Non-interventional Study Protocol

Document Number:	**c20892554-01**
BI Study Number:	1237-0073
BI Investigational Product(s):	Spiolto® Respimat®
Title:	Changes in health and functional status in patients with Chronic Obstructive Pulmonary Disease (COPD) during therapy with Spiolto® Respimat® [ELLACTO]
Brief lay title	Not applicable
Protocol version identifier:	2.0
Date of last version of protocol:	28 Aug 18
PASS:	No
EU PAS register number:	EUPAS21422
Active substance:	R03AL06 Tiotropium bromide + Olodaterol
Medicinal product:	Spiolto® Respimat® 2.5 microgram/2.5 microgram, inhalation solution; tiotropium/olodaterol
Product reference:	NL/H/3157/001/DC
Procedure number:	n.a.
Marketing authorization holder(s):	Market Authorization Holder: Boehringer Ingelheim International GmbH Binger Straße 173 55216 Ingelheim am Rhein Study Initiator: Boehringer Ingelheim Ellas Leoforos Andrea Sygrou 340,17673, Kallithea,Athens Greece
Joint PASS:	No

Research question and objectives:	The objective of this NIS is to measure changes in health status including functional status using CCQ scores in COPD patients receiving treatment with Spiolto® Respimat® after approximately 6 weeks in routine clinical practice. **Primary objective:** Assess proportion of patients achieving "therapeutic success" (= 0.4 point decrease in the CCQ score between baseline and approximately week 6) **Secondary objectives** are assessment of changes in CCQ and CCQ-4, the patient's general condition (physician's evaluation) at visit 1 (baseline visit at the start of the study) and at visit 2 (final visit at the end of the study, approx. 6 weeks after visit 1), as well as patient satisfaction with Spiolto® Respimat® at Visit 2.
Country(-ies) of study:	Greece
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Date:	28/08/2018

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2. LIST OF ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse Event
BI	Boehringer Ingelheim
CA	Competent Authority
CCQ	Clinical COPD Questionnaire
CI	Confidence Interval
CML	Local Clinical Monitor
COPD	Chronic Obstructive Pulmonary Disease
CRA	Clinical Research Associate
eCRF	Electronic Case Report Form
DMP	Data Management Plan
EU	European Union
FDC	Fix Dose Combination
FEV1	Forced expiratory volume in one second
GCP	Good Clinical Practice
GEP	Good Epidemiological Practice
GPP	Good Pharmacoepidemiology Practice
GOLD	Global Initiative for Chronic Obstructive Lung Disease
HCPs	Health Care Professionals
HH	HandiHaler Inhaler Device
ICH	International Conference on Harmonisation
ICS	Inhalative Corticosteroides
IEC	Independent Ethics Committee
ISF	Investigator Site File
LABA	Long-acting $beta_2$ adrenoceptor agonist
LAMA	Long-acting muscarinic antagonist
MedDRA	Medical Dictionary for Drug Regulatory Activities
mMRC	Modified Medical Research Council
NIS	Non-Interventional Study
RMT	Respimat Inhaler Device
PGE	Physician's Global Evaluation
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SF-36	36-Item Short Form Health Survey
SGRQ	St George's Respiratory Questionnaire
SmPC	Summary of Product Characteristics
WHO	World Health Organisation

3. RESPONSIBLE PARTIES

Therapeutic Area Respiratory Medicine (TA)	
Team Member Medical Affairs (TM MA)	
Team Member Epidemiology (TM Epi)	
Global Epidemiology (GEpi)	
Therapeutic Area Risk Management (TA RM), and Pharmacovigilance Working Group (PVWG)	
GPV Study Coordination	
Trial Statistician (TSTAT)	
Trial Data Manager (TDM)	
Trial Programming	
Trial Clinical Monitor (TCM)	
Coordinating Investigator (CI)	Not applicable
CRO --	

4. ABSTRACT

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: Spiolto® Respimat®			
Name of active ingredient: R03AL06 Tiotropium bromide +Olodaterol			
Protocol date: 18 December 2017	**Study number:** 1237-0073	**Version/Revision:** 2.0	**Version/Revision date:** Not applicable
Title of study:	Changes in functional status in patients with COPD during therapy with Spiolto® Respimat®		
Rationale and background:	Reduced physical activity resulting in deconditioning and restricted physical functioning is a key problem of COPD patients, which even in early disease stages is of concern. Clinical studies investigating treatment with Spiriva® or with Striverdi® Respimat® and as well as with the combination Spiolto® Respimat ®, have shown significant improvement in exercise capacity in patients with COPD [PO5-09483, R13-2524, P17-04769, P17-06396]. However, real life data with regards to the effects of a combination therapy with the approved brand Spiolto® Respimat® in COPD patients who need two long-acting bronchodilators are not yet available. This study aims to investigate functional status of COPD patients treated with Spiolto ® Respimat® by means of the CCQ questionnaire, more specifically by its 'functional status' subdomain (CCQ-4).		
Research question and objectives:	The primary objective of this NIS is to measure changes in health and functional status using the CCQ score, in COPD patients on treatment with Spiolto® Respimat® after approximately 6 weeks. The secondary objectives are to evaluate the absolute change in the CCQ and CCQ-4 between Visit 1 (baseline visit at the start of the study) and Visit 2 (final visit at the end of the study, approx. 6 weeks after Visit 1), the patient's general condition (physician's evaluation) at Visit 1 and at Visit 2, as well as patient satisfaction (and in a subset, preference) with Spiolto® Respimat® at Visit 2 and treatment continuation of Spiolto® Respimat® after the study.		
Study design:	Open-label observational study: including COPD patients receiving treatment with Spiolto® Respimat® for approximately 6 weeks, which is the average time between two medical consultations.		
Population:	COPD patients requiring a fixed combination therapy of two long-acting bronchodilators (LAMA + LABA) according to approved SmPC and the updated COPD GOLD 2017 guidelines regarding groups B to D [P17-01597].		

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Protocol date: 18 December 2017	**Study number:** 1237-0073	**Version/Revision:** 2.0	**Version/Revision date:** Not applicable
Title of study:	Changes in functional status in patients with COPD during therapy with Spiolto® Respimat®		
Variables:	Patient demographics (age, gender, height & weight) Concomitant diseases / Comorbidities Concomitant medication General condition of patient based on Physician's Global Evaluation (PGE) Smoking history Exacerbations Breathlessness based on mMRC score Health Status based on CCQ scores Functional Status based on the CCQ subdomain 4 (CCQ-4) Patient satisfaction with Spiolto® Respimat® and preference (abbreviated PASAPQ Part 1 + Part 2) Safety; ADR (serious and non-serious), fatal AEs, pregnancies GOLD spirometric classifications (1, 2, 3, 4) (when available). GOLD patient groups (B, C, D)		
Data sources:	To be completed by the physician: - Patient demographics - Patient medical files - Physician's Global Evaluation (PGE) at Visit 1 and Visit 2 To be completed by the patient at Visit 1: - mMRC breathlessness scale To be completed by the patient at Visit 1 and at Visit 2: - Physical Functioning Questionnaire (CCQ) To be completed by the patient at Visit 2 only: - Patient satisfaction and preference survey (abbreviated PASAPQ Part 1 + Part 2)		
Study size:	1300 COPD patients will be recruited by 100 pulmonologists in private practice and 2 hospital centers throughout Greece. Each investigator will include 10-15 consecutive patients for whom he/she decided for a treatment with Spiolto ® Respimat®.		

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Title of study:	Changes in functional status in patients with COPD during therapy with Spiolto® Respimat®		
Data analysis:	**Primary endpoint:** proportion of patients achieving "therapeutic success" (= 0.4 point decrease in the CCQ score between baseline and week 6) [R17-0254]. 0.4 points is the well accepted MCID [R17-0256] Secondary endpoints: Absolute change in the CCQ Absolute change in CCQ-4. Patient´s general condition: Physician´s Global Evaluation (PGE) score at baseline and end of study. Patient satisfaction with (tiotropium and olodaterol) Respimat® at end of study using a seven-point ordinal scale (ranging from very dissatisfied to very satisfied) (abbreviated PASAPQ Part 1). Patient preference HH (HandiHaler) vs RMT (Respimat) Inhaler devices – only for those patients that used Spiriva HH previous to the study (PASAPQ Part 2). Treatment continuation of Spiolto® Respimat® after the study.		
Milestones:	Start of data collection: FPI: Jan 2018 End of data collection: LPO: June 2018 Final report of study results: Mar 2019		

5. AMENDMENTS AND UPDATES

Number	Date	Section of study protocol	Amendment or update	Reason
02	28 Aug 2018	1,4,7,8,9		clarification of primary endpoint, addition of a secondary endpoint and correction in Section 9.7.3

6. MILESTONES

Milestone	Planned Date
IRB/IEC approval	14 Mar 2018
Start of data collection	19 Mar 2018
End of data collection	30 Nov 2018
Final report of study results:	30 April 2019

7. RATIONALE AND BACKGROUND

7.1 MEDICAL BACKGROUND

COPD is defined as a quite preventable and treatable disease of the airways, with significant systemic consequences especially in cardiology. Inactivity is believed to be crucial to the further development of extrapulmonary effects of the disease like skeletal muscle weakness, osteoporosis and cardiovascular disease. Recent data suggest that patients suffering from COPD combined with low levels of physical activity have increased risk for hospital admissions and have significantly enhanced mortality. Epidemiological data suggest that this may directly or indirectly lead to more rapid decline in lung function [R13-3633].
Physical activity is reduced early in concomitance with the disease progression, as of GOLD Stage 2 [R13-3633]. More recent evidence from large placebo-controlled clinical trials indicates that COPD patients experience a steeper absolute decline in lung function with GOLD 2 airflow limitation than with GOLD 3 and 4 [R15-5015]. All these observations suggest the importance of early and optimal treatment of the disease.
Long-acting bronchodilators, such as long-acting muscarinic antagonists (LAMAs), are the cornerstone of maintenance therapy for patients with moderate to very severe chronic obstructive pulmonary disease (COPD) whose symptoms are not adequately controlled by short-acting bronchodilators alone [P13-05794, P14-01052].
An option recommended by GOLD guideline for patients not adequately controlled on a single long-acting bronchodilator is to combine a LAMA with a long-acting β2-agonist (LABA) [P14-01052]. This has prompted the development of combining LAMA+LABA as fixed-dose combinations [P13-05794].
The rationale for combining bronchodilators with different mechanisms is based on the notion of additive, synergic relaxation of airway smooth muscle by direct inhibition of cholinergic activity and functional antagonism of bronchoconstriction through β2-adrenergic pathways, with the expectation of an increased degree of bronchodilation for equivalent or even lesser side effects. Several recent studies have provided evidence in support of this increased bronchodilatory effect when LABAs are combined to LAMAs.
When long acting beta-agonists (LABA) and long acting muscarinic antagonists (LAMA) with similar or equivalent posologies are combined, the opportunity exists for offering a simpler and more convenient administration regimen with the development of fixed combinations within the same inhaler device. Fixed-dose combinations of a short-acting β2– agonist and a short-acting anticholinergic have been developed and have been shown to be safe, efficacious and convenient for the patient (e.g., Berodual®: Fenoterolhydrobromid + Ipratropiumbromid, Combivent®: salbutamol + ipratropium bromide; [P94-1346]). Olodaterol is a highly selective and nearly full β2 agonist [P10-07776, P11-07720] that provides 24-h bronchodilation in patients with COPD [P13-11467, P13-14112, P13-11346, P13-11345]. Olodaterol is also associated with symptomatic relief [P13-11341] and enhanced exercise capacity [P13-14109].
The complementary modes of action of tiotropium and olodaterol have previously been demonstrated in animal models, phase II clinical trials and during Phase IIIa programs [P10-09337, P14-12073, P13-02357]. In Phase III programs, additional benefits of the tiotropium + olodaterol fixed-dose combination (FDC) has been assessed on lung function over its mono-components, as well as quality of life (St. George's Respiratory Questionnaire-SGRQ), dyspnea (Transition Dyspnea Index-TDI) and exercise endurance time. Another clinically important potential benefit of the tiotropium + olodaterol FDC over the mono components is the impact on exacerbations of COPD.

7.2 DRUG PROFILE

Tiotropium + olodaterol FDC is an aqueous solution of tiotropium and 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 pivotal clinical trials and for the intended marketed product, the clinical dose consists of two puffs once daily. The Respimat® inhaler uses mechanical energy to create a soft mist which is released over a period of approximately 1.5 seconds.
Tiotropium + olodaterol FDC was shown to be safe and well tolerated over 1 year in a moderate to very severe COPD population. The overall incidences of adverse events (AEs), serious adverse event (SAEs), fatal AEs, frequencies for cardiac events and major adverse cardiovascular event in the tiotropium + olodaterol FDC treatment group were similar to the components alone. 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 [P15-03349].
In conclusion, the clinical trials conducted to date have shown tiotropium + olodaterol FDC to be a safe, well tolerated and efficacious combination therapy according to treatment guidelines in a moderate to very severe COPD patient population [P15-04531, P15-03349]. The observed incremental bronchodilator response due to the combination compared to the components alone, was translated into clinical benefits that were meaningful to the patient, with improvements in several patient centered outcomes. For further information please refer to the SmPC of Spiolto® Respimat®.

8. RESEARCH QUESTION AND OBJECTIVES

8.1 RATIONALE FOR PERFORMING THE STUDY

The contribution of physical inactivity to disability in COPD is difficult to distinguish from disease progression; however, it is clear that physical activity is significantly lower in patients with COPD than in healthy controls [R13-3633]
COPD prevents patients from carrying out daily activities due to exercise intolerance, which is often attributed to limited pulmonary ventilation. Physical inactivity may be related to avoidance of exertion as a result of fear of dyspnea. Furthermore, physical inactivity has been associated with skeletal muscle weakness and exercise intolerance [R15-4459, R15-4561].
The loss of physical activity in COPD is associated with increased mortality. Data from a study of 2386 patients with COPD demonstrated that, following adjustment for relevant confounders, subjects who reported low, moderate or high physical activity had a significantly lower risk of all-cause mortality than those with very low physical activity ($p = 0.001$) [R15-4564]. Clinical studies of both Spiriva® [P13-04267, P05-09483, P13-14109] and Striverdi® Respimat® in COPD patients have demonstrated significant improvement in exercise capacity [P13-14109].
The benefits of tiotropium + olodaterol FDC have been studied in controlled Phase III programs on exercise endurance, however, data regarding physical activity when treated with Spiolto® Respimat® in a real world setting is not available.

8.2 STUDY OBJECTIVES

The objective of this NIS is to measure changes in health and functional status by the CCQ, in COPD patients receiving treatment with Spiolto® Respimat® after approximately 6 weeks in routine clinical practice. Each of the 10 CCQ questions is scored by the patient on a 7-point scale between 0 and 6 at baseline and end of the observation after approximately 6 weeks. The sum of the scores divided by 10 gives the CCQ score, which measures the health and functional status. A higher CCQ score is indicative of worse status. The functional status (CCQ-4) is calculation as the sum of the 4 questions (#'s 7, 8, 9, 10) divided by 4. A change of 0.4 points is considered to be the MCID for both CCQ score and CCQ-4. [R17-0256]
Primary objective: Assess the proportion of patients achieving "therapeutic success" (= 0.4 point decrease in the CCQ score between baseline and approximately week 6).

The secondary objectives are to evaluate the absolute change in the CCQ and CCQ-4 between Visit 1 (baseline visit at the start of the study) and Visit 2 (final visit at the end of the study, approx. 6 weeks after Visit 1), the patient's general condition (physician's evaluation) at Visit 1 and at Visit 2, as well as patient satisfaction (and in a subset, preference) with Spiolto® Respimat® at Visit 2.

9. RESEARCH METHODS

9.1 STUDY DESIGN

This is a self-controlled non interventional study enrolling consented COPD patients who will be treated with Spiolto® Respimat® according to approved SmPC. The Patients will be enrolled consecutively and will be followed over an observational period of approx. 6 weeks. Data as listed in Table 9.1.1 will be collected.
Baseline characteristics of eligible patients and provided Informed Consent but were not treated in the study will also be collected.
The intended Health Care Professionals (HCPs) are private practice physicians who are treating symptomatic and COPD patients every day, being aware that most of their patients suffer from the physical restrictions induced by the disease per se.
Study results will be used to document the effectiveness of Spiolto® Respimat® in improving the functional status of COPD patients impaired in activity of daily living (ADL). It will complement the results of a previous trial using the PF-10 (1222.56). The biggest advantage of the current proposal is that the CCQ is a very well-known and widespread questionnaire, which is also included in the GOLD guidelines [R17-3684] and is validated in Greek [R17-3682, R17-3681].

Table 9.1.1: Visit flow chart and data collection parameters

Parameter	Visit 1 baseline visit	Visit 2 approx. 6 weeks after baseline visit	Telephone contact 2 weeks after baseline visit
Informed Consent	X		
Inclusion / Exclusion Criteria	X		
Patient demographics (age, gender, height, and weight)	X		
Smoking history	X	X	
Start of COPD	X		
Number of exacerbations in the last 12 months	X		
Number of exacerbations leading to hospitalization in the last 12 months	X		
Past COPD therapies (6 months before Visit 1)	X		
COPD related and other relevant concomitant medication	X	X	
Concomitant diseases / Comorbidities	X	X	
Respimat® training (yes/no)	X		
COPD severity based on GOLD assessment1	X		

Table 9.1.1: Visit flow chart and data collection parameters (cont'd)

mMRC breathlessness scale, completed by the patient	X		
CCQ completed by the patient	X	X	
General condition of patient evaluated by Physician's Global Evaluation (PGE)	X	X	
Adverse Drug Reactions (serious and non-serious), fatal AE, pregnancy	X	X	X
Patient satisfaction with Spiolto® Respimat®, survey completed by the Patient (abbreviated PASAPQ part 1). Patient preference for who used HH in precedence (PASAPQ part 2).		X	
Rational for Spiolto® Respimat® treatment discontinuation (if applicable)		X	X
Continuation or discontinuation of treatment with Spiolto® Respimat® after the study (yes/no)		X	X

GOLD patient group (B, C or D) will be automatically calculated within the eCRF based on available exacerbation history, mMRC and GOLD spirometric classification of airflow limitation based on post-bronchodilator FEV_1 if available.

9.2 SETTING

It is planned that data of approximately 1300 patients from approximately 102 sites (around 100 pulmonologists in private practice and 2 hospital sites) throughout Greece will be collected. Each investigator (site) will include 10-15 consecutive patients for whom he/she decided for a treatment with Spiolto ® Respimat®
A log of all patients included into the study (i.e. having given informed consent) will be maintained in the ISF at the investigational site irrespective of whether they have been treated or not.

9.2.1 Study sites

Patients will undergo visits 1 and 2 in private practice services disposed by pulmonologists who will participate in the study. In the case of hospital setting this will be guaranteed by outpatient clinics in agreement with the investigator pulmonologist.

9.2.2 Study population

1300 patients with chronic obstructive pulmonary disease (COPD) in whom combination treatment with long-acting bronchodilators is indicated in accordance with the guidelines are to be observed by approx. 100 pulmonologists in the setting of private practice. The NIS will take place in Greece and sites in urban as well as rural areas will be included. The nationwide distribution of the participating pulmonologists as well as the number of patients enrolled are intended to ensure that the data collected are representative.
Possible contraindications are to be checked prior to treatment with Spiolto® Respimat®. See also the latest Summaries of Product Characteristics on Spiolto® Respimat®.
Every physician should enroll the first consecutive patients he/she chooses to treat with Spiolto® Respimat®. The inclusion of ten to fifteen patients is planned per pulmonologist.
The decision to treat will be taken independently of participation in this NIS and will be made before participation is considered.

Inclusion criteria

- Therapeutic indication before entering the enrollment phase is patients diagnosed with COPD requiring a combination therapy of two long-acting bronchodilators (LAMA + LABA) according to approved SmPC and guidelines, COPD GOLD 2017 groups B to D.
- Female and male patients ≥40 years of age
- Treatment with Spiolto ® Respimat® acc. to SmPC and at the discretion of the physician.
- Written informed consent prior to participation

Exclusion criteria

- Patients with contraindications according to Spiolto® Respimat® SmPC
- Patients who have been treated with a LABA/LAMA combination (free and fixed dose) in the previous 6 weeks or patients already on a combination of LAMA and LABA therapy; either as a fixed combination product or as separate components

Note: Patients previously treated with LABA or LAMA (with or without ICS) are eligible to be included in the study

- Patients continuing LABA-ICS treatment should not be additionally treated with Spiolto® Respimat® in order to avoid a double dosing of long-acting beta-agonists
- Patients for whom further follow-up is not possible at the enrolling site during the planned study period of approx. 6 weeks
- Pregnancy and lactation
- Patients currently listed for lung transplantation
- Current participation in any clinical trial or any other non-interventional study of a drug or device.

9.2.3 Study visits

Enrolled patients will undergo 2 study visits. Visit 1 (baseline visit) during screening and enrollment, visit 2 (follow up visit) at the end of 6 weeks therapy with the product. A telephone contact will take place 2 weeks after first day of therapy to check for compliance and safety issues.

9.2.4 Study discontinuation

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

1. Failure to meet expected enrolment goals overall or at a particular study site.
2. Emergence of any efficacy/safety information that could significantly affect continuation of the study, or any other administrative reasons, i.e. lack of recruitment.
3. Violation of the protocol, the contract, or applicable laws and regulations for non-interventional studies, which could disturb the appropriate conduct of the NIS.

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

9.3 VARIABLES

In this NIS the following information about the effect of a dual long-acting bronchodilation with Spiolto® Respimat® on functional status in 1300 COPD patients treated in private practice will be collected in an e-CRF.

- **Baseline:** documentation of patient demographics, COPD and other relevant medical history,

comorbidities, reported exacerbations based on medical history in the last 12 months and exacerbations leading to hospitalization in the last 12 months, GOLD patient groups (B, C, D), based on GOLD guidelines, GOLD spirometric classifications (1, 2, 3, 4) (when available),

mMRC, smoking history, previous and concomitant pulmonary medication, self-administered (patient) Clinical COPD Questionnaire (CCQ (total as well as functional status subdomain CCQ-4)), patient´s general condition (Physician´s Global Evaluation (PGE) score). Pregnancies at the beginning of the study.

- **Next medical consultation (at 6 weeks):** self-administered (patient) 4-item Clinical COPD Questionnaire (Total CCQ and CCQ-4, subdomain of CCQ), patient´s general condition (Physician´s Global Evaluation (PGE) score), Patient satisfaction (and in a subset also preference) with Spiolto® Respimat®, adverse events and safety Reporting; Adverse Drug Reactions (serious and non-serious), fatal AEs, pregnancies at the end of the study, withdrawal from treatment since baseline.
- **Safety Reporting:** Adverse Drug Reactions (serious and non-serious), fatal AEs, pregnancies at the beginning and at the end of the study
- **The PGE** (Physician´s Global Evaluation) assesses the patient´s general condition using an eight-point scale (ranging from poor to excellent).
- **Patient satisfaction** with Respimat® will be measured with the abbreviated PASAPQ (part 1) and patient preference Spiriva HH vs RMT for those that used Spiriva HH previous to the study will be measured using PASAPQ (part 2), a practical, valid, reliable and responsive instrument for measuring respiratory device satisfaction [P05-02607].
- Treatment continuation of Spiolto® Respimat® after the study.
- **The CCQ questionnaire** contains 10 questions; each question can be scored by patients on a 7-point scale between 0 and 6. The sum of the scores divided by 10 gives the CCQ score. For the functional status calculation the sum of the 4 questions is divided by 4. A change of 0.4 points is considered to be the MCID. This questionnaire will be filled out by the patient and entered into the database.

9.3.1 Exposures

All patients will receive LAMA/LABA combination treatment with Spiolto® Respimat® according to the Greek SmPC.
Spiolto® Respimat® contains

- the long-acting anticholinergic tiotropium bromide. The dose dispensed is 2.5 micrograms of tiotropium per puff, equivalent to 3.124 micrograms tiotropium bromide 1 H2O. The dose dispensed is the quantity available to patients after crossing the mouthpiece.
- the selective beta2-adrenoceptor agonist olodaterol. The dose dispensed is 2.5 micrograms of olodaterol per puff (as olodaterol hydrochloride). The dose dispensed is the quantity available to patients after crossing the mouthpiece.

The recommended daily dose of Spiolto® Respimat® for adults is 5 micrograms of tiotropium ion (tiotropium) plus 5 micrograms of olodaterol, equivalent to inhaling 2 puffs from the Respimat® inhaler once daily at the same time of day.
The Summaries of Product Characteristics on Spiolto® Respimat® is contained in the NIS ISF in the "Summary of Product Characteristics" section.
Note: The recommended doses stated in the Summary of Product Characteristics should not be exceeded.

9.3.2 Outcomes

9.3.2.1 Primary outcome:

The primary outcome is to measure the proportion of patients achieving the "therapeutic success" defined as a ≥ 0.4 point of decrease in the Clinical COPD Questionnaire (CCQ) score between baseline and week 6. [R17-02546] .

As already known 0.4 points is the well accepted minimal clinically important difference (MCID) of the clinical COPD questionnaire [R17-0256].
The CCQ is a very short 10 question survey through which patients are requested to recall their experiences during the previous week with regards to their symptoms, functional and mental state. It is self-administered and takes patients approximately 2 minutes to complete. It is subdivided into three domains: symptom related (items 1-2-5-6), functional state related (items 7-8-9-10) and mental state related (items 3-4). Subjects respond to each question on a 7 point scale (ranging between 0=asymptomatic/no-limitation, to 6=extremely symptomatic/totally limited). The overall clinical COPD control score and the score of the three domains is calculated by adding all the scores together and dividing the sum by the number of questions.

9.3.2.2 Secondary outcomes:

- Absolute change in the CCQ
- Absolute change in CCQ-4.
- Patient´s general condition: Physician´s Global Evaluation (PGE) score at baseline and end of study.
- Patient satisfaction with (tiotropium and olodaterol) Respimat® at end of study using a seven-point ordinal scale (ranging from very dissatisfied to very satisfied) of the abbreviated PASAPQ (Part 1).
- Patient preference HH vs RMT (PASAPQ Part 2) – only for those patients that used Spiriva HH previous to the study.
- Treatment continuation of Spiolto® Respimat® after the study.

9.4 DATA SOURCES

Patient files (paper and/or electronically) of COPD patients as documented by the treating physician in his/her daily practice will be used as data source.
All participating physicians will be obliged to make a note of the patient's participation in the NIS in the patient's original documents.
In the event of possible queries, the participating physician must be able to identify the patient observed.
Medical information on the patient must be communicated and analyzed only using the patient number.
During this trial the following has to be completed:
To be completed by the physician:
- Patient demographics
- Patient medical files
- Physician's Global Evaluation (PGE) at Visit 1 and Visit 2

To be completed by the patient at Visit 1:
- mMRC breathlessness scale

To be completed by the patient at Visit 1 and at Visit 2:
- Physical Functioning Questionnaire (CCQ)

To be completed by the patient at Visit 2 only:
- Patient satisfaction survey (abbreviated PASAPQ Part 1) and Patient Preference only for those patients that used Spiriva HH previous to the study (PASAPQ Part 2)

9.5 STUDY SIZE

We assume that patients treated with Spiolto® Respimat® will have a CCQ therapeutic success rate similar to SGRQ responder rate considering the following:
1) CCQ has the great advantage of simplicity for the patient, having a very good correlation (rho = 0.67 to rho = 0.72) with the St George respiratory questionnaire (SGRQ) [R04-2815].

2) In TONADO studies [P15-03349] patients treated with Spiolto® Respimat® had a 57.5% SGRQ responder rate after 24 weeks..
The TONADO was a selected trial population, so a real-world population would probably show somewhat lower numbers due to the wide diversity of potential patients that will be followed up. Therefor a 50% CCQ responder rate is a reasonable assumption.
Assuming a 50% therapeutic success rate and a sample size of about 1170 patients, the 95% confidence interval for the therapeutic success rate would be between 47.1% (lower limit) and 52.9% (upper limit).
Subgroups with long acting bronchodilators at baseline (i.e., LABA only, LAMA only, LABA and ICS) will be analyzed only if they include more than 20% of all patients. In the smallest subgroup (with at least 234 patients), assuming a 50% therapeutic success rate, the 95% confidence interval would be between 43.6% and 56.4%. To account for a 10% drop-out rate, the sample size becomes 1300 patients.

9.6 DATA MANAGEMENT

A data management plan (DMP) will be created to describe all functions, processes, and specifications for data collection, cleaning and validation. The electronic Case Report Forms (eCRFs) will include programmable edits to obtain immediate feedback if data are missing (also negative answers, unknown), out of range, illogical or potentially erroneous. These rules may encompass simple checks such as range validation or presence/absence of data. Concurrent manual data review may be performed based on parameters dictated by the DMP. Ad hoc queries to the sites may be generated and followed up for resolution. A source data quality audit may be initiated to ensure that the data in the database is accurate. Source data verification (SDV) will be performed at sites identified by a risk-based approach as needed. The database will be housed in a physically and logically secure computer system maintained in accordance with a written security policy. The system will meet the standards of the International Committee on Harmonization guideline E6R1 regarding electronic study data handling. Patient confidentiality will be strictly maintained.

9.7 DATA ANALYSIS

All patients who have received at least one dose of Spiolto® Respimat® will be included in the analyses; this is the treated set. All analyses will be performed on the treated set (as treated analysis). If patients have missing values for an outcome, those patients will be excluded for that outcome's analysis. For example, if a patient is missing the CCQ score at Visit 1 and/or Visit 2, that patient will be excluded from the analyses for the primary endpoint of therapeutic success and the secondary endpoint of change in CCQ from Visit 1 to Visit 2.
The statistical characteristics presented in the end-of-text tables will be N / mean / SD / min / median / max for continuous variables. Tabulations of relative and absolute frequencies will be presented for categorical variables. Proportion and 95% CI will be given when appropriate.
The analyses will relate to the following data:

- Patient demographics (age, gender, height, and weight).
- Comorbidities (main diagnosis and concurrent diagnosis according to MedDRA, version valid as at the time of database closure).
- COPD related and other concomitant medication (according to the WHO classification, version valid at the time of database closure).
- History of smoking.
- Exacerbations.
- Breathlessness based on mMRC score at Visit 1.
- Physical Functioning based on CCQ scores (therapeutic success at Visit 2); primary outcome.
- Changes from Visit 1 to Visit 2 in the CCQ score; secondary outcome.
- Changes from Visit 1 to Visit 2 in the CCQ-4 score (subdomain of the CCQ); secondary outcome.
- Patient satisfaction with Spiolto® Respimat® and device preference for those patients that used Spiriva HH previous to the study, at Visit 2 only; secondary outcome.
- Treatment continuation of Spiolto® Respimat® after the study; secondary outcome
- General condition of the patient: evaluated by the physician (Physician´s Global Evaluation (PGE)); secondary outcome.
- Adverse Drug Reactions (ADR & SADR), fatal AEs, pregnancies.
- GOLD spirometric classification (1,2, 3, 4), if available.
- GOLD patient groups (B, C, D).
- Details of treatment with inhaled respiratory agents before the study.
- Details of treatment with respiratory agents during the study
- Reasons for ending treatment during the observation period
- Details of treatment continuation / discontinuation

9.7.1 Main analysis

For the primary outcome, the proportion of patients with therapeutic success will be presented together with the 95% confidence interval.

9.7.3 Handling of missing data

CCQ missing values: as already mentioned, the questions in the Clinical COPD Questionnaire (CCQ) are divided into three areas, or domains:
Symptoms: items 1, 2, 5, 6
Functional state: items 7, 8, 9, 10
Mental state: items 3, 4
In case of missing data or ambiguous answers (e.g. double answers) the following rules have to be applied to calculate the CCQ scores:

Domain	No. items in domain	No. items required	% required items
Symptoms	4	3	75
Functional state	4	3	75
Mental state	2	2	100

The total CCQ score can still be calculated when the individual domains can be calculated even if data is missing. For both, symptoms and functional state domains, 75% of answered items is required. The mental domain can be calculated only if all items are answered. Also, when a patient fills in two answers on one question the data should be considered as missing.
When the three domain scores can be calculated, the total score is calculated by multiplying the domain score with the original amount of questions and adding these numbers and dividing by 10.
For example, when question 5 is not completed, or there are two answers, the scores will be calculating as follows:
For the symptom domain add the score from questions 1,2, and 6 and divide by 3. Calculate the other domain scores as usual.
To calculate the total score use the following algorithm: ((symptom domain score)*4+(functional state domain score)*4+(mental state domain score)*2)/10 = CCQ total score (www.ccq.nl section: healthcare professionals/missing data rules).

Any removal from the analysis will be documented, stating the site and patient number as well as the reason for removal.

9.8 QUALITY CONTROL

To improve and secure data quality, automatic data checks upon data entry will be done within the eCRF. In the eCRF, plausible ranges of values for numeric data entries as well as logical data entries and listings will be provided for each entry field. Based on this, checks on completeness and plausibility will be performed upon data entry in the eCRF.
Validity of data entry thus is ensured by integrated validation checks performed by the system, indicating missing or implausible entries to the document list or investigator. All corrections will be visible from the systems audit trail.
No regular source data verification is planned in this study. However, in case of decreasing compliance (i.e. of missing data, data discrepancies, protocol violations, etc.) a for-cause audit or risk-based monitoring visit will be performed.

9.9 LIMITATIONS OF THE RESEARCH METHODS

The intention of this NIS is to collect new data on the physical functioning and exercise capacity of COPD patients on treatment with Spiolto® Respimat® in a real-world setting.

Per definition, non-interventional studies do not allow randomization or any other procedure outside clinical routine that would reduce the risk of biases. No interventions for improving follow-up, compliance, event reporting etc. are allowed. Thus, real life setting studies can only deliver data and results that have to be regarded and interpreted in the limits of this context.
Consecutive enrolment is expected to reduce selection bias. The entry criteria are non-restrictive which will permit the enrolment of a broad patient population. The choice of treatment is at the discretion of the investigator.
Selection bias could occur at the site level and the patient level. Therefore, to reduce the site level selection bias, the goal is to have participating pulmonologists/centers that have access to all available treatment options which are approved for use in Greece for the targeted COPD patients. Information bias will be minimized by the use of standard eCRF, questionnaire and physicians' training on the study protocol.

9.10 OTHER ASPECTS

9.10.1 Data quality assurance

A quality assurance audit/inspection of this study may be conducted by the sponsor or sponsor's designees or by Institutional Review Board (IRBs) / Independent Ethics Committee (IECs) or by regulatory authorities. The quality assurance auditor will have access to all medical records, the investigator's study-related files and correspondence, and the informed consent documentation of this study.

9.10.2 Study records

Case Report Forms (CRFs) for individual patients will be provided by the sponsor via remote data capture.

9.10.2.1 Source documents

Source documents provide evidence for the existence of the patient and substantiate the integrity

of the data collected. Source documents are filed at the investigator's site.
Data entered in the eCRFs that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study; also current medical records must be available.

For the eCRF, the following data must be derived from source documents:
- Patient demographics (age, gender, height, and weight);
- History of smoking
- Reported exacerbations
- Past COPD therapies (6 months before visit 1)
- Respimat® training (Yes/No)
- GOLD patient groups (B, C, D)
- GOLD spirometric classifications (1, 2, 3, 4) (if available).
- Concomitant diseases / Comorbidities
- Concomitant COPD and other relevant medication
- Breathlessness based on mMRC score
- Physical Functioning (CCQ)
- Patient Satisfaction and Preference Questionnaire (abbreviated PASAPQ Part 1 + Part 2)
- Adverse Drug Reactions (ADR & SADR), fatal AEs, pregnancies
- Rational for Spiolto® Respimat® treatment discontinuation (if applicable)
- Details of treatment continuation / discontinuation

9.10.2.2 Direct access to source data and documents

The investigator / institution will permit study-related monitoring, audits, IRB / IEC review and regulatory inspection, providing direct access to all related source data / documents.
E-CRFs and all source documents, including progress notes and copies of laboratory and medical test results must be available at all times for review by the sponsor's clinical study monitor, auditor and inspection by health authorities. The Clinical Research Associate (CRA) / Clinical Monitor Local (CML) and auditor may review all CRFs/eCRFs, and written informed consents.

9.10.3 Completion of study

The IRB/IEC in hospital sites in Greece need to be notified about the end of the study (last patient/patient out, unless specified differently in Section 6 of the observational plan) or early termination of the trial.

9.10.4 Protocol violations

All protocol violations must be reported to the sponsor immediately.

10. PROTECTION OF HUMAN SUBJECTS

The study will be carried out in compliance with the protocol, the principles laid down in the Declaration of Helsinki, in accordance with the ICH Harmonised Tripartite Guideline for Good Clinical Practice (GCP) (to the extent applicable to the NIS setting and required by local regulations), Good Epidemiological Practice (GEP) [R10-4560], Guidelines for Good Pharmacoepidemiology Practice (GPP) [R09-0182], and relevant BI Standard Operating Procedures (SOPs). Standard medical care (prophylactic, diagnostic and therapeutic procedures) remains in the responsibility of the treating

physician of the patient.
The investigator should inform the sponsor immediately of any urgent safety measures taken to protect the study subjects against any immediate hazard, and also of any serious breaches of the protocol/ICH GCP.
Insurance Cover: The requirements for insurance depend on local law and legislations in Greece. If required, the terms and conditions of the insurance cover are made available to the investigator and the patients, and the documentation must be archived in the Investigator Site File (ISF).

10.1 STUDY APPROVAL, PATIENT INFORMATION, AND INFORMED CONSENT

This study will be initiated only after all required legal documentation has been reviewed and approved by the respective Institutional Review Board (IRB) / Independent Ethics Committee (IEC) according to national and international regulations. The same applies for the implementation of changes introduced by amendments.
Prior to patient participation in the study, written informed consent must be obtained from each patient (or the patient's legally accepted representative) according to ICH GCP and to the regulatory and legal requirements of Greece. 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 study records. A signed copy of the informed consent and any additional patient information must be given to each patient or the patient's legally accepted representative.
The patient must be informed that his/her personal study-related data will be used by Boehringer Ingelheim in accordance with the local data protection law. The level of disclosure must also be explained to the patient.
The patient must be informed that his / her medical records may be examined by authorized monitors (CML/CRA) or Quality Medicine auditors appointed by Boehringer Ingelheim, by appropriate IRB / IEC members, and by inspectors from regulatory authorities.

10.2 STATEMENT OF CONFIDENTIALITY

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

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

11.1 DEFINITIONS OF ADVERSE EVENTS

Adverse event
An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (e.g. an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

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

Serious adverse event
- A serious adverse event is defined as any AE which
- results in death,
- is life-threatening,
- requires in-patient hospitalization, or
- prolongation of existing hospitalization,
- results in persistent or significant disability or incapacity, or
- is a congenital anomaly/birth defect.

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

Medical and scientific judgement should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed above.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse. Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

Adverse Event of Special Interest (AESI)
The term Adverse Event of Special Interest (AESI) relates to any specific AE that has been identified at the project level as being of particular concern for prospective safety monitoring and safety assessment within this study, e.g. the potential for AEs based on knowledge from other compounds in the same class.
No AESIs have been defined for this study.

11.2 ADVERSE EVENT AND SERIOUS ADVERSE EVENT COLLECTION AND REPORTING

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

Collection of AEs
The study design is of non-interventional nature and the study is conducted within the conditions of the approved marketing authorization. Sufficient data from controlled interventional trials are available to support the evidence on the safety and efficacy of the studied BI drug. For this reason, the following AE collection and reporting requirements have been defined.

The following must be collected by the investigator in the (e)CRF from signing the informed consent onwards until the end of the study:

- all adverse drug reaction (ADRs) (serious and non-serious),
- all AEs with fatal outcome

All ADRs, including those persisting after study completion must be followed up until they are resolved, have been sufficiently characterized, or no further information can be obtained.

The investigator carefully assesses whether an AE constitutes an ADR using the information below.

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

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

Arguments that may suggest **a reasonable 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. preexisting 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 diminished).

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

- No plausible time to onset of the event relative to the time of drug exposure is evident (e.g. pre-treatment cases, diagnosis of cancer or chronic disease within days/weeks of drug administration; an allergic reaction weeks after discontinuation of the drug

concerned)

- Continuation of the event despite the withdrawal of the medication, taking into account the pharmacological properties of the compound (e.g. after 5 half-lives).
  Of note, this criterion may not be applicable to events whose time course is prolonged despite removing the original trigger.
- Additional arguments amongst those stated before, like alternative explanation (e.g. situations where other drugs or underlying diseases appear to provide a more likely explanation for the observed event than the drug concerned).
- Disappearance of the event even though the study drug treatment continues or remains unchanged.

Intensity of adverse event

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

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

The intensity of adverse events should be classified and recorded according to the Common Terminology Criteria for Adverse Events (CTCAE) criteria in the (e)CRF.

Pregnancy:

In rare cases, pregnancy might occur in a study. Once a subject has been enrolled into the study, after having taken, the investigator must report any drug exposure during pregnancy, which occurred in a female subject or in a partner to a male subject to the Sponsor by means of Part A of the Pregnancy Monitoring Form. The outcome of the pregnancy associated with the drug exposure during pregnancy must be followed up and reported by means of Part B of the Pregnancy Monitoring Form.

In the absence of a reportable AE, only the Pregnancy Monitoring Form must be completed, otherwise the NIS AE form is to be completed and forwarded as well within the respective timelines.

Expedited Reporting of AEs and Drug Exposure During Pregnancy
The following must be reported by the investigator on the NIS AE form from signing the informed consent onwards until the end of the study:

Type of Report	Timeline
All serious ADRs associated with Spiolto® Respimat®	immediately within 24 hours
All AEs with fatal outcome in patients exposed to Spiolto® Respimat®	immediately within 24 hours
All non-serious ADRs associated with Spiolto® Respimat®	7 calendar days
All pregnancy monitoring forms associated with Spiolto® Respimat®	7 calendar days

The same timelines apply if follow-up information becomes available for the respective events. In specific occasions the Investigator could inform the Sponsor upfront via telephone. This does not replace the requirement to complete and fax the NIS AE form.

Information required

For each reportable adverse event, the investigator should provide the information requested on the appropriate (e)CRF pages and the NIS AE form.

Reporting of related Adverse Events associated with any other BI drug

The investigator is encouraged to report all adverse events related to any BI drug other than the according to the local regulatory requirements for spontaneous AE reporting at the investigator's discretion by using the locally established routes and AE report forms. The term AE includes drug exposure during pregnancy, and, regardless of whether an AE occurred or not, any abuse, off-label use, misuse, medication error, occupational exposure, lack of effect, and unexpected benefit.

11.3 REPORTING TO HEALTH AUTHORITIES

Adverse event reporting to regulatory agencies will be done by the MAH according to local and international regulatory requirements.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The rights of the investigator and of the sponsor with regard to publication of the results of this study are described in the investigator contract. As a general rule, no study results should be published prior to finalization of the Study Report.

13. REFERENCES

R13-3633 Troosters T1, Sciurba F, Battaglia S, Langer D, Valluri SR, Martino L, Benzo R, Andre D, Weisman I, Decramer M. Physical inactivity in patients with COPD, a controlled multi-center pilot-study. Respir Med. 2010 Jul;104(7):1005-11. doi: 10.1016/j.rmed.2010.01.012. Epub 2010 Feb 18

R15-5015 Claudio Tantucci, Denise Modina. Lung function decline in COPD. International Journal of COPD. 2012:7, 95-99.

P13-05794 Tashkin DP, Ferguson GT. Combination bronchodilator therapy in the management of chronic obstructive pulmonary disease. Respir Res (Lond) 14, 49 (2013)

P14-01052 Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease (updated 2014). http://www.goldcopd.org/uploads/users/files/GOLD_Report_2014.pdf (access date: 22 January 2014) ; Global Initiative for Chronic Obstructive Lung Disease (GOLD) (2014)

P10-07776 Bouyssou T, Casarosa P, Naline E, Pestel S, Konetzki I, Devillier P, Schnapp A. Pharmacological characterization of olodaterol, a novel inhaled beta2-adrenoceptor agonist exerting a 24-hour-long duration of action in preclinical models. J Pharmacol Exp Ther 334 (1), 53 - 62 (2010)

P11-07720 Casarosa P, Kollak I, Kiechle T, Ostermann A, Schnapp A, Kiesling R, Pieper M, Sieger P, Gantner F. Functional and biochemical rationales for the 24 -hour-long duration of action of olodaterol. J Pharmacol Exp Ther 337 (3), 600 - 609 (2011)

P13-11467 Lange P, Aumann JL, Derom E, Hamilton A, Tetzlaff K, Ting N, Noord JA van. The 24-h FEV1 time profile of olodaterol QD delivered via Respimat in COPD: results from two 6-week studies. 23rd Ann Cong of the European Respiratory Society (ERS), Barcelona, 7 - 11 Sep 2013

P13-14112 Feldman G, Bernstein JA, Hamilton A, Nivens C, LaForce C. The 24 -hour FEV1 time profile of olodaterol once daily (QD) via Respimat and formoterol twice daily (BID) via Aerolizer in patients with COPD: results from two 6-week studies. Chest 2013, 79th Ann Mtg of the American College of Chest Physicians, Chicago, 26 - 31 Oct 2013. Chest 144 (4) (Suppl), 749A, Abstr (2013)

P13-11346 Ferguson G, Feldman G, Hofbauer P, Hamilton A, Allen L, Korducki L, Sachs P. Lung function efficacy of olodaterol QD delivered via Respimat in COPD patients: results from two 48-week studies. 23rd Ann Cong of the European Respiratory Society (ERS), Barcelona, 7 - 11 Sep 2013

P13-11345 Koch A, Pizzichini E, Hamilton A, Hart L, Korducki L, Salvo MC de, Paggiaro P. Lung function efficacy of olodaterol QD delivered via Respimat vs placebo and

formoterol BID in patients with COPD: two 48-week studies. 23rd Ann Cong of the European Respiratory Society (ERS), Barcelona, 7 - 11 Sep 2013

P13-11341 Koch A, Paggiaro P, Hamilton A, Hart L, Korducki L, Salvo MC de, Pizzichini E. Symptomatic benefit of olodaterol QD delivered via Respimat vs placebo and formoterol BID in patients with COPD: combined analysis from two 48-week studies. 23rd Ann Cong of the European Respiratory Society (ERS), Barcelona, 7 - 11 Sep 2013

P13-14109 Maltais F, Kirsten AM, Hamilton A, Sousa D de, Wang F, Decramer M Evaluation of the effects of olodaterol on exercise endurance in patients with COPD: results from two 6-week studies. Chest 2013, 79th Ann Mtg of the American College of Chest Physicians, Chicago, 26 - 31 Oct 2013 Chest 144 (4) (Suppl), 748A, Abstr (2013)

P10-09337 Bouyssou T, Schnapp A, Casarosa P, Pieper MP. Addition of the new once-daily LABA BI 1744 to tiotropium results in superior bronchoprotection in pre -clinical models. ATS 2010, 106th Int Conf of the American Thoracic Society (ATS), New Orleans, 14 - 19 May 2010. Am J Respir Crit Care Med 181, A4445, Abstr (2010)

P14-12073 Bouyssou T, Casarosa P, Pieper M, Schnapp A, Gantner F. Synergistic bronchoprotective activity of the long-acting beta 2-agonist olodaterol with tiotropium (long-acting M3 antagonist) and ciclesonide (inhaled steroid) on the ovalbumin- induced bronchoconstriction in anaesthetized guinea pigs. ERJ September 1, 2011 vol. 38 no. Suppl 55 3451

P13-02357 Aalbers R, Maleki-Yazdi MR, Hamilton A, Waitere-Wijker S, Pivovarova A, Schmidt O, Bjermer L. Dose-finding study for tiotropium and olodaterol when administered in combination via the Respimat inhaler in patients with COPD. 22nd Ann Cong of the European Respiratory Society (ERS), Vienna, 1 - 5 Sep 2012. Eur Respir J 40 (Suppl 56), 525S - 526S, Abstr P2882 (2012)

P15-03349 Buhl R, Maltais F, Abrahams R, Bjermer L, Derom E, Ferguson G, Flezar M, Hébert J, McGarvey L, Pizzichini E, Reid J, Veale A, Grönke L, Hamilton A, Korducki L, Tetzlaff K, Waitere-Wijker S, Watz H, Bateman E. Tiotropium and olodaterol fixed - dose combination versus mono-components in COPD (GOLD 2–4) Eur Respir J 2015; DOI: 10.1183/09031936.00136014

P15-04531 Kai-Bichael Beeh et al.The 24-h lung-function profile of once-daily tiotropium and olodaterol fixed-dose combination in chronic obstructive pulmonary disease. Elsevier Ltd, 2015. 1094-5539

R15-4559 Katz P, Chen H, Omachi TA, Gregorich SE, Julian L, Cisternas M, Balmes J, Blanc PD The role of physical inactivity in increasing disability among older adults with obstructive airway disease. J Cardiopulm Rehabil Prev 31 (3), 193 - 197 (2011)

R15-4561 Maltais F, LeBlanc P, Simard C, Jobin J, Berube C, Bruneau J, Carrier L, Belleau R Skeletal muscle adaptation to endurance training in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 154, 442 - 447 (1996)

R15-4564 Garcia-Aymerich J, Lange P, Benet M, Schnohr P, Anto JM Regularphysical activity reduces hospital admission and mortality in chronic obstructive pulmonary disease: a population based cohort study. Thorax 61, 772 - 778 (2006)

P13-04267 Cooper CB, Celli BR, Jardim JR, Wise RA, Legg D, Guo J, Kesten S. Treadmill endurance during 2-year treatment with tiotropium in patients with COPD: a randomized trial. Chest 144 (2), 490 - 497 (2013)

P05-09483 Maltais F, Hamilton A, Marciniuk D, Hernandez P, Sciurba FC, Richter K, Kesten S, O'Donnell D Improvements in symptom-limited exercise performance over 8 h with once-daily tiotropium in patients with COPD. Chest 128 (3), 1168 - 1178 (2005)

P94-1346 Bone R, et al. In chronic obstructive pulmonary diseasae, a combination of ipratropium and albuterol is more effective than either agent alone: an85 -day multicenter trial. Chest 105 (5), 1411 – 1419 (1994)

R09-0182 Guidelines for Good Pharmacoepidemiology Practices (GPP). Pharmacoepidemiology and Drug Safety 17, 200 - 208 (2008).

R10-4560 Good Epidemiological Practice (GEP). IEA Guidelines for Proper Conduct of Epidemiological Reseach (2007)

R13-2524 Maltais F, O'Donnell DE, Porszasz J, Clerisme-Beaty E, Guo Z, Paden H, Casaburi R The impact Of GOLD 1 and 2 COPD on self -reported functional limitations, activity, and correlations with symptom-limited exercise compared with age- and gender-matched control subjects. ATS 2013, 109th Int Conf of the American Thoracic Soci ety (ATS), Philadelphia, 17 - 22 May 2013 Am J Respir Crit Care Med 187, A1376, Abstr (2013)

P17-04769 O'Donnell D, Casaburi R, Frith P, Kirsten A, De Sousa D, Hamilton A, Xue W, Maltais F. Effects of combined tiotropium/olodaterol on inspiratory capaci ty and exercise endurance in COPD Eur Respir J. (2017)

P17-06396 Maltais F, O'Donnell DE, Hamilton A, Zhao Y, Casaburi R Comparative measurement properties of constant work-rate cycling and endurance shuttle walking in patients with COPD: data from the T ORRACTO study. ATS 2017, 113th Int Conf of the American Thoracic Society (ATS), Washington, 19 - 24 May 2017 Am J Respir Crit Care Med 195, A5675, Abstr (2017)

R17-3684 Van Dam van Isselt EF, Spruit M, Groenewegen-Sipkema KH, Chavannes NH, Achterberg WP Health status measured by the Clinical COPD Questionnaire (CCQ) improves following post-acute pulmonary rehabilitation in patients with advanced COPD: a prospective observational study. NPJ Prim Care Respir Med. 2014 May 20;24:14007. doi: 10.1038/npjpcrm.2014.7.

R17-3682 Papadopoulos G, Vardavas CI, Limperi M, Linardis A, Georgoudis G, Behrakis P. Smoking cessation can improve quality of life among COPD patients: validation of the clinical COPD questionnaire into Greek. BMC Pulm Med 2011;

R17-3681 Tsiligianni IG, van der Molen T, Moraitaki D, Lopez I, Kocks JW, Karagiannis K, Siafakas N, Tzanakis N Assessing health status in COPD. A head-to-head comparison between the COPD.

R17-0254 Kocks, M. van de Ven, S.M. Uil, J.W.K. van den Berg, G.M. Asijee, T. van der Molen Functional Status measurement in COPD: The value of the functional status domain of the CCQ J.W.H.. THORAX 2006;61(Suppl II):ii40s

R17-0256 Kocks JW1, Tuinenga MG, Uil SM, van den Berg JW, Ståhl E, vander Molen T. Health status measurement in COPD: the minimal clinically important difference of the clinical COPD questionnaire. Respir Res. 2006;7:62.

R04-2815 Van der Molen T, Willemse BWM, Schokker S, ten Haken NHT, Postma DS, Juniper EF: Development, validity and responsiveness of the Clinical COPD Questionnaire. Health Qual Life Outcomes 2003, 1:13

P05-02607 Kozma CM, Slaton TL, Monz BU, Hodder R, Reese PR. Development and validation of a patient satisfaction and preference questionnaire for inhalation de vices. Treat Respir Med. 2005;4(1):41-52.

R17-3683 Miravitlles M, García-Sidro P, Fernández-Nistal A, Buendía MJ, Espinosa de los Monteros MJ, Molina J Course of COPD assessment test (CAT) and clinical COPD questionnaire (CCQ) scores during recovery from exacerbations of chronic obstructive pulmonary disease. Health Qual Life Outcomes. 2013 Aug 29;11:147. doi: 10.1186/1477-7525-11-147.

P17-01597 Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management, and prevention of chronic obstructive lung disease (2017 report). http://goldcopd.org/gold-2017-global-strategy-diagnosis-management-prevention-co pd/ (accessd date: 9 February 2017) ; Global Initiative for Chronic Obstructive Lung Disease (GOLD) (2017)

P15-03349 Buhl R, Maltais F, Abrahams R, Bjermer L, Derom E, Ferguson G et al. Tiotropium and olodaterol fixed-dose combination versus mono-components in COPD (GOLD 2–4). Eur Respir J. 2015; DOI: 10.1183/09031936.00136014 .

ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

The stand-alone documents for this non-interventional study are:

- Informed Consent Form
- Physicians' Global Evaluation (PGE)
- CCQ Questionnaire
- Breathlessness Scale (mMRC)
- Patient Satisfaction and Patient Preference Questionnaire (abbreviated PASAPQ Part 1 + Part 2)
- Statistical Epidemiological Analysis Plan (SEAP)
- Data Management Plan (DMP)
- Pregnancy Monitoring Form
- Serious Adverse Event Report in Non-Interventional Studies (NIS (S)AE Form)
- Publication Plan

All of the above documents will be archived in the Trial Master File in its original English master version.

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Not applicable

ANNEX 3. ADDITIONAL INFORMATION

CCQ Questionnaire

CLINICAL COPD QUESTIONNAIRE

Please **circle** the number of the response that best describes how you have been feeling during the **past week**. (Only **one** response for each question).

On average, **during the past week**, how often did you feel:	never	hardly ever	a few times	several times	many times	a great many times	almost all the time
1. Short of breath **at rest**?	0	1	2	3	4	5	6
2. Short of breath **doing physical activities**?	0	1	2	3	4	5	6
3. **Concerned** about getting a cold or your breathing getting worse?	0	1	2	3	4	5	6
4. **Depressed (down)** because of your breathing problems?	0	1	2	3	4	5	6
In general, **during the past week**, how much of the time:							
5. Did you **cough**?	0	1	2	3	4	5	6
6. Did you **produce phlegm**?	0	1	2	3	4	5	6
On average, **during the past week**, how limited were you in these activities **because of your breathing problems**:	not limited at all	very slightly limited	slightly limited	moderately limited	very limited	extremely limited	totally limited /or unable to do
7. **Strenuous physical activities** (such as climbing stairs, hurrying, doing sports)?	0	1	2	3	4	5	6
8. **Moderate physical activities** (such as walking, housework, carrying things)?	0	1	2	3	4	5	6
9. **Daily activities at home** (such as dressing, washing yourself)?	0	1	2	3	4	5	6
10. **Social activities** (such as talking, being with children, visiting friends/ relatives)?	0	1	2	3	4	5	6

Modified Medical Research Council (mMRC) dyspnea (breathlessness) scale

Please circle the number which best describes your grade of breathlessness.

I only get breathless with strenuous exercise. 0

I get short of breath when hurrying on level ground or walking up a slight hill. 1

On level ground, I walk slower than people of the same age because of breathlessness, or have to stop for breath when walking at my own pace. 2

I stop for breath after walking about 100 yards or after a few minutes on level ground. 3

I am too breathless to leave the house or I am breathless when dressing. 4

Patient Satisfaction Questionnaire (PASAPQ)

PART 1 (abbreviated): RATING OF SATISFACTION WITH INHALER ATTRIBUTES

Instructions: For the following questions, please check the response that best describes how satisfied you are with each of the following items. Please take as much time as you need to answer each question.

How satisfied are you…			Very Dissatisfied	Dissatisfied	Somewhat Dissatisfied	Neither Satisfied nor Dissatisfied	Somewhat Satisfied	Satisfied	Very Satisfied
1.	With the feeling that the inhaled dose goes to your lungs?	Inhaler 1	☐	☐	☐	☐	☐	☐	☐
		Inhaler 2	☐	☐	☐	☐	☐	☐	☐
2.	That the inhaler works reliably?	Inhaler 1	☐	☐	☐	☐	☐	☐	☐
		Inhaler 2	☐	☐	☐	☐	☐	☐	☐
3.	With the ease of inhaling a dose from the inhaler?	Inhaler 1	☐	☐	☐	☐	☐	☐	☐
		Inhaler 2	☐	☐	☐	☐	☐	☐	☐

Patient Satisfaction Questionnaire (PASAPQ)

PART II: RATING OF PREFERENCE AND WILLINGNESS TO CONTINUE WITH INHALER

1. Comparing the two inhalers that you have used during the study, overall, would you prefer to use Inhaler 1 or Inhaler 2?

Please check one box

I prefer Inhaler 1 ☐

I prefer Inhaler 2 ☐

No preference ☐

2. Comparing the two inhalers that you have used during the study, overall, how would you feel about continuing to use Inhaler 1 or Inhaler 2?

Please indicate your willingness to continue using each of the inhalers that you used during the study by providing a value between 0 and 100.

0 indicates that you would not be willing to continue using this inhaler and 100 indicates that you would definitely be willing to continue.

Please write in a number in **each** box that is between 0 and 100.

Inhaler 1 ☐

Inhaler 2 ☐

Both boxes should contain a number between 0 and 100.

Physicians' Global Evaluation (PGE) to be used directly within the eCRF

General condition of the patient at the initial examination (Visit 1)

Please mark with a cross as applicable

Poor	Satisfactory	Good	Excellent
1 2	3 4	5 6	7 8

General condition of the patient after approximately 6 weeks of treatment (Visit 2)

Please mark with a cross as applicable

Poor	Satisfactory	Good	Excellent
1 2	3 4	5 6	7 8