasone+umeclidinium, vilanterol)	Permitted[1]	**NOT** permitted	**NOT** permitted	**NOT** permitted
Miscellaneous	Other investigational drugs (1 month or 6 half-lives (whichever is greater) prior to V1)	Permitted	**NOT** permitted	**NOT** permitted	**NOT** permitted
	Cromolyn sodium / nedocromil sodium (if prescribed for non-asthma condition)	Permitted	Permitted	Permitted	Permitted
	Antihistamines, antileukotrienes (if prescribed for non-asthma condition)	Permitted	Permitted	Permitted	Permitted
	Methylxanthines (if prescribed for non-asthma condition)	Permitted	Permitted	Permitted	Permitted
	Mucolytics (not containing bronchodilators; stabilized 6 wks. prior to V1)	Permitted	Permitted	Permitted	Permitted
	Phosphodiesterase type 4 (PDE-4) inhibitor (e.g. roflumilast)	Permitted[5]	**NOT** permitted	**NOT** permitted	**NOT** permitted
	Biologics or other immunomodulators (until 3 months or 6 half-lives, whichever is greater prior to visit1)	Permitted	**NOT** permitted	**NOT** permitted	**NOT** permitted

Footnotes for Table 4.2.3.1: 1

1. Permitted until 6 months prior to visit 1
2. Permitted until 6 weeks prior to visit 1

3. Refer to washout criteria before PFTs at visits 2, 3, and 4. Note: inhaled short-acting β–adrenergics, short-acting anticholinergics and combinations of these medications are permitted up to 8 hours prior to visit 2.
4. Permitted until 72 hours prior to visit 2
5. Permitted until 3 months prior to visit 1

Medication restrictions for pulmonary function testing (Visits 2, 3, and 4)

- Trial medication should not be taken at home on the morning of visits 3 and 4.
- At least an 8-hour washout of rescue medication prior to visits 2, 3 and 4. In this trial salbutamol is supplied as rescue medication by the sponsor or a designated vendor.
- Medication washout restrictions for randomization visit (visit 2) can be found in Table 4.2.3.1: 1.

4.2.3.2 Restrictions on diet and life style

Restrictions prior to PFT visits:

- Medication washout restrictions should be adhered to before the PFTs.
- The patient should remain in the building where the pulmonary function testing is performed and should return to the laboratory at least ten minutes prior to the start of each test.
- On pulmonary function test days during the treatment period, patients should refrain from strenuous activity for at least 12 hours prior to pulmonary function testing and throughout the testing period. Patients should also avoid cold temperatures, environmental smoke, dust or areas with strong odors (e.g. perfumes).
- Coffee, tea, chocolate, cola and other caffeine-containing beverages and foods, and ice-cold beverages are not allowed for at least 2 hours prior to and during the pulmonary function testing at clinic visits. 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.

4.2.3.3 Contraception requirements

WOCBP (for the definition refer to section 3.3.3) who is a trial participant will be required to use an acceptable method of birth control throughout the trial, and for a period of at least 21 days after last trial drug intake.

WOCBP who is a trial participant must use a highly effective method of birth control per ICH M3 (R2) that results in a low failure rate of less than 1% per year when used consistently and correctly if their sexual partner is a man able to father a child.

- Combined (estrogen and progestogen containing) hormonal birth control that prevents ovulation (oral, intravaginal, transdermal)
- Progestogen-only hormonal birth control that prevents ovulation (oral, injectable, implantable)
- Intrauterine device (IUD) or intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion

Or

Patients must abstain from male-female sex. This is defined as being in line with the preferred and usual lifestyle of the patient. Periodic abstinence e.g. calendar, ovulation, symptothermal, post-ovulation methods, declaration of abstinence for the duration of exposure to study drug; and withdrawal are not acceptable.

4.3 TREATMENT COMPLIANCE

Patients are requested to bring all remaining trial medication including empty package material with them when attending visits 3 and 4. Trial medication adherence should be reviewed by the investigator and reported in the eCRF.

Estimating compliance to trial medication

Knowing the time interval between clinic visits, it is possible to calculate the number of puffs that should have been administered by the patient. The Respimat® Inhaler contains 60 actuations (30 daily doses). The dose indicator shows approximately how much medication is left. The dose indicator scale is divided into 4 quarters. One quarter used accounts for 7 days of treatment (14 actuations). When the pointer enters the red area of the scale, there is approximately medication for 7 days (14 actuations left). Once the dose indicator has reached the end of the red scale (i.e. all 30 daily doses have been used) the Respimat® inhaler is empty. Patient compliance should be estimated using the dose indicator.

The acceptable medication compliance should have an overall value in the range 80% to 120%. If the compliance is outside this range, patient needs to be re-trained.

Randomized patients should not be discontinued for lack of medication compliance without prior discussion with the sponsor.

5. ASSESSMENTS

5.1 ASSESSMENT OF EFFICACY

This study is designed to demonstrate the efficacy of inhaled tiotropium + olodaterol 5µg/5µg via Respimat® on lung function in patients with moderate to severe COPD with optimal (≥60 L/min) and a sub-optimal (<60 L/min) PIFR.

5.1.1 Pulmonary function testing

[redacted] spirometers will be provided to sites for the on-site spirometry measurements. The spirometers and their use, including daily calibration on test days, must meet American Thoracic Society (ATS) and European Respiratory Society (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. The best of three efforts will be defined as the highest FEV_1 and the highest FVC, each obtained on any of three blows meeting the ATS criteria (with a maximum of five attempts). The highest FEV_1 and FVC will be selected 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.

The clock time of the start and end of inhalation procedure of trial medication will be captured by the [redacted] spirometer.

At the screening visit, pulmonary function tests will be performed to determine patient eligibility (inclusion criteria 3, section 3.3.2). At visit 2, the PFTs should begin between 07: 00 a.m. and 10:00 a.m. At visits 3 and 4, PFTs should begin within ± 30 minutes of the time it started at visit 2. At visits 2 and 4, PFTs will be measured up to 3 hours with serial spirometry (specified time points are provided in the Flow Chart). At visit 3, only trough FEV_1 measurements are performed.

5.1.2 Peak inspiratory flow rate measurements

The [redacted] a hand held device to measure PIFR will be provided to each patient. At the randomization visit the optimal and sub-optimal groups will be determined based on the PIFR measurements completed at the clinic at visit 2. PIFR values obtained from med/low resistance level will be used for stratifying the patients via IRT. Additional PIFR measurements will also be done in the clinic during visits 2, 3, and 4. Measurements will be made in triplicate using med/low and high resistance and the highest value for each resistance setting will be recorded. In addition, patients will use the [redacted] at home to collect the PIFR data and record the measurements in the patient diary. Additional guidance on PIFR measurements in the clinic and at home are presented in section 6.1.

5.2 ASSESSMENT OF SAFETY

There are no safety endpoints in this trial. Safety and tolerability will be assessed in a descriptive way based on:

- Adverse events
- Serious adverse events
- Physical examination

5.2.1 Physical examination

A physical examination according to the local practice will be performed at the time points specified in the Flow Chart. It includes at a minimum general appearance, neck, lungs, cardiovascular system, abdomen, extremities, and skin. Measurement of height and body weight will be performed. The results must be included in the source documents available at the site.

5.2.2 Vital signs

Vital signs will be evaluated at the time points specified in the flowchart, prior to blood sampling. This includes systolic and diastolic blood pressure and pulse rate (electronically or by palpation count for 1 minute) in a seated position after 5 minutes of rest. The results must be included in the source documents available at the site.

5.2.3 Safety laboratory parameters

Safety lab assessments will be performed by a central laboratory service provider. For the sampling time points, see the Flow Chart. All analyses will be performed by a central laboratory, and the reference ranges will be provided in the ISF. Patients do not have to be fasted for the blood sampling for the safety laboratory.

Hematology panel should include the following
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 should include the following
Alkaline phosphatase, Lactate Dehydrogenase (LDH), gamma-GT, SGOT, SGPT, glucose, calcium, inorganic phosphorus, uric acid, urea nitrogen, creatinine, total protein, potassium, sodium, chloride, total bilirubin, creatinine phosphokinase.

Urinalysis assessment to include
Specific gravity, pH, glucose, protein and occult blood.

A serum human chorionic gonadotrophin (HCG) pregnancy test will be performed on all females of child-bearing potential at the screening visit. A urine dip stick pregnancy test will be performed at the site for all clinic visits. If the urine test is positive, a serum pregnancy test will be performed at the central lab. If serum pregnancy test is positive, patient will be discontinued from the study.

Instructions regarding sample collection, sample handling/ processing and sample shipping are provided in the Laboratory Manual.

The lab reports from central laboratory will be made available to the investigator. It is the responsibility of the investigator to evaluate the laboratory reports. Clinically relevant abnormal findings as judged by the investigator will be reported as adverse events (section 5.2.6).

The central laboratory will transfer the results of the analysis to the sponsor.

5.2.4 Electrocardiogram

The 12-lead electrocardiogram (ECG) must be administered by a qualified technologist and results will be recorded as scheduled in the Flow Chart. The investigator or a designee will evaluate whether the ECG is normal or abnormal and assess clinical relevance. ECGs may be repeated for quality reasons. Additional ECGs may be recorded for safety reasons. Dated and signed printouts of ECG with findings should be documented in patient's medical record.

Clinically relevant abnormal findings will be reported either as baseline condition (if identified at the screening visit) or otherwise as AEs and will be followed up and/or treated as medically appropriate.

5.2.5 Other safety parameters

Not applicable for this trial.

5.2.6 Assessment of adverse events

5.2.6.1 Definitions of AEs

5.2.6.1.1 Adverse event

An 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 unfavorable 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.

The following should also be recorded as an AE in the eCRF and BI 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 exist prior to trial inclusion, they will be considered as baseline conditions and should be collected in the eCRF.

5.2.6.1.2 Serious adverse event

A SAE is defined as any AE, which fulfils at least one of the following criteria:

- results in death,
- is life-threatening, which refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if more severe,
- requires inpatient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability or incapacity,
- is a congenital anomaly / birth defect,
- is deemed serious for any other reason if it is an important medical event when based on appropriate medical judgement which may jeopardize the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse.

5.2.6.1.3 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 defined above.

The latest list of "Always Serious AEs" can be found in the electronic data capture (eDC) system. A copy of the latest list of "Always Serious AEs" will be provided upon request. These events should always be reported as SAEs as described in section 5.2.6.2.

Cancers of new histology and exacerbations of existing cancer must be classified as a serious event regardless of the time since discontinuation of the drug and must be reported as described in 5.2.6.2, subsections "AE Collection" and "**AE reporting to sponsor and timelines".**

5.2.6.1.4 Adverse events of special interest

No adverse events of special interest have been defined for this trial.

5.2.6.1.5 Intensity (severity) of AEs

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

Mild:	Awareness of sign(s) or symptom(s) that is/are easily tolerated.
Moderate:	Sufficient discomfort to cause interference with usual activity.
Severe:	Incapacitating or causing inability to work or to perform usual activities.

5.2.6.1.6 Causal relationship of AEs

Medical judgement should be used to determine whether there is a reasonable possibility of a causal relationship between the adverse event and the given study treatment, 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.

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

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

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

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

5.2.6.2 Adverse event collection and reporting

5.2.6.2.1 AE Collection

The investigator shall maintain and keep detailed records of all AEs in the patient files.
The following must be collected and documented on the appropriate eCRF(s) by the investigator:

- From signing the informed consent onwards until the individual patient's end of trial (completion of follow-up period):
  all AEs (serious and non-serious).

- After the individual patient's end of trial: the investigator does not need to actively monitor the patient for new AEs but should only report any occurrence of cancer and trial treatment related SAEs of which the investigator may become aware of by any means of communication, e.g. phone call. Those AEs should be reported on the BI SAE form (section 5.2.6.2.2), but not on the eCRF.

5.2.6.2.2 AE reporting to the sponsor and timelines referring

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

With receipt of any further information to these events, a follow-up SAE form has to be provided. For follow-up information the same rules and timeline apply as for initial information. All (S)AEs, including those persisting after individual patient's end of trial must be followed up until they have resolved, have been assessed as "chronic" or "stable", or no further information can be obtained.

5.2.6.2.3 Pregnancy

In rare cases, pregnancy might occur in a clinical trial. Once a patient has been enrolled in the clinical trial and has taken trial medication, the investigator must report any drug exposure during pregnancy in a trial participant immediately (within 24 hours) by means of Part A of the Pregnancy Monitoring Form for Studies to the sponsor.

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 Studies (Part B). The ISF will contain the Pregnancy Monitoring Form for Studies (Part A and 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 Studies and not the SAE form is to be completed. If there is an SAE associated with the pregnancy an SAE form must be completed in addition.

5.2.6.2.4 COPD Exacerbation

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

A complex of lower respiratory events is defined as at least two of the following:

- Shortness of breath
- Sputum production (volume)
- Change in sputum color

- Cough
- Wheezing
- Chest tightness

"Onset of exacerbation" will be defined by the onset of first recorded symptom. The "end of Exacerbation" will be decided by the investigator based on clinical judgment.

Exacerbations will be classified as follows:

Moderate: patient receiving an exacerbation-related prescription of oral corticosteroids and/ or antibiotic not requiring hospitalization.
Severe: COPD-related hospitalization

If a patient experiences a moderate, or severe COPD exacerbation, the patient will be discontinued from the study (section 6.2.2).

5.3 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

Not applicable for this trial.

5.4 ASSESSMENT OF BIOMARKERS

Not applicable for this trial.

5.5 BIOBANKING

Not applicable in this trial.

5.6 OTHER ASSESSMENTS

Body Plethysmography

Patients participating in this optional trial procedure will have to sign a separate informed consent. Relative lung volumes can be measured by spirometry. The absolute volumes of air in the lung can be measured by body plethysmography, where the residual volume, functional residual capacity, and total lung capacity can be determined.

The site's own equipment will be used for the body plethysmography measurements. The volume-constant body plethysmography devices and their use, including daily calibration, must meet ATS/ERS criteria [R08-1121; R98-1487]. Body plethysmography will be conducted with the patient in a seated position and it is preferable that the same trained individual performs the measurements for a given patient. The body plethysmography measurements for assessment of FRC, total lung capacity (TLC), Residual Volume (RV) and IC should be performed as linked maneuver (i.e. without the patient coming off the mouthpiece prior to the completion of the maneuver; refer to Appendix 10.1) and to the body plethysmography manual in the ISF.

FRC is the sum of Expiratory Reserve Volume (ERV) and RV. This sum corresponds to the volume of gas present in the lung and airways at the average end-expiratory level. At least three technically acceptable FRC values should be obtained which agree within 5% (i.e. the difference between the highest and the lowest value divided by the mean is smaller or equal to 0.05). If this repeatability is not accomplished, i.e. the observed deviation is larger, additional values should be obtained until the repeatability criterion is achieved or a maximum of six efforts have been performed. If repeatability is not accomplished after the maximum of six efforts, no more efforts should be performed and mean FRC data will be regarded as acceptable, as long as they fulfill technical satisfactory quality criteria. All acceptable efforts must be used for calculation of mean values of FRC (and ERV), and exclusion of tests for the sake of achieving repeatability is not permitted. The mean FRC value should be reported. Linked to technically acceptable ERV and Inspiratory Vital Capacity (IVC) maneuver, mean FRC value is used for calculating the RV and TLC.

Please refer to Appendix 10.1 and to the body plethysmography manual in the ISF for further details in calculation of Residual Volume (RV), TLC and Inspiratory Capacity (IC).

The 24-hour clock time of the first maneuver for each body plethysmography measurement time-point will be recorded. Clock of [redacted] used is relevant for all visit activities and clock of body plethysmography system should be synchronized.

5.7 APPROPRIATENESS OF MEASUREMENTS

Spirometry

Pulmonary function tests are a validated and well established measurement tool for lung function testing. Pulmonary function tests will be conducted at clinic visits using standardized spirometry equipment. FEV_1 is a standard measurement for the assessment of lung function.

Peak inspiratory flow rate measurements

The [redacted] is a hand held device to measure PIFR. It is commonly used in patients diagnosed with lung diseases like COPD and asthma. Clinicians use this device to train the patients on the correct inspiratory technique to be used when inhaling the medications from the device the patient will use to take the prescribed medication. [redacted] is calibrated by the manufacturer to ensure accuracy. Each patient will be provided an [redacted] and a sufficient quantity of disposable mouthpieces for daily use.

Body Plethysmography

Pathology of COPD is not only characterized by progression in airflow limitation but also by progressive destruction of supporting tissues and elastin fibers of the lung. This results in progressive air trapping distally with increased RV, FRC and TLC and a decrease in IC. Hence, evaluation of static lung volumes (such as FRC, TLC, RV and IC) using body

plethysmography is a valuable tool for assessment of hyperinflation. This contributes to COPD symptoms like breathlessness and physical limitations while IC has the highest correlation with dyspnea (R11-4386; P03-10426).

Body plethysmography is technically more challenging than spirometry and requires a high level of experience in performance. Prerequisite for study site participation in the body plethysmography procedures will be the availability of a volume-constant (i.e. pressure variable) body plethysmography device as measurements will be performed using their own equipment.

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

The trial consists of a screening period, a 4-week treatment period, followed by a 3-week follow-up period. The follow-up visit will be by telephone. If visit 3 has to be rescheduled, visit 4 should follow the original visit date schedule.

Patients should make every attempt to complete the study. Investigators should encourage patient treatment compliance and adherence to other protocol specific procedures. Please refer to the Flow Chart for the trial procedures at each visit, and the time windows for the visits. All deviations from the planned visit schedule will be documented.

If a patients does not meet medication washout criteria at visits 2, 3, or 4, the visit should be rescheduled. The rescheduled visit should occur as soon as possible. If visit 3 is rescheduled, the EOT visit (visit 4) should be scheduled on the originally planned date (28 days after the randomization visit). If a patient missed visit 3, and rescheduling was not possible, visit 4 should be completed on the originally planned date.

At selected sites who have their own body plethysmography equipment, patients can participate in the body plethysmography procedures. Patients should indicate their willingness to participate in this optional trial procedure by signing a separate informed consent.

- All blood draws should be done after the ECG is completed.
- PIFR measurements should be completed before the PFTs performed with the [redacted]
- Plethysmography measurements, in patients who signed a separate consent for the optional trial procedure should be completed after completing the PFTs with the [redacted]

If a patient experiences a COPD exacerbation (moderate or severe) during the screening period, patient will be screen failed. If a patient experiences a COPD exacerbation (moderate or severe) during the treatment period, patient will be discontinued from the study. The definition of a COPD exacerbation (for the purpose of this trial) can be found in Section 5.2.6.2.4.

Using the [redacted]

All patients will be coached to use the [redacted] and will receive instructions on how the PIFR measurements should be done at home, and how the PIFR values are entered in the paper diary. Below are the basic steps involved in the use of the [redacted]

- Align the scale with the desired resistance level (med/low or high)
- Attach a clean mouthpiece
- Patient should exhale slowly and deeply
- Seal lips around the mouthpiece, and instruct the patient to inhale hard and fast

- Record the inspiratory flow from the position of the red cursor against the scale.
- Reset, and repeat two more times.

Resetting the [redacted]

- Hold the device vertically with the mouthpiece uppermost, so that the rounded end of the meter can be tapped against the other hand or a horizontal surface, such as a table.

- A gentle tap will dislodge the magnetic resetting weight, which will return the red cursor to a start position. When this has happened, the meter must turn through 180 degrees to return the magnetic weight to its resting position.

In-clinic measurement of PIFR using the [redacted]

- Select the proper setting in the [redacted]
- Perform PIFR in a seated position
- Use maximum inspiratory effort, by first breathing out fully, and breathing in as hard and fast as possible. Repeat the maneuver two more times, and record the highest value in the eCRF.
- The highest PIFR value obtained with med/low setting is used for stratification in the IRT at the randomization visit (visit 2).
- Repeat the procedure again to do the measurements in triplicate with high resistance, and record the highest value in eCRF.
- PIFR measurements should be completed before PFTs are done in the [redacted]
- If the patient experiences any discomfort during the measurements, short breaks should be allowed.
- PIFR measurements done at the screening visit are for training purpose only and are not recorded in the eCRF.

Home measurement of PIFR: Using the [redacted]

Patients will record their PIFR using the [redacted] once a day in the evening. Patients should be coached on the proper use of the [redacted] 16 during the screening visit, before dispensing the device. Patients should also be coached at future visits if the study site staff deems necessary. The following steps should be followed when PIFR measurements are collected at home.

- Select the “med/low” setting in the [redacted]
- Perform PIFR in a seated position.
- Use maximum inspiratory effort, by first breathing out fully, and breathing in as hard and fast as possible. Repeat the maneuver two more times. Record all three PIFR measurements in the patient diary.
- If the patient experiences any discomfort during the measurements, short breaks are allowed.
- Patient will bring the diary to the clinic for visits 2, 3, and 4.
- The highest PIFR values obtained with the “med/low” setting on each day of the treatment period will be entered in the eCRF.

- PIFR measurements done between the screening visit (visit 1) and randomization visit (visit 2) are for training purpose only and are not entered in the eCRF.

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

6.2.1 Screening period

To keep the number of screen failures as low as possible, patients should be very carefully selected for this trial. Therefore, investigators should make a preliminary check of major inclusion and exclusion criteria when considering patients for enrollment in the trial.

Patient numbers will be assigned in the IRT system and transferred to EDC, thereby creating the subject in EDC. Details of any patient who is screened for the trial but is found to be ineligible must be entered in the enrollment log and documented in the eCRF.

No trial procedures should be performed until the patient has consented to take part in the trial. Each patient will be assigned a unique patient number and enrollment will be recorded.

Baseline conditions, medical history, and eligibility criteria will be assessed at visit 1. Concomitant therapy and AE (if any) will be recorded. At the conclusion of visit 1, patients should receive instructions on procedures to be followed during the screening period.

If the patient is expected to meet all the eligibility criteria, randomization visit (visit 2) will be scheduled. Rescue medication (salbutamol) will be dispensed with instructions for use. Patients will receive the [redacted] to measure the PIFR at home during the screening period. Patient will also receive a paper diary with instructions on how to record the PIFR obtained from the [redacted] Patients will complete the PIFR measurements each evening. The PIFR measurements will be done in triplicate at the med/low resistance level. Patients should be reminded that they can take breaks in between measurements, if needed. Adequate training should be provided to the patients before they leave after the completion of the screening visit. Patient will be asked to bring the device to each clinic visit.

PIFR measurements obtained at the screening visit must not be used for stratification at the randomization visit. PIFR value is not an eligibility criteria. However, there is cap of approximately 100 patients in each strata (section 3.1). Once the cap in a particular strata is reached, additional patients cannot be randomized in this strata. Once a cap in a particular strata is reached, PIFR values at the screening visit will be used to determine eligibility for the study. If the PIFR value obtained at the screening visit will make the patient eligible for the strata that is closed, patient will be screen failed at the screening visit.

Screening period may be extended by two weeks for administrative reasons after consultation with the Clinical Trial Manager. Total screening period should not exceed 4 weeks (informed consent to randomization) unless written approval is obtained from the Clinical Trial Leader. If screening period exceeds 4 weeks, the Investigator should review the laboratory reports from the screening visit (visit 1), and make a determination if any labs

specified in the protocol must be repeated before the randomization visit. If deemed necessary, test samples should be drawn and sent to the central laboratory.

Discontinuation during the screening period

If patients discontinue from the study during the screening period, no additional clinic visits are required, and they will be marked as screen failures.

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 randomized, and should be screen failed.

Rescreening and retesting

Patients may be rescreened once with approval from the sponsor. This includes patients who met all the inclusion criteria but were screen failed due to acute medical conditions that have since been resolved or those who were screen failed for administrative reasons (e.g., extended travel, life events).

If the investigator believes that an ineligible lab test result is the result of an error or extenuating circumstance, then that lab test can be retested once without the patient having to be rescreened.

6.2.2 Treatment period

Patients who meet all the protocol criteria will be randomized at visit 2. After randomization, patients will start the 4-week treatment period. All visits during the treatment period should preferably be on the same day of the week. Procedures to be completed at each visit can be found in the Flow Chart.

At the randomization visit (visit 2), patients will be adequately trained to use the Respimat® inhaler. Patients will inhale the study medication in the mornings. Medication should be taken approximately on the same time of the day during the 28-day treatment period. Site should ensure patient has adequate supply of study medication at visit 3. Patients should be instructed not to take their dose of study medication at home on the day of visits 3 and 4.

Investigator should ensure that patient has adequate supply of rescue medication for the treatment period. The intake of rescue medication (number of puffs) will not be collected.

PIFR measurements will be done at home (evenings) by the patient during the treatment period. Measurements will be completed and readings will be recorded in the paper diary as described in Section 6.2.1.

At the beginning of each visit, the investigator and site personnel should ensure the well-being of the patient, and complete the following:

- Any adverse events and changes in concomitant therapies will be recorded.

- Medication washout compliance and lifestyle restrictions will be verified.
- Before dosing with trial medication site personnel should ensure that the patient knows how to inhale properly from the Respimat® Inhaler.
- At the close of each visit during treatment period, the investigator and site personnel should ensure that the patient is provided with all instructions for the next visit.
- Patient will be instructed at each visit to bring all rescue medication to the site.
- Patient will be instructed to bring the study medication (both inhalers including the reserve) at visits 3 and 4.

Unscheduled clinic visits may be arranged if necessary and the procedures completed during the unscheduled visit will depend on the circumstances under which the visit was scheduled, and will be at the discretion of the investigator.

After completion of the treatment phase (visit 4), all patients will enter the 3-week follow-up period.

Discontinuation during the treatment period

If patients discontinue from the study during the treatment period for any reason, study drug should be stopped, and the patient will complete the EOT visit (visit 4), and the follow-up visit by telephone should be scheduled 3 weeks after the last dose of study drug. The investigator may schedule the follow-up visit as a clinic visit if deemed necessary.

6.2.3 Follow-up period and trial completion

The three-week follow-up period ends with a visit by telephone. Procedures to be completed at the follow-up visit can be found in the Flow Chart. Patients will not do the PIFR measurements at home during the follow-up period. Adverse events and concomitant therapies will be reviewed and recorded. At the end of this follow-up visit, patient should be advised to continue with their regular COPD medication.

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 STATISTICAL DESIGN - MODEL

Design

This is a randomized, double-blind, placebo-controlled , multicenter, parallel group, study designed to assess efficacy of tiotropium + olodaterol delivered by Respimat® on FEV_1 AUC_{0-3h} and trough FEV_1 in patients with moderate to severe COPD and in the subgroups of patients with peak inspiratory flow rate less than and greater than or equal to 60 L/min.

Objective

The primary objective of the trial is to describe the efficacy of inhaled tiotropium + olodaterol via Respimat® on lung function in patients with moderate to severe COPD and in the subgroups of patients with optimal and a sub-optimal PIFR.

7.2 NULL AND ALTERNATIVE HYPOTHESES

The following hypotheses will be tested in the study on the primary and key secondary endpoints. Each hypotheses will be tested in hierarchical order at 5% level of significance (two-sided) to protect the overall type I error at 5% (two-sided). The baseline value will be the measurement made prior to the first dosing at Visit 2.

- $H_{0\text{-}1}$: Mean FEV_1 AUC_{0-3h} change from baseline (tiotropium + olodaterol via Respimat®) = Mean FEV_1 AUC_{0-3h} change from baseline (Placebo) in the optimal PIFR group at 4 weeks

  vs.

  $H_{1\text{-}1}$: Mean FEV_1 AUC_{0-3h} change from baseline (tiotropium + olodaterol via Respimat®) ≠ Mean FEV_1 AUC_{0-3h} change from baseline (Placebo) in the optimal PIFR group at 4 weeks.
- $H_{0\text{-}2}$: Mean FEV_1 AUC_{0-3h} change from baseline (tiotropium + olodaterol via Respimat®) = Mean FEV_1 AUC_{0-3h} change from baseline (Placebo) in the sub-optimal PIFR group at 4 weeks

  vs.

  $H_{1\text{-}2}$: Mean FEV_1 AUC_{0-3h} change from baseline (tiotropium + olodaterol via Respimat®) ≠ Mean FEV_1 AUC_{0-3h} change from baseline (Placebo) in the sub-optimal PIFR group at 4 weeks.
- $H_{0\text{-}3}$: Mean trough FEV_1 change from baseline (tiotropium + olodaterol via Respimat®) = Mean trough FEV_1 change from baseline (Placebo) in the optimal PIFR group at 4 weeks

vs.
$H_{1\text{-}3}$: Mean trough FEV_1 change from baseline (tiotropium + olodaterol via Respimat®) ≠ Mean trough FEV1 change from baseline (Placebo) in the optimal PIFR group at 4 weeks.

- $H_{0\text{-}4}$: Mean trough FEV_1 change from baseline (tiotropium + olodaterol via Respimat®) = Mean trough FEV_1 change from baseline (Placebo) in the sub-optimal PIFR group at 4 weeks

  vs.

  $H_{1\text{-}4}$: Mean trough FEV_1 change from baseline (tiotropium + olodaterol via Respimat®) ≠ Mean trough FEV_1 change from baseline (Placebo) in the sub-optimal PIFR group at 4 weeks.

Each of the tests will only be considered confirmatory if all previous tests are successful, i.e. the hypotheses tests were significant at 2-sided 5% level and the treatment effect favored tiotropium + olodaterol over placebo in each PIFR subgroup.

7.3 PLANNED ANALYSES

The efficacy analysis will be performed in all randomized patients who were documented to have received any dose of trial medication and who have both baseline and any evaluable post-baseline measurement for at least one of the efficacy endpoints. This set will be called Full Analysis Set (FAS). The FAS definition will be fully specified or updated in the trial statistical analysis plan (TSAP).

For efficacy and safety analyses, patients will be analysed according to their planned treatment group.

7.3.1 Primary endpoint analyses

The primary endpoint will be analysed using an ANCOVA model including the fixed, categorical effect of treatment and the fixed continuous effect of baseline.

Significance tests will be based on adjusted means using a two-sided $\alpha = 0.05$ (two-sided 95% confidence intervals).

The primary analysis will be performed on the FAS within the optimal and sub-optimal PIFR groups, respectively. Patients will be analysed according to the PIFR stratum to which they belong (regardless of any misassignment to treatment based on identification of the wrong stratum), as such an error occurs before randomization and is therefore consistent with regulatory guidance.

To assess the homogeneity of the treatment effect on the primary endpoint across the levels of PIFR subgroups, the same ANCOVA model as in the primary analysis will be fitted in the overall population but replacing the treatment term by a treatment-by-PIFR subgroup term. A

descriptive p-value of treatment effect homogeneity at week 4 will be calculated. No overall treatment effect will be estimated from this model as it is not interpretable.

Similarly, the same ANCOVA model as in the primary analysis will be fitted in the overall population but replacing the treatment term by a treatment-by-continuous baseline PIFR term. A descriptive p-value of treatment effect homogeneity at week 4 will be calculated. No overall treatment effect will be estimated from this model as it is not interpretable.

The results of the analysis of the primary endpoints for tiotropium + olodaterol FDC within the optimal and sub-optimal PIFR groups will be presented in a forest plot and the treatment by PIFR subgroup interaction p-value will be provided. Sensitivity analysis will be performed by including additional covariates such as severity, gender and age in the model to adjust for potential differences in prognostic factors between sub-optimal and optimal PIFR subgroups.

7.3.2 Secondary endpoint analyses

The key secondary endpoint will be analysed using the restricted maximum likelihood (REML) based approach using a mixed model with repeated measurements (MMRM). The analysis will be performed on the FAS within the optimal and sub optimal PIFR groups, respectively.

The analysis will include the fixed, categorical effect of treatment at each visit and the fixed continuous effect of baseline at each visit. Visits will be treated as repeated measures with an unstructured covariance structure used to model the within-patient measurements.

The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors. Significance tests will be based on least-squares means using a two-sided $\alpha = 0.05$ (two-sided 95% confidence intervals).

A selected set of analyses as that of the primary endpoint will be performed on the key secondary endpoint as well.

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 REP, a period of 21 days after the last dose of trial medication, will be assigned to the treatment period for evaluation. All randomized patients who have taken at least one dose of study drug (i.e., the

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

Statistical analysis and reporting of adverse events will concentrate on treatment-emergent adverse events. To this end, all adverse events occurring between start of treatment and end of the residual effect period will be considered 'treatment-emergent'. The residual effect period is defined as 21 days. Adverse events that start before first drug intake and deteriorate under treatment will also be considered as 'treatment-emergent'.

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

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.

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 summarized. Treatment groups will be compared descriptively with regard to distribution parameters as well as with regard to frequency and percentage of patients with abnormal values or clinically relevant abnormal values.

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 Interim Analyses

An interim analysis is not planned in this clinical trial.

7.4 HANDLING OF MISSING DATA

Missing completely at random is assumed for the primary endpoint as very little missing data is expected and no imputation will be performed.The REML-based MMRM model described in section 7.3.2 will handle missing data due to early drop outs or missing data in between visits which are assumed to be missing at random. Additional details on the imputation of missing data will be specified in the TSAP prior to unblinding.

7.5 RANDOMIZATION

Approximately 200 patients will be randomized in blocks to double-blind treatment stratified by PIFR optimal and sub-optimal subgroups Approximately equal numbers of patients will be randomized to each treatment group (50 in tiotropium + olodaterol Respimat® and 50 in placebo Respimat® for each PIFR subgroup). BI will arrange for the randomization and the packaging and labelling of trial medication. The randomization list will be generated using a validated system, which involves a pseudo-random number generator so that the resulting treatment will be both reproducible and non-predictable. The block size will be documented in the Clinical Trial Report. Access to the codes will be controlled and documented.

7.6 DETERMINATION OF SAMPLE SIZE

From previous studies, an appropriate estimate of the standard deviation (SD) for change from baseline in FEV_1 $AUC_{0\text{-}3h}$ (Δ FEV_1 $AUC_{0\text{-}3h}$) and trough FEV_1 ($\Delta TFEV_1$) is 210 mL (c02098902-03, c02037872-05). Based on an assumed treatment difference of 260 ml in Δ FEV_1 $AUC_{0\text{-}3h}$ and 140 ml in $\Delta TFEV_1$ between tiotropium + olodaterol Respimat® and placebo Respimat®, two-sided alpha of 0.05 and SD of 210 ml, a total of 98 patients will provide 99% power within the optimal and sub-optimal PIFR subpopulations for FEV_1. $AUC_{0\text{-}3h}$ and 90% power for trough FEV_1.The results of power calculations are shown in Tables 7.6: 1 and 7.6: 2. From previous studies (c02098902-03, c02037872-05), the discontinuation rate is assumed to be low within the first 2-4 weeks.

Therefore, a sample size of 200 patients overall with 1:1 randomization ratio and 100 within each subpopulation (100 in optimal PIFR and 100 in sub-optimal PIFR) will provide adequate power to detect a treatment difference of 260 ml for FEV_1 $AUC_{0\text{-}3h}$ and to detect a treatment difference of 140 ml for trough FEV_1.

Table 7.6: 1 Sample size to achieve 90% power assuming two-sided alpha=0.05 and standard deviation of 210 ml

Power	Difference in $\Delta TFEV_1$	SD	N Total
90%	120 ml	210 ml	132
90%	130 ml	210 ml	112
90%	140 ml	210 ml	98
90%	150 ml	210 ml	86
90%	160 ml	210 ml	76
Power	Difference in $\Delta FEV1$ $AUC_{0\text{-}3h}$	SD	N Total
90%	260 ml	210 ml	30
90%	280 ml	210 ml	26
90%	300 ml	210 ml	24

Table 7.6: 2 Power for given sample size of 98 patients assuming a two-sided alpha=0.05 and standard deviation of 210 ml

Difference in $\Delta TFEV_1$	SD	N Total	Power
120 ml	210 ml	98	80%
130 ml	210 ml	98	86%
140 ml	210 ml	98	90%
Difference in $\Delta FEV1\ AUC_{0-3h}$	SD	N Total	Power
260 ml	210 ml	98	>99%
280 ml	210 ml	98	>99%
300 ml	210 ml	98	>99%

Calculations were performed using SAS PROC POWER in SAS v9.4.

8. INFORMED CONSENT, TRIAL RECORDS, DATA PROTECTION, PUBLICATION POLICY, AND ADMINISTRATIVE STRUCTURE

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 Guideline for GCP, relevant BI Standard Operating Procedures (SOPs), the EU directive 2001/20/EC / EU regulation 536/2014. Investigators and site staff must adhere to these principles. Deviation from the protocol, the principles of ICH GCP or applicable regulations as will be treated as protocol deviation.

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

The investigator will inform the sponsor immediately of any urgent safety measures taken to protect the trial patients against any immediate hazard, as well as of any serious breaches of the protocol or of ICH GCP.

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

8.1 TRIAL APPROVAL, PATIENT INFORMATION, INFORMED CONSENT

This trial will be initiated only after all required legal documentation has been reviewed and approved by the respective IRB / Independent Ethics Committee (IEC) and competent authority 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 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. The patient must be given sufficient time to consider participation in the trial. The investigator or delegate 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 or [redacted] delegate must sign (or place a seal on) and date the informed consent form.

Re-consenting may become necessary when new relevant information becomes available and should be conducted according to the sponsor's instructions. The consent and re-consenting process should be properly documented in the source documentation.

8.2 DATA QUALITY ASSURANCE

A risk-based approach is used for trial quality management. It is initiated by the assessment of critical data and processes for trial subject protection and reliability of the results as well as identification and assessment of associated risks. An Integrated Quality and Risk Management Plan documents the rationale and strategies for risk management during trial conduct including monitoring approaches, vendor management and other processes focusing on areas of greatest risk.

Continuous risk review and assessment may lead to adjustments in trial conduct, trial design or monitoring approaches.

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

Electronic CRFs for individual patients will be provided by the sponsor. See section 4.1.5.2 for rules about emergency code breaks. For drug accountability, refer to section 4.1.8.

8.3.1 Source documents

In accordance with regulatory requirements, the investigator should prepare and maintain adequate and accurate source documents and trial records that include all observations and other data pertinent to the investigation on each trial patient. Source data as well as reported data should follow the "Attributable, Legible, Contemporaneous, Original, Accurate (ALCOA) principles" and be **a**ttributable, **l**egible, **c**ontemporaneous, **o**riginal and **a**ccurate. Changes to the data should be traceable (audit trail). Data reported on the eCRF must be consistent with the source data or the discrepancies must be explained.

The current medical history of the patient may not be sufficient to confirm eligibility for the trial and the investigator may need to request previous medical histories and evidence of any diagnostic tests. In this case, the investigator must make every attempt to retrieve previous medical records.

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

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

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

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

8.3.2 Direct access to source data and documents

The sponsor will monitor the conduct of the trial by regular on-site monitoring visits. The investigator /institution will allow site trial-related monitoring, audits, IRB / IEC review and regulatory inspections. Direct access must be provided to the eCRF and all source documents/data, including progress notes, copies of laboratory and medical test results, which must be available at all times for review by the CRA, auditor, and regulatory inspector (e.g. FDA). They may review all eCRFs and informed consents. The accuracy of the data will be verified by direct comparison with the source documents described in section 8.3.1. The sponsor will also monitor compliance with the protocol and GCP.

8.3.3 Storage period of records

Trial sites:
The trial sites must retain the source and essential documents (including ISF) according to contract or the local requirements valid at the time of the end of the trial (whatever is longer).

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

8.4 EXPEDITED REPORTING OF ADVERSE EVENTS

BI is responsible to fulfil their legal and regulatory reporting obligation in accordance with regulatory requirements.

8.5 STATEMENT OF CONFIDENTIALITY AND PATIENT PRIVACY

Data protection and data security measures are implemented for the collection, storage and processing of patient data in accordance with the principles 7 and 12 of the WHO GCP handbook.

Individual patient data obtained as a result of this trial is considered confidential and disclosure to third parties is prohibited with the following exceptions: Personalized 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 at the site as a result of the

trial need to be available for inspection on request by the participating physicians, the sponsor's representatives, by the IRB / IEC and the regulatory authorities.

8.6 TRIAL MILESTONES

The **start of the trial** is defined as the date when the first patient in the whole trial signs informed consent.

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

The "**Last Patient Last Treatment"** (LPLT) date is defined as the date on which the last patient in the whole trial is administered the last dose of trial treatment (as scheduled per protocol or prematurely). Individual investigators will be notified of SUSARs occurring with the trial medication until 30 days after LPLT at their site.
Early termination of the trial is defined as the premature termination of the trial due to any reason before the end of the trial as specified in this protocol.

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

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

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

A final report of the clinical trial data will be written only after all patients have completed the trial in all countries (EU or non-EU) to incorporate and consider all data in the report. The sponsor will submit to the EU database a summary of the final trial results within one year from the end of a clinical trial as a whole, regardless of the country of the last patient (EU or non-EU).

8.7 ADMINISTRATIVE STRUCTURE OF THE TRIAL

The trial is sponsored by Boehringer Ingelheim. A Coordinating Investigator is responsible to coordinate investigators at the different sites participating in this trial. Tasks and responsibilities are defined in a contract.

Relevant documentation on the participating (Principal) Investigators (e.g. their curricula vitae) will be filed in the ISF. The investigators will have access to the BI clinical trial portal (Clinergize) to facilitate document exchange and maintain electronic ISF.

Investigators targeted for this study will include pulmonologists and general physicians who have access to the patient population. Equipment for central spirometry will be provided by a vendor designated by the sponsor. For sites participating in the body plethysmography procedures, will need to have their own equipment.

BI has appointed a Clinical Trial Leader, responsible for coordinating all required activities, in order to

- manage the trial in accordance with applicable regulations and internal SOPs,
- direct the clinical trial team in the preparation, conduct, and reporting of the trial,
- ensure appropriate training and information of Clinical Trial Managers, CRAs, and investigators of participating countries.

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

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

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

A central laboratory service, and an IRT vendor will be used in this trial. Details will be provided in the IRT user manual and central laboratory manual.

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10. APPENDICES

10.1 BODY PLETHYSMOGRAPHY MEASUREMENT TECHNIQUE

Detailed instructions on the procedures will be provided in a body plethysmography manual in the ISF. The body plethysmography procedures will be performed in "linked" maneuver, i.e. without the patient coming off the mouthpiece prior to the completion of the maneuvers.

- Quiet tidal volume breathing, ensuring stable End-expiratory Lung Volume (EELV), followed by
- Shutter closing at EELV and panting with hands over cheeks, followed by
- Opening of the shutter and return to quiet tidal breathing (ensuring stable EELVs, which are at the same position as those prior to shutter closing), followed by
- An ERV maneuver, followed by a slow IVC maneuver.

Note:

The term "body plethysmography" is being used to specifically refer to body plethysmography system procedures that are performed with system´s door closed.

Spirometry (FEV_1, FVC) will not be performed using the body plethysmography system, but rather with a stand-alone [redacted] spirometer supplied by a vendor designated by the sponsor.

Calculation of RV, TLC and IC:

Residual Volume (RV) is the volume of gas remaining in the lung at the end of a full expiration. The reported value for RV is the reported value for FRC minus the mean of technically acceptable ERV measurements, linked to technically acceptable FRC determinations (a maximum of six efforts).

Total Lung Capacity (TLC) is the volume of gas in the lung at the end of a full inspiration. The reported value of TLC is the reported value for RV plus the largest of the technically acceptable IVCs. A good quality IVC is thus required for the calculation of TLC. For IVC, the two best efforts (of at least three) MUST NOT differ by more than 150 mL. If repeatability is not achieved after three efforts, additional efforts up to a maximum of six need to be performed.

Inspiratory Capacity (IC) is the maximal volume which can be inspired from FRC. IC is calculated for each individual effort as the difference between IVC and ERV. At least three efforts must be performed, and the individual efforts must lie within ±6% of their mean. If repeatability is not achieved after three efforts, additional efforts of up to a maximum of six need to be performed.

10.2 ADDITIONAL INFORMATION REGARDING IN/EX CRITERIA

Smoking: calculation of number of pack years

Calculation of pack years based on number of cigarettes:

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

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

11.1 GLOBAL AMENDMENT 1

Date of amendment		05 December 2019
EudraCT number **EU number**		2019-001719-21
BI Trial number		1237-0095
BI Investigational Medicinal Product(s)		Tiotropium + olodaterol Respimat®
Title of protocol		A randomized, double blind, placebo-controlled, multi-center, parallel group study to compare the efficacy of inhaled tiotropium + olodaterol, fixed dose combination (5µg/5µg) vs. placebo delivered by Respimat inhaler in patients with moderate to severe COPD, stratified by peak inspiratory flow rate [TRONARTO].
Global Amendment due to urgent safety reasons		
Global Amendment		x
Section to be changed		Synopsis and Section 3.3.2 – Inclusion criteria 3.
Description of change		In the Synopsis, Inclusion Criteria 3: Diagnosis of chronic obstructive pulmonary disease and must meet the following spirometric criteria: patients with a post-bronchodilator FEV_1 > 30% and <80% of predicted normal; and a post-bronchodilator FEV_1/FVC <70%, at the screening visit. **Was changed to:** Diagnosis of chronic obstructive pulmonary disease and must meet the following spirometric criteria: patients with a post-bronchodilator $FEV_1 \geq$ 30% and <80% of predicted normal; and a post-bronchodilator FEV_1/FVC <70%, at the screening visit. In section 3.3.2, Inclusion Criteria 3: All patients must have a diagnosis of COPD and must meet the following spirometric criteria: patients with a post-bronchodilator FEV_1 >30% and <80% of predicted normal (ECSC, [R94-1408]); and a post-

		bronchodilator FEV_1/FVC <70%, at the screening visit. **Was changed to:** All patients must have a diagnosis of COPD and must meet the following spirometric criteria: patients with a post-bronchodilator FEV_1 ≥30% and <80% of predicted normal (ECSC, [R94-1408]); and a post-bronchodilator FEV_1/FVC <70%, at the screening visit.
Rationale for change		Formatting issue corrected
Section to be changed		Flowchart: Footnote 1
Description of change		The interval between visits 1 and 2 (screening period can be extended up to 4 weeks (28 days) for administrative reasons (section 6.2.1). **Was changed to:** The interval between visits 1 and 2 (screening period can be extended up to 2 weeks for administrative reasons (section 6.2.1).
Rationale for change		Footnote 1 of the Flowchart was clarified to align with section 6.2.1.
Section to be changed		Flowchart: Footnote 14
Description of change		PIFR measurements using med/low resistance in the [redacted] will be collected in the clinic at visits 2, 3, and 4. **Was changed to:** PIFR measurements using med/low and high resistance in the [redacted] will be collected in the clinic at visits 2, 3, and 4.
Rationale for change		Footnote 14 of the Flowchart was clarified to align with section 6.1: In clinic measurement of PIFR using the [redacted]
Section to be changed		First footnote for Flowchart - Pulmonary Function Tests: Visits 2 and 4*
Description of change		*At visit 2, PFTs done at 10 min pre-dose only **Was changed to:** *At visit 3, PFTs done at 10 min pre-dose (trough)

		only, including pre-dose vital signs
Rationale for change		Editorial change and clarification regarding the conduct of Visit 3 PFTs.
Section to be changed		Abbreviations
Description of change		**The following abbreviation was removed:** DILI – Drug Induced Liver Injury
Rationale for change		This abbreviation was removed as the term is no longer referenced in the protocol.
Section to be changed		Section 3.1
Description of change		Body plethysmography measurements will be an optional trial procedure in this study, and will be performed at selected sites at visit 2. Approximately 30 (15%) patients are expected to participate in this procedure. Patients participating in this optional trial procedure will have to sign a separate informed consent. **Was changed to:** Body plethysmography measurements will be an optional trial procedure at visit 2 and will be done only at selected sites on selected patients.Approximately 30 (15%) patients are expected to participate in this procedure. Patients participating in this optional trial procedure will have to sign a separate informed consent. At the screening visit, an assessment will be completed to see if the patient can perform technically acceptable body plethymography measurements.
Rationale for change		Clarification and alignment with Flowchart footnote 8
Section to be changed		Section 5.1.2
Description of change		PIFR measurements will also be done in the clinic during visits 3, and 4. Measurements will be made in triplicate using med/low resistance and the highest value will be used. **Was changed to:** Additional PIFR measurements will also be done in the clinic during visits 2, 3, and 4. Measurements will be made in triplicate using med/low and high resistance and the highest value

		for each resistance setting will be recorded.
Rationale for change		Clarification and alignment with Section 6.1: In clinic measurement of PIFR using the [redacted]
Section to be changed		Section 5.2.3
Description of change		**The following content was removed:** In case the criteria for hepatic injury are fulfilled, a number of additional measures will be performed (section 5.2.6.1), and the drug induced liver injury (DILI) checklist provided in the ISF. The amount of blood taken from the patient concerned will be increased due to this additional sampling.
Rationale for change		As noted in Section 5.2.6.1.4, there are no adverse events of special interest. This DILI content was included in error.
Section to be changed		Section 6.1 – Home measurement of PIFR: Using the [redacted]
Description of change		The following content was removed: • Change the setting to "high" and complete three maneuvers as done with the "med/low" setting. Record all three PIFR measurements in the patient diary.
Rationale for change		Reduction in the complexity of patient procedures at home.
Section to be changed		Section 6.2.1
Description of change		Patients will complete the PIFR measurements each evening. The PIFR measurements will be done with two different resistance levels (med/low and high). At each resistance levels, measurements will be done in triplicate. **Was changed to:** Patients will complete the PIFR measurements each evening. The PIFR measurements will be done in triplicate at the med/low resistance level.
Rationale for change		Reduction in the complexity of patient procedures at home.
Section to be changed		Section 6.2.2

Description of change		**Addition of the following content:** Patients should be instructed not to take their dose of study medication at home on the day of visits 3 and 4.
Rationale for change		Clarification and alignment with Section 4.2.3

11.2 GLOBAL AMENDMENT 2

Date of amendment		28 January 2020
EudraCT number **EU number**		2019-001719-21
BI Trial number		1237-0095
BI Investigational Medicinal Product(s)		Tiotropium + olodaterol Respimat®
Title of protocol		A randomized, double blind, placebo-controlled, multi-center, parallel group study to compare the efficacy of inhaled tiotropium + olodaterol, fixed dose combination (5µg/5µg) vs. placebo delivered by Respimat inhaler in patients with moderate to severe COPD, stratified by peak inspiratory flow rate [TRONARTO].
Global Amendment due to urgent safety reasons		
Global Amendment		
Section to be changed		Abbreviations
Description of change		**The following abbreviations were added:** CKD-EPIcr – Chronic Kidney Disease Epidemiology Collaboration Equation eGFR – Estimated Glomerular Filtration Rate
Rationale for change		These abbreviations were added as terms are referenced in Section 3.3.3 Exclusion criteria 21 and Flow Chart
Section to be changed		Section 3.3.3 – Exclusion criteria 1
Description of change		Patients with a significant disease other than COPD; a significant disease defined as a disease which, in the opinion of the investigator, could (i) put the patient at risk because of participation in the trial, (ii) influence the results of the trial, or (iii) cause concern regarding the patient's ability to participate in the trial. **Was changed to:**

		Patients with a significant disease other than COPD; a significant disease defined as a disease which, in the opinion of the investigator, and referring to the warnings to be observed as quoted in the locally applicable SmPC or prescribing information, could (i) put the patient at risk because of participation in the trial, (ii) influence the results of the trial, or (iii) cause concern regarding the patient's ability to participate in the trial
Rationale for change		Provide additional guidance regarding Exclusion Criteria 1.
Section to be changed		Section 3.3.3 – Exclusion criteria 21
Description of change		Patients with creatinine >2x upper limit of normal **Was changed to:** Patients with creatinine >2x upper limit of normal or an estimated glomerular filtration rate (eGFR) determined below 50 ml/min/1.73 m2 (as derived from CKD-EPIcr equation [R12-1392])
Rationale for change		Additional parameter for assessment of renal function in Exclusion Criteria 21.
Section to be changed		Flow Chart and Footnote 10
Description of change		**The following content was added to the Flow Chart:** eGFR eGFR will be derived from serum creatinine values, age, sex and race based on the CKD-EPIcr equation [R12-1392].
Rationale for change		Additional parameter for assessment of renal function in Exclusion Criteria 21.
Section to be changed		Section 3.3.4.1 – Discontinuation of trial treatment
Description of change		**The following content was added**: In terms of discontinuation of trial treatment, the following criteria must also be taken into account: • Trial treatment must be stopped immediately if a paradoxical bronchospasm or an allergic reaction of the immediate type occurs. • If two or more eye symptoms (triggering or

<table>
<tr><td></td><td></td><td>aggravation of narrow angle glaucoma, eye pain or discomfort, temporary blurred vision, eye halos or altered color perception associated with reddened eyes due to conjunctival congestion or corneal edema) occur, trial treatment should be discontinued and the patient should consult a specialist immediately.
For safety reasons, the investigator may decide that the patient should discontinue trial treatment.</td></tr>
<tr><td>Rationale for change</td><td></td><td>To specify more precise termination criteria for trial treatment.</td></tr>
<tr><td>Section to be changed</td><td></td><td>Table 4.2.3.1:1 – Overview of permitted and restricted medications</td></tr>
<tr><td>Description of change</td><td></td><td>Under Combinations the following content was added:
<table>
<tr><th rowspan="2">Sub-class</th><th rowspan="2">Prior to study</th><th colspan="3">Study Period</th></tr>
<tr><th>Screening Period</th><th>Treatment Period</th><th>Follow-up Period</th></tr>
<tr><td>ICS, long-acting anticholinergics, long-acting β-adrenergics, (e.g. fluticasone + umeclidinium, vilanterol)</td><td>Permitted[1]</td><td>NOT permitted</td><td>NOT permitted</td><td>NOT permitted</td></tr>
</table>
Footnotes for Table 4.2.3.1: 1
1. Permitted until 6 months prior to visit 1</td></tr>
</table>

Rationale for change		Clarification that all combination products containing inhaled corticosteroids are restricted medications and their use is not permitted within 6 months of study entry and during the screening, treatment and follow-up periods.
Section to be changed		9.1 Published References
Description of change		**The following reference added:** R12-1392 - Levey AS, Stevens LA, Schmid CH, Zhang Y, Castro AF, Feldman HI, Kusek JW, Eggers P, Lente F van, Greene T, Coresh J, Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI). A new equation to estimate glomerular filtration rate. Ann Intern Med 150 (9), 604 - 612 (2009)
Rationale for change		Reference required for eCFR equation

11.3 GLOBAL AMENDMENT 3

Date of amendment		
EudraCT number **EU number**		2019-001719-21
BI Trial number		1237-0095
BI Investigational Medicinal Product(s)		Tiotropium + olodaterol Respimat®
Title of protocol		A randomized, double blind, placebo-controlled, multi-center, parallel group study to compare the efficacy of inhaled tiotropium + olodaterol, fixed dose combination (5µg/5µg) vs. placebo delivered by Respimat inhaler in patients with moderate to severe COPD, stratified by peak inspiratory flow rate [TRONARTO].
Global Amendment due to urgent safety reasons		
Global Amendment		x
Section to be changed		
Description of change		
Rationale for change		