Boehringer Ingelheim

Non-interventional Study Protocol

Document Number:	**c29837867-04**
BI Study Number:	1237-0098
BI Investigational Product(s):	Spiolto® Respimat® (tiotropium bromide plus olodaterol)
Title:	Quality of life and preference of COPD patients after Switching from Tiotropium monotherapy (Spiriva® Handihaler®) to dual therapy with Tiotropium bromide plus Olodaterol (Spiolto® Respimat®) under real life conditions in Greece (ELLACTO II study)
Brief lay title	Quality of life in Chronic Obstructive Pulmonary Disease (COPD) patients after switching to tiotropium plus olodaterol fixed dose combination in Greece
Protocol version identifier:	Final Version 4.0
Date of last version of protocol:	09 Jul 2021
PASS:	No
EU PAS register number:	Study not registered
Active substance:	R03AL06 (Tiotropium bromide plus 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 authorisation holder(s):	Market Authorization Holder: [redacted] Study Initiator: [redacted]
Joint PASS:	No

Research question and objectives:	The primary objective of this non-interventional study (NIS) is to evaluate changes within 3 months in quality of life according to health status evaluated with the COPD Assessment Test (CAT) in COPD patients who have recently switched (within one week) from tiotropium monotherapy (Spiriva® Handihaler®) to dual therapy with tiotropium bromide plus olodaterol (Spiolto® Respimat®), in the Greek private and public sector pulmonary offices and clinics. The secondary objectives are to evaluate change in the proportion of patients with CAT ≥10 (representing impaired health status) within three-months after the switch, to evaluate changes in quality of life (QoL) according to EQ-5D-5L questionnaire within three-months after the switch, to describe the [redacted] and clinical characteristics of COPD patients who have switched, to describe treatment adherence of COPD patients according to Simplified Medication Adherence Questionnaire (SMAQ) and patients' satisfaction and preference with inhaler devices according to Patient Satisfaction Questionnaire (PASAPQ) before and after the switch and to describe patients' dyspnea status according to modified Medical Research Council (mMRC) scale within three months after the switch.
Country(-ies) of study:	Greece
Author:	[redacted]
In case of PASS, add: **MAH Contact Person:**	N/A
In case of PASS, add: **<EU-QPPV:>**	N/A
In case of PASS, add: **<Signature of EU-QPPV:>**	N/A
Date:	09 Jul 2021

1. TABLE OF CONTENTS

[redacted]

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2. LIST OF ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse Event
AESI	Adverse Event of Special interest
BI	Boehringer Ingelheim
CA	Competent Authority
CAT	COPD Assessment Test
CCDS	Company Core Data Sheet
CI	Confidence Interval
CTM	Clinical Trial Manager
COPD	Chronic Obstructive Pulmonary Disease
CRA	Clinical Research Associate
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
CTP	Clinical Trial Protocol
eCRF	Electronic Case Report Form
DMP	Data Management Plan
EMA	European Medicines Agency
ENCePP	European Network of Centers for Pharmacoepidemiology and Pharmacovigilance
EQ-5D-5L	EuroQoL-5D-5L questionnaire
EU	European Union
FDA	Food and Drug Administration
FDC	Fix Dose Combination
FEV1	Forced expiratory volume in one second
GCP	Good Clinical Practice
GEP	Good Epidemiological Practice
GPP	Good Pharmacoepidemiology Practice
GVP	Good Pharmacovigilance Practices
GOLD	Global Initiative for Chronic Obstructive Lung Disease
HCPs	Health Care Professionals
IB	Investigator's Brochure
ICH	International Conference on Harmonization
ICS	Inhaled Corticosteroids
IEC	Independent Ethics Committee
ISF	Investigator Site File
LABA	Long-acting $beta_2$ adrenoceptor agonist
LAMA	Long-acting muscarinic antagonist
MAH	Marketing Authorization Holder
MedDRA	Medical Dictionary for Drug Regulatory Activities
mMRC	Modified Medical Research Council
NIS	Non-Interventional Study
PASAPQ	Abbreviated Patient Satisfaction Questionnaire
PASS	Post-Authorization Safety Study
PGE	Physician's Global Evaluation

SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SDV	Source data verification
SMAQ	Simplified Medication Adherence Questionnaire
SmPC	Summary of Product Characteristics
WHO	World Health Organization

3. RESPONSIBLE PARTIES

Study Sponsor	[redacted]
Therapeutic Area Head Respiratory Medicine (TAH)	
Team Member Medical Affairs (TM MA)	
Team Member Epidemiology (TM Epi)	
Head Global Epidemiology (H GEpi)	
Therapeutic Area Head Risk Management (TAH RM), and Pharmacovigilance Working Group (PVWG) chairperson	

4. ABSTRACT

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: Spiolto® Respimat®			
Name of active ingredient: R03AL06 Tiotropium bromide plus olodaterol			
Protocol date: 04 June 2020	**Study number:** 1237-0098	**Version/Revision:** Final Version 4.0	**Version/Revision date:** 09 Jul 2021
Title of study:	Quality of life and preference of COPD patients after switching from Tiotropium monotherapy (Spiriva® Handihaler®) to dual therapy with Tiotropium bromide plus Olodaterol (Spiolto® Respimat®) under real life conditiOns in Greece (ELLACTO II study)		
Rationale and background:	Both pharmacologic and non-pharmacologic therapies in chronic obstructive pulmonary disease (COPD) should be guided, mainly, by disease severity, although the aim of any treatment is to improve patient symptoms, decrease exacerbations, and improve patient function and quality of life. Within the LABA/LAMA combinations, efficacy and safety of tiotropium plus olodaterol fixed-dose combination (FDC) compared with the mono-components was evaluated in patients with moderate to severe COPD in clinical trials, and demonstrated significant improvements in lung function and health-related quality of life measured by the St George Questionnaire. The COPD Assessment Tool (CAT) has shown, that it has properties, very similar to much more complex health status questionnaires. Only since the last years, it has been incorporated as the preferred measure of symptomatic impact of COPD into clinical assessment schemes. Due to the lack of real-world evidence data on LABA/LAMA combinations in Greece, this non-interventional study (NIS) plans a prospective analysis of the change in the quality of life and health status in COPD patients who have recently switched (within one week) from tiotropium monotherapy (Spiriva® Handihaler®) to dual therapy with tiotropium bromide plus olodaterol (Spiolto® Respimat®) in Greece.		

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Research question and objectives:	**Primary objective** The primary objective of this non-interventional study (NIS) is to evaluate changes within 3 months in quality of life according to health status evaluated with the COPD Assessment Test (CAT) in COPD patients who have recently switched (within one week) from tiotropium monotherapy (Spiriva® Handihaler®) to dual therapy with tiotropium bromide plus olodaterol (Spiolto® Respimat®), in the Greek private and public sector pulmonary offices and clinics. **Secondary objectives** The secondary objectives are - To evaluate change in the proportion of patients with CAT ≥10 (representing impaired health status) within three months after the switch. - To evaluate changes in quality of life (QoL) according to EQ-5D-5L questionnaire within three-months after the switch. - To describe treatment adherence of COPD patients according to Simplified Medication Adherence Questionnaire (SMAQ). - To describe patients' satisfaction and preference with inhaler devices according to Patient Satisfaction Questionnaire (PASAPQ) before and after the switch. - To describe patients' dyspnea status according to modified Medical Research Council (mMRC) scale within three months after the switch.		
Study design:	Non-interventional, 3-months prospective, two visits, single-cohort, multicenter, nationwide study in patients with stable COPD under maintenance therapy with tiotropium monotherapy (Spiriva® Handihaler®) who, according to their treating physician, have recently required a switch (within one week) to dual therapy with tiotropium bromide plus olodaterol (Spiolto® Respimat®) in the Greek private and public sector pulmonary offices and clinics.		

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Population:	COPD patients who have been using tiotropium administered with Spiriva® Handihaler® for at least 3 months before the decision to switch to a combination therapy with tiotropium bromide plus olodaterol administered with Spiolto® Respimat® has been made. In all cases, the decision to switch the treatment strategy and the initiation of the combination therapy with tiotropium bromide plus olodaterol will be previous and completely independent from the initiation of this non-interventional study. Additionally, the decision of the treating physician should be taken according to the daily clinical practice in the corresponding center.		
Variables:	Patient [redacted] COPD history and clinical characteristics (including exacerbations) Respiratory comorbidities and allergies Other comorbidities Current and past COPD therapies Relevant concomitant medications COPD Assessment Test (CAT) Quality of life based on EQ-5D-5L questionnaire Simplified Medication Adherence Questionnaire (SMAQ) Breathlessness based on Modified British Medical Research Council (mMRC) Dyspnea Scale Patient Satisfaction and Preference using the abbreviated Patient Satisfaction Questionnaire (PASAPQ) Assessment of inhaler handling in daily use [redacted] Adverse drug reactions (ADRs), fatal adverse events (AEs) and pregnancies		

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Data sources:	Patient medical records (paper and/or electronically) and patient reported outcomes from 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 medical records. 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 study the following has to be completed in both study visits: To be completed by the physician: - Patient [redacted] (only at Visit 1) - Patient [redacted] files (including comorbidities and concomitant medications) - [redacted] To be completed by the patient at Visit 1 and Visit 2: - COPD Assessment Test (CAT) - EQ-5D-5L questionnaire - Modified Medical Research Council (mMRC) questionnaire To be completed by the patient only at Visit 2 (3-month visit): - Simplified Medication Adherence Questionnaire (SMAQ) - Abbreviated Patient Satisfaction Questionnaire (PASAPQ)		
Study size:	Approximately 1500 COPD patients will be recruited by 148 office-based pulmonologists and from 2 Hospital pulmonary clinics throughout Greece. Each investigator will recruit up to 10 eligible patients in a consecutive manner who have recently switched (within one week) from Spiriva® Handihaler® to Spiolto® Respimat® according to the daily clinical practice in the center.		

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Data analysis:	**Primary outcome** Mean change in patient's quality of life (QoL) according to the total CAT score within three-months after the switch from Spiriva® Handihaler® to Spiolto® Respimat® according to the daily clinical practice. **Secondary outcomes:** 1. Change in the proportion of patients with CAT ≥10 (representing impaired health status) within three months after the switch 2. Mean change from baseline in the total EQ VAS within three-months after the switch 3. Proportion of patients that change (improve/worsen) each of the 5 dimensions of the EQ-5D-5L within three-months after the switch 4. Rate of t adherence to medication of COPD patients according to the Simplified Medication Adherence Questionnaire (SMAQ) three-months after the switch 5. Mean total score in abbreviated Patient Satisfaction Questionnaire (PASAPQ; first 13 questions of Part 1) (patients' satisfaction with inhaler devices) three-months after the switch 6. Mean score of overall satisfaction according to Question 14 of PASAPQ (Part 1) three-months after the switch 7. Proportion of preference (Spiriva® Handihaler® vs Spiolto® Respimat®) according to PASAPQ (Part 2) three-months after the switch. 8. Mean score of willingness to continue with inhaler (Spiolto® Respimat®) according to PASAPQ (Part 2) three-months after the switch 9. Mean change of patients' dyspnea status according to the modified Medical Research Council (mMRC) scale within three- months after the switch		

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	For the primary outcome, mean and 95% confidence interval will be presented. Primary and secondary outcome variables will be summarized and compared between the baseline visit (based on previous tiotropium monotherapy using Spiriva® Handihaler®) and the 3-months study visit after the switch to tiotropium bromide plus olodaterol (Spiolto® Respimat Baseline data analysis will be carried out. Comorbidities, [redacted] information and clinical characteristics will be described for the overall population. All categorical variables will be summarized in frequency and percentage. The continuous variables will be reported by sample statistics: n (number of observations), number of missing data, mean, standard deviation (SD), minimum, first quartile (Q1), median, third quartile (Q3), and maximum. For the primary analysis, no treatment of missing data is planned except the imputation using the last-observation carried forward [LOCF] method if any post-baseline value is available in patients who discontinued before three months and for whom the value will be set as the last available measure. [redacted]		
Milestones:	Start of data collection: Feb 2021 End of enrolment period (9 months): Nov 2021 End of data collection: Feb 2022 Final report of study results: Sep 2022		

5. AMENDMENTS AND UPDATES

Number	Date	Section of study protocol	Amendment or update	Reason
1	20 July 2020	N/A	EQ-5D-3L questionnaire was replaced by EQ-5D-5L questionnaire	Typo error
2	20 July 2020	N/A	Information about number of patients and sites were corrected with 1500 COPD patients from approximately 150 sites (around 148 office-based pulmonologists and 2 Hospital pulmonary	Compliance in document
3.	20 July 2020	RESPONSIBLE PARTIES	**Study Sponsor** Boehringer-Ingelheim Ellas **Therapeutic Area Head Respiratory Medicine (TAH)** [redacted] **Team Member Medical Affairs (TM MA)** [redacted] **Team Member Epidemiology (TM Epi)** [redacted] **Head Global Epidemiology (H GEpi)** [redacted] **Therapeutic Area Head Risk Management (TAH RM), and Pharmacovigilance Working Group (PVWG)** [redacted] [redacted]	Update with new study's information

Number	Date	Section of study protocol	Amendment or update	Reason
4.	19 Nov 2020	6.MILESTONES	IRB/IEC approval: January 2021 Start of data collection: January 2021 End of enrolment period: July 2021 End of data collection: October 2021 Final report of study results: June 2022	Update with new timelines
5.	09 Jul 2021	6.MILESTONES	IRB/IEC approval: January 2021 Start of data collection: February 2021 End of enrolment period: November 2021 End of data collection: February 2022 Final report of study results: September 2022	Update with new timelines

6. MILESTONES

The following table estimated timelines for the milestones of this study:

Milestone	**Planned Date**
IRB/IEC approval	January 2021
Start of data collection	February 2021
End of enrolment period	November 2021
End of data collection	February 2022
Registration in the EU PAS register	N/A
Final report of study results	September 2022

7. RATIONALE AND BACKGROUND

7.1 CURRENT COPD MANAGEMENT AND ASSESSMENT

Both pharmacologic and non-pharmacologic therapies in chronic obstructive pulmonary disease (COPD) should be guided, mainly, by disease severity, although the aim of any treatment is to improve patient symptoms, decrease exacerbations, and improve patient activity and quality of life (1).

The contribution of physical inactivity to disability in COPD and its impact on quality of life and health status is difficult to be distinguished from disease progression. However, it is clear that quality of life and health status is significantly lower in patients with COPD (2,3), evidencing that health status should be measured in addition to lung function in those patients in order to reach the management goals (2).

COPD prevents patients from carrying out daily activities due to exercise intolerance, which is often attributed to limited pulmonary function. Additionally, this inactivity may be related to avoidance of exertion as a result of fear of dyspnea. Furthermore, data from a study of 434 patients with COPD demonstrated that physical inactivity and fatigue is strongly correlated with health status and quality of life in its mental and physical components. Moreover, multivariate models adjusting for covariates, shown that increased fatigue and decreased physical and mental dimensions of health status were all associated to mortality in subjects with COPD, but not in non-COPD (4).

Treatment recommendations in GOLD report and NICE guidelines has based on symptoms and exacerbation history. GOLD assessment tool has divided COPD patients in four GOLD groups: A, B, C and D, which have had different recommendation for medication. Current international guidelines for COPD recommended long-acting inhaled bronchodilators, including β2-agonists (LABA) and anti-muscarinic antagonists (LAMA) as first choice maintenance therapies in the treatment of COPD for GOLD B and C, D groups (1). LABA/LAMA fixed dose combination is recommended as a choice for group D (symptomatic frequent exacerbator) and may be considered as the initial choice for group B patients who have severe breathlessness.

Most studies with LABA/LAMA combinations have been performed in patients with limited rate of exacerbations (5). One study (6) in patients with a history of exacerbations indicated that a combination of long-acting bronchodilators is more effective than long-acting bronchodilator monotherapy for preventing exacerbations. Another study (7) in patients with a history of exacerbations confirmed that a LABA/LAMA decreased exacerbations to a greater extent than a combination of an inhaled corticosteroid (ICS) and a LABA.

Within the LABA/LAMA combinations, efficacy and safety of tiotropium plus olodaterol fixed-dose combination (FDC) compared with the mono-components was evaluated in patients with moderate to very severe COPD in two replicate, randomised, double-blind, parallel-group, multicentre, phase III trials. These studies demonstrated significant improvements in lung function and health-related quality of life (QoL) with once-daily tiotropium plus olodaterol FDC versus mono-components over one year in patients with moderate to very severe COPD (8).

Besides the efficacy evaluation based on lung function, several instruments and scales have been designed to provide a simple and reliable measure of health status in COPD patients to

aid their assessment and promote communication between patients and clinicians. The COPD Assessment Tool (CAT) has showed that it has properties very similar to much more complex health status questionnaires, such as the St George's Respiratory Questionnaire (SGRQ) (9). A recent systematic review confirmed that the CAT provides reliable measurement of health status and is responsive to change with treatment and exacerbations (10). Only since the last years it has been incorporated as the preferred measure of symptomatic impact of COPD into clinical assessment schemes. It has been included in the COPD Foundation guide (11) and in the GOLD guideline to healthcare professionals (1).

Together with the CAT and other tools for the evaluation of COPD related health status and QoL, the assessment of the adherence to the treatment has an enormous impact on COPD patient's status. Adherence to COPD therapy is still low, despite it has been directly associated with up to 10-fold higher risk of exacerbations leading to hospitalization (12). Additionally, the specific attributes of inhaler devices and [redacted] can influence patient satisfaction and treatment compliance, and may ultimately impact on clinical outcomes of COPD (13).

7.2 TIOTROPIUM BROMIDE PLUS OLODATEROL (SPIOLTO RESPIMAT)

Tiotropium bromide plus olodaterol fix dose combination (FDC) is an aqueous solution of tiotropium bromide and olodaterol contained in a cartridge. It is administered by using the Respimat® inhaler. Although no clinically relevant differences regarding patient and prescribing characteristics were revealed (14), a recent review of tiotropium trials in COPD supports the use of the marketed once-daily dose of Respimat® for the maintenance treatment of patients with COPD compared with the HandiHaler® inhaler (15). One cartridge is used per inhaler, which is inserted into the device prior to first use. In pivotal clinical trials and for the marketed product, the clinical dose consists of 5 microgram tiotropium and 5 microgram olodaterol given as two puffs once daily, at the same time of the day. The Respimat® inhaler uses mechanical energy to create a soft mist which is released over a period of approximately 1.5 seconds.

Tiotropium bromide plus olodaterol FDC 5/5 µg significantly improved FEV1 AUC0-3, FEV1 AUC0-24, and trough FEV1 response versus the mono-components in two recent studies including moderate to very severe COPD patients ($p<0.0001$ for all comparisons) (8,16). Statistically significant improvements in SGRQ total score versus the mono- components were also demonstrated for the FDC 5/5 µg ($p<0.0001$ vs olodaterol and $p=0.0001$ vs tiotropium) (8).

The tiotropium bromide plus olodaterol FDC 5/5 µg has also 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 events in the tiotropium bromide plus olodaterol FDC treatment group were similar to the components alone (8). 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 (8).

In conclusion, the clinical trials conducted to date have shown tiotropium bromide plus 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 (8,16). 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 benefits of tiotropium bromide plus olodaterol FDC have been studied in controlled Phase III trials, however, data regarding quality of life and health status when treated with Spiolto® Respimat® in a real world setting is not available, especially in patients that have switched from previous monotherapy with tiotropium.

Due to the lack of real-world evidence data on LABA/LAMA combinations in Greece, this non-interventional study (NIS) plans a prospective analysis of COPD patients who switch from tiotropium monotherapy (Spiriva® Handihaler®) to dual therapy with tiotropium bromide plus olodaterol (Spiolto® Respimat®) in the Greek private and public sector pulmonary offices and clinics, and specifically to assess the change in the quality of life in relation to health status variations in this target population of COPD patients.

The results from this study will be used to scientifically support the improvement on the impact of COPD on the patient's health and quality of life after three months of dual therapy with tiotropium bromide plus olodaterol (Spiolto® Respimat®), as well as to understand how switch of therapy in COPD patients who initiated this dual therapy after using Spiriva® Handihaler® is approached by the Greek healthcare providers.

8.2 STUDY OBJECTIVES

8.2.1 Primary objective

The primary objective of this non-interventional study (NIS) is to evaluate changes within 3 months in quality of life according to health status evaluated with the COPD Assessment Test (CAT) in COPD patients who have recently switched (within one week) from tiotropium monotherapy (Spiriva® Handihaler®) to dual therapy with tiotropium bromide plus olodaterol (Spiolto® Respimat®), in the Greek private and public sector pulmonary offices and clinics.

8.2.2 Secondary objectives

The secondary objectives are:

- To evaluate change in the proportion of patients with CAT ≥10 (representing impaired health status) within three months after the switch
- To evaluate changes in quality of life (QoL) according to EQ-5D-5L questionnaire within three-months after the switch
- To describe treatment adherence of COPD patients according to Simplified Medication Adherence Questionnaire (SMAQ)
- To describe patients' satisfaction and preference with inhaler devices according to Patient Satisfaction Questionnaire (PASAPQ) before and after the switch
- To describe patients' dyspnea status according to modified Medical Research Council (mMRC) scale within three months after the switch

9. RESEARCH METHODS

9.1 STUDY DESIGN

This is a non-interventional, 3-months prospective, two visits, single-cohort, multicenter, nationwide study in patients with stable COPD who have been using maintenance therapy with tiotropium monotherapy (Spiriva® Handihaler®) for at least 3 months before, and for whom, according to their treating physician, a recent switch (within one week) to dual therapy with tiotropium bromide plus olodaterol (Spiolto® Respimat®) have been required, in the Greek private and public sector pulmonary offices and clinics.

In all cases, the decision to switch the treatment strategy from Spiriva® Handihaler® to Spiolto® Respimat® will be previous and completely independent from the initiation of this non-interventional study. Additionally, the decision of the treating physician will be according to the daily clinical practice in the corresponding center.

The intended Health Care Professionals (HCPs) are office-based pulmonologists and practice physicians from Hospital pulmonary clinics, who are treating symptomatic COPD patients every day, being aware that most of their patients suffer from the physical restrictions induced by the disease *per se*.

Enrolment of patients will not be competitive. Each investigator will recruit up to 10 eligible patients in a consecutive manner from those who come to control visits and have been using tiotropium administered with Spiriva® Handihaler® for at least 3 months before the decision to switch to a combination therapy with tiotropium bromide plus olodaterol administered with Spiolto® Respimat® has been made. The enrolment period will last for a maximum of 9 months. All centers will stop recruitment once the total sample size of 1500 patients is achieved or, alternatively, at the end of the 9-months planned period of enrolment.

The study will collect data from two visits: baseline (within one week after the time of treatment switch) and approximately at 3 months (±2 weeks, according to clinical practice) (see Figure 1). In case of premature discontinuation of Spiolto® Respimat® for any reason (including treatment discontinuation, withdrawal of patient willingness to participate, or unexpected patient problems to continue with the study), an additional unscheduled visit will be performed, if possible according to clinical practice. In this visit, the specific reason for discontinuation will be assessed and all the effectiveness and quality of life variables will be collected as planned for the regular final visit at 3 months (see Table 1).

Study results will be used to document the effectiveness of Spiolto® Respimat® in reducing the impact of COPD on patient's life. The biggest advantage of the current proposal is that the CAT is a well-known and widespread questionnaire, which is also included in the most recent GOLD guidelines (1). The CAT questionnaire also exhibits high reproducibility and is independent of various languages, as well (17,18).

Figure 1. Study scheme

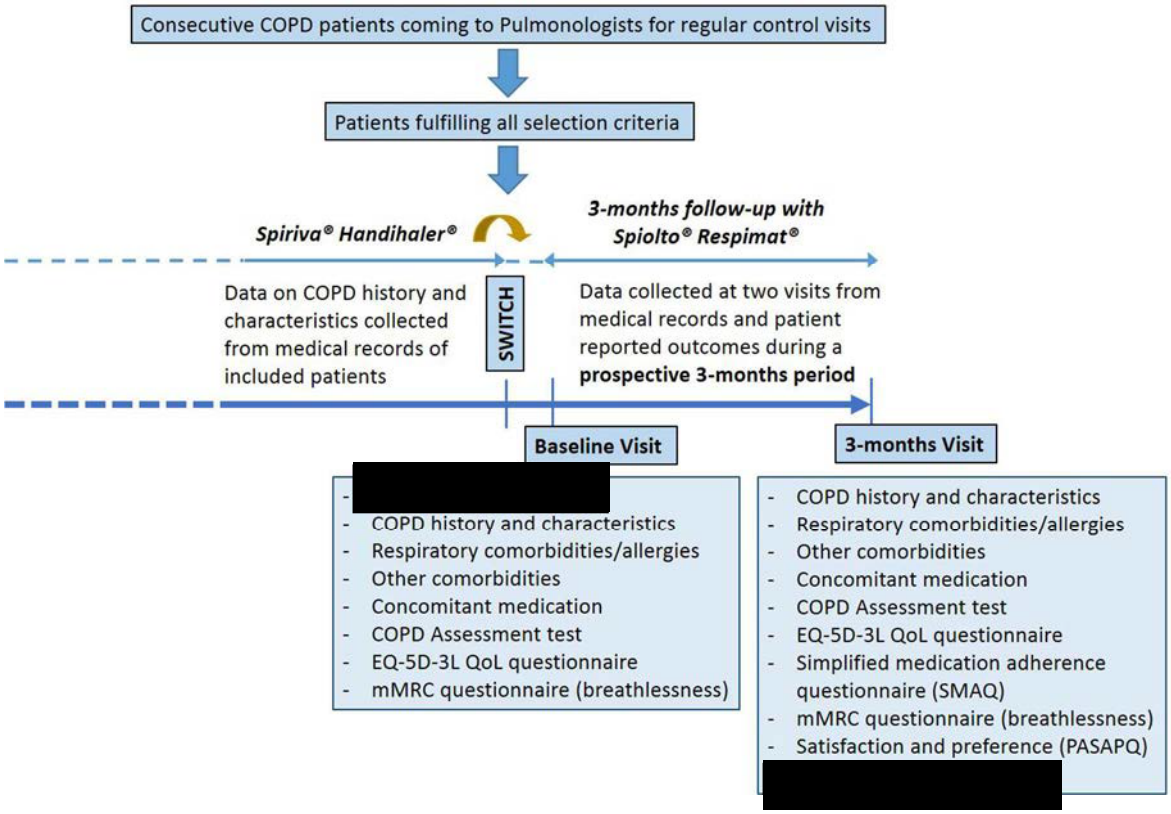

Table 1. Visit flow chart and data collection parameters

Parameter	**Visit 1** (baseline visit)	**Visit 2** (3 months ± 2 weeks after baseline visit)[1]	**Unscheduled Visit** (in case of premature discontinuation)
Informed Consent	X		
Inclusion / Exclusion Criteria	X		
[redacted]	[redacted]		
COPD history and clinical characteristics	X	X	X
History of exacerbations in the year before	X		
History of exacerbations since baseline		X	X
Past COPD therapies (12 months before Visit 1)	X		
COPD related and other relevant concomitant medication	X	X	X
Respiratory comorbidities and allergies	X	X	X
Concomitant diseases / Comorbidities	X	X	X
[redacted]	[redacted]		
COPD severity based on GOLD assessment[2]	X	X	X
COPD Assessment Test (CAT)	X	X	X
EQ-5D-5L questionnaire	X	X	X
Simplified Medication Adherence Questionnaire (SMAQ)		X	X
Modified British Medical Research Council (mMRC) questionnaire	X	X	X
Abbreviated Patient Satisfaction Questionnaire (PASAPQ)		X	X
[redacted]		[redacted]	[redacted]
Adverse Drug Reactions (serious and non-serious), fatal AEs, pregnancy	X	X	X
Rationale for Spiolto® Respimat® treatment discontinuation (if applicable)		X	X
Continuation or discontinuation of treatment with Spiolto® Respimat® after the study (yes/no)		X	X

[1] Premature discontinuation of the study will be considered for any reason including treatment discontinuation, withdrawal of patient willingness to participate, or unexpected patient problems to continue with the study.

[2] GOLD patient group (B, C or D) will be automatically calculated within the eCRF based on available exacerbation history, mMRC and CAT score.

9.2 SETTING

It is planned that data of approximately 1500 COPD patients from approximately 150 sites (around 148 office-based pulmonologists and 2 Hospital pulmonary clinics) throughout Greece will be collected. Each investigator will recruit up to 10 eligible patients in a consecutive manner who have been using tiotropium administered with Spiriva® Handihaler® for at least 3 months before the decision to switch to a combination therapy with tiotropium bromide plus olodaterol administered with Spiolto® Respimat® has been made, according to the daily clinical practice in the corresponding site.

9.2.1 Study sites

Patients will undergo visits 1 and 2 in private practice services and Hospital Pulmonary Clinics (centers) disposed by pulmonologists who will participate in the study.

9.2.2 Study population

Approximately 1500 patients with chronic obstructive pulmonary disease (COPD) who have recently switched (within one week) from Spiriva® Handihaler® to Spiolto® Respimat® according to the daily clinical practice in the corresponding site, are to be observed by approximately 148 pulmonologists in the setting of private practice and 2 Hospital Pulmonary Clinics all over Greece. Hospital Pulmonary Clinics will act as coordinating sites of the study.

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 switch treatment to Spiolto® Respimat®. See also the latest Summary of Product Characteristics of Spiolto® Respimat®.

Every physician should enroll the first consecutive patients presented for regular control visits immediately after the switch to Spiolto® Respimat®. As a consequence, enrolment of patients will not be competitive and each investigator will recruit up to 10 eligible patients in a consecutive manner up to the moment when the total sample size of 1500 patients is achieved or, alternatively, until the end of the 6-months planned period of enrolment.

The decision to treat will be taken independently of participation in this NIS, according to the daily clinical practice in the site, and will be made before participation is considered. Additionally, enrolled patients in the current NIS have to be already taking the new medication before the inclusion in the study is considered by the study investigators.

Inclusion criteria:

1. Female and male patients ≥40 years of age
2. Patients diagnosed with COPD who have been using tiotropium administered with Spiriva® Handihaler® for at least 3 months before a recent switch (within last week) to a combination therapy with tiotropium bromide plus olodaterol administered with Spiolto® Respimat® has been made
3. Written informed consent prior to participation

4. Patient should be able to read, comprehend and complete study questionnaires

Exclusion criteria:

1. Patients with contraindications according to Spiolto® Respimat® SmPC
2. Patients who have been treated with inhaled corticosteroids (ICS) as maintenance therapy* or with a LABA/LAMA combination (free or fixed dose) in the previous 6 weeks

   **Note: patients with temporary corticosteroids (CS) use during acute exacerbations in the previous 6 weeks can enter the study*
3. Patients who have been treated with Spiriva® Respimat®, with other LAMA different than Spiriva®, or with a combination of Spiriva®+LABA/ICS in the previous 6 weeks
4. Patients diagnosed with asthma or with asthma COPD overlap syndrome (ACO)
5. Patients for whom availability at the enrolling site during the planned study period of approximately 3 months is not possible
6. Pregnancy and lactation
7. Patients currently listed for lung transplantation
8. Current participation in any clinical trial or any other non-interventional study of a drug or device.
9. Patients who initiated the treatment with tiotropium bromide plus olodaterol older than 7 days before their enrolment in the present study.

A subject screening log should be kept at the site, recording basic information (e.g. initials, gender, date of birth, reason for not enrolling the patient etc.) on all patients who were invited to participate in the study, with the information on the eligibility (or reasons for non- eligibility) and date of signed informed consent. In the case of refusal, reasons for refusal should be given. In addition, a log of all patients included into the study (i.e. having given informed consent) will be maintained in the study file at the study site.

9.2.3 Study visits

The enrolment period of the study will last for a maximum of 9 months. Enrolled patients will undergo two study visits: visit 1 (baseline visit) during screening and enrolment, and visit 2 (follow up visit) 3 months (±2 weeks) after the baseline visit. Instead of the regular visit 2 at 3-months, an unscheduled visit will take place in case of premature discontinuation to assess the specific reason for discontinuation, to complete main data collection parameters and 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).

Patients will be automatically discontinued from the study immediately after the treatment of interest in the study has been discontinued.

Additional specific withdrawing reasons for discontinuing a patient from this NIS are: voluntary discontinuation by the patient who is at any time free to withdraw from the study, any situation where the investigator believes that the continuation in the study may be detrimental to the patient's health, and if a patient is included in an interventional clinical trial at any time during his/her participation in this NIS.

9.3 VARIABLES

9.3.1 List of variables

In this NIS, the following data collection about the changes after the switch from a maintenance therapy with tiotropium monotherapy (Spiriva® Handihaler®) to dual therapy with tiotropium bromide plus olodaterol (Spiolto® Respimat®) on quality of life and health status in 1500 COPD patients treated in the Greek private and public sector pulmonary offices and clinics will be collected in an e-CRF.

The data collection both at the baseline visit (immediately after the switch) and at 3 months visit (three months later) will consist of the following list of variables:

[redacted]

- ***COPD history and clinical characteristics at baseline and changes up to 3-months visit***:
  Time since COPD diagnosis
  COPD severity based on GOLD assessment (B, C, D group), if available
  COPD: Chronic bronchitis/Emphysema/Other COPD
  Smoking history and current status
  Eosinophilia
  FEV1/FVC ratio, if available
  History of exacerbations in the year before baseline visit and between baseline and 3-months visit
- ***Respiratory comorbidities and allergies at baseline and changes up to 3-months visit:***
  Pneumonia
  Allergic rhinitis
  Bronchiectasis

Lung diseases due to external agents

- ***Comorbidities at baseline and changes up to 3-months visit***:
  Diabetes mellitus
  Osteoporosis
  Cardiovascular diseases (including heart failure, atrial fibrillation and other arrhythmias)
  Malignancies
  Anxiety/depression
  Insomnia
  Pulmonary artery hypertension
  Sleep apnea
  Gastroesophageal reflux disease
  Hemolytic anemia
  Atopy
  Sinusitis
  Emphysema
- ***Current and past COPD therapies*** (in the period of one year before enrolment)
- ***Relevant concomitant medications at baseline and changes up to 3-months visit***:
  Use of concomitant inhalers
  Other concomitant medications
- [redacted])
- ***COPD Assessment Test (CAT)*** (9) (see ANNEX 3)

  The CAT is a patient-completed questionnaire assessing globally the impact of COPD (cough, sputum, dysnea, chest tighteness) on health status. It is a unidimensional score based on 8 items each of them scaling from 0 to 5.

  The measurement properties and responsiveness of the instrument were very similar to those of the more complex and longer St George's Respiratory Questionnaire (SGRQ). Further research has supported these findings and established the CAT as a valuable measure of health status in research (9,10,19–21). Following extensive translation and linguistic validation, the measurement properties and responsiveness of the CAT have been evaluated in many different countries and found to be similar (9,10,19–21).

  Range of CAT scores from 0–40. Higher scores denote a more severe impact of COPD on a patient's life. The difference between stable and exacerbation patients was five units. No target score represents the best achievable outcome, however, CAT scores <10 corresponding to mild impact on patients life are usually considered those representing patients without impaired health status (21,22).

- ***EQ-5D-5L questionnaire*** (23,24) (see ANNEX 3)

  The EQ-5D-5L questionnaire is a well-established and commonly used tool for the measurement of a patients QoL. The EQ-5D-5L essentially consists of two parts: the EQ-

5D descriptive system and the EQ visual analogue scale (EQ VAS). The questionnaire was translated and validated for more than 170 languages.

The EQ-5D-5L descriptive system comprises five dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression). Each dimension has three levels (no problems, some problems, and extreme problems) and was self-reported by the patient. The patient's decision results into a 1-digit number that expresses the level selected for that dimension.

The EQ VAS records the patient's self-rated health on a vertical visual analogue scale where the endpoints are labelled 'best imaginable health state' and 'worst imaginable health state'. The VAS can be used as a quantitative measure of health outcome that reflects the patient's own judgement.

- ***Simplified medication adherence questionnaire (SMAQ)*** (25) (see ANNEX 3)

  This tool is a short and simple questionnaire based on questions posed directly to the patient regarding his/her medication-taking habits, which was originally validated for the measurement of adherence in patients on anti-retroviral treatment (25). The SMAQ has been extensively used for evaluating compliance with treatment for different chronic conditions.

  The aim is to assess whether the patient adopts correct attitudes in relation to the treatment for his disease. It is assumed that if the attitudes are incorrect, the patient is not compliant. It has the advantage that it provides information about the causes of non-compliance. The patient is considered as compliant if all questions are answered correctly.

- ***Modified British Medical Research Council (mMRC) Dyspnea Scale (26)*** (ANNEX 3)

  The mMRC Dyspnea Scale quantifies disability attributable to breathlessness, and is useful for characterizing baseline dyspnea in patients with respiratory diseases, especially COPD.

  It consists of a five-level rating scale based on the patient's perception of dyspnea in daily activities. For patients with COPD, it is a simple and valid tool to assess disability (27), and has been reported to be more relevant to patients' health and psychological status than FEV1 (28).

- ***Patient Satisfaction and Preference*** (29) (see ANNEX 3)

  Patient satisfaction with Respimat® will be measured with the part 1 of the abbreviated Patient Satisfaction Questionnaire (PASAPQ) (29). The patient preference Spiriva® Handihaler® vs Spiolto® Respimat® will be measured using PASAPQ (part 2).

  PASAPQ has been proved as a practical, valid, reliable and responsive instrument for measuring respiratory device satisfaction (29).

[redacted]

- ***Adverse drug reactions (ADRs), fatal adverse events (AEs) and pregnancies***

9.3.2 Exposures

All included patients will be already receiving LAMA/LABA combination treatment with Spiolto® Respimat® after a recent switch (within one week) from previous maintenance therapy with tiotropium monotherapy (Spiriva® Handihaler®), according to the Greek SmPC. The decision of the treating physician to switch the treatment strategy will be previous and completely independent from the initiation of this NIS. Additionally, the decision will be according to the daily clinical practice in the corresponding center.

The same group of patients at two different time-points (three-months ahead) will be considered for the comparison analyses: within one week after the switch of COPD treatment from tiotropium monotherapy (Spiriva® Handihaler®) to dual therapy with tiotropium bromide plus olodaterol (Spiolto® Respimat®) and three-months after the baseline visit. However, no minimal exposure will be required. Subjects with premature drug discontinuation for any reason will not be excluded from the analysis.

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 monohydrate. 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.

9.3.3 Outcomes

9.3.3.1 Primary outcome

The primary outcome of this NIS will be the mean change in patients' quality of life (QoL) according to the total score of COPD Assessment Test (CAT) within three months after the switch from Spiriva® Handihaler® to Spiolto® Respimat® according to the daily clinical practice.

9.3.3.2 Secondary outcomes

The secondary outcomes of the NIS include:

- Change in the proportion of patients with COPD Assessment Test (CAT) ≥10 (representing impaired health status) within three months after the switch
- Mean
- change from baseline in the total EQ VAS within three- months after the switch
- Proportion of patients that change (improve/worsen) each of the 5 dimensions of the

EQ-5D-5L within three-months after the switch

- Rate of adherence to medication of COPD patients according to the SMAQ three-months after the switch
- Mean total score in abbreviated PASAPQ (first 13 questions of Part 1) (patient satisfaction with the inhaler device) approximately three-months after the switch.
- Mean score of overall satisfaction according to Question 14 of PASAPQ (Part 1) three-months after the switch.
- Proportion of preference (Spiriva® Handihaler® vs Spiolto® Respimat®) according to PASAPQ (Part 2) three-months after the switch
- Mean score of willingness to continue with inhaler (Spiolto® Respimat®) according to PASAPQ (Part 2) three-months after the switch.

Mean change of patients' dyspnea status according to the mMRC scale within three-months after the switch.

[redacted]

9.4 DATA SOURCES

Patient medical records (paper and/or electronically) and patient reported outcomes from 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 medical records.

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 study, the following has to be completed:

To be completed by the physician:

- [redacted]
- Patient medical files (including comorbidities and concomitant medications)
- [redacted]

To be completed by the patient at Visit 1 (baseline) and Visit 2 (3-months visit):

- COPD Assessment Test (CAT) (9)
- EQ-5D-5L questionnaire (23,24)
- Modified Medical Research Council (mMRC) questionnaire (26)

To be completed by the patient only at Visit 2 (3-months visit):

- Simplified Medication Adherence Questionnaire (SMAQ) (25)
- Abbreviated Patient Satisfaction Questionnaire (PASAPQ) (29)

9.5 STUDY SAMPLE SIZE

The sample size determination is not based on a power calculation because no hypotheses will be tested. The primary endpoint of change in score of COPD Assessment Test (CAT) within three months after the switch from Spiriva® Handihaler® to Spiolto® Respimat® will be analysed descriptively by mean and 95% confidence interval. From other studies a mean difference in CAT score of 1.0 and standard deviation of 9.0 are expected.

With a sample size of 1310, a two-sided 95% confidence interval for the difference in paired mean scores will have an interval that extends by no more than 0.5 from the observed difference in means (e.g. an interval from 0.5 to 1.5 for a difference of 1.0), with 90% coverage probability, assuming that the true standard deviation of differences is 9.0 and that the confidence interval is based on the t statistic. The calculation was performed using the MOC3 routine from commercial software nQuery Advisor® 7.0 ([R15-1331]). To account for a 15% dropout rate, 1507 patients will be needed. Therefore, it was decided to enroll 1500 patients in the study.

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 all current legal requirements regarding electronic study data handling. Patient confidentiality will be strictly maintained.

9.7 DATA ANALYSIS

All patients who were included, fulfilled all selection criteria and have received at least one dose of Spiolto® Respimat® will constitute the treated set for the analyses. All analyses will be performed on the treated set. If patients have missing values for an outcome, those patients will be excluded for that outcome's analysis, unless otherwise indicated in Section 9.7.3. For example, if a patient is missing the CAT score at baseline visit and/or at the 3- months visit, that patient will be excluded from the analyses for the primary endpoint of COPD related health status according to CAT and the secondary endpoint of change in CAT after three months of the switch from Spiriva® Handihaler® to Spiolto® Respimat®.

The analyses will relate to the following data:

-)

- COPD history and clinical characteristics
- Reported exacerbations in the year before and during the 3-months study period
- Past COPD therapies (12 months before enrolment)
- COPD related and other relevant concomitant medication
- Respiratory comorbidities and allergies
- Concomitant diseases / Comorbidities
- Respimat® training (Yes/No)
- COPD severity based on GOLD assessment (if available).
- COPD impact on patient's life based on CAT
- Patient's QoL based on EQ-5D-5L
- Adherence to treatment based on SMAQ
- Breathlessness based on mMRC score
- Satisfaction and Preference (abbreviated PASAPQ)
- [redacted]
- Adverse Drug Reactions (non-serious & serious), fatal AEs, pregnancies
- Rationale for Spiolto® Respimat® treatment discontinuation (if applicable)
- Details of treatment continuation / discontinuation

9.7.1 Main analysis

For the primary outcome, mean and 95% confidence interval will be presented.

Secondary outcomes will be evaluated by descriptive statistics:

All categorical variables will be summarized as relative and absolute frequencies. Proportions and 95% CI will be presented when appropriate.

The continuous variables will be reported by sample statistics: n (number of observations), number of missing data, mean, standard deviation (SD), minimum, first quartile (Q1), median, third quartile (Q3), and maximum.

[redacted]

[redacted]

9.7.3 Handling of missing data

The extent of missing data will be evaluated and described.

For the primary analysis, no treatment of missing data is planned except the imputation using the last-observation carried forward [LOCF] method if any post-baseline value is available in patients who discontinued before three months and for whom the value will be set as the last available measure.

[redacted]

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 quality of life and health status 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.

One possible concern regarding the classification of the study as observational may be the use of patient-reported questionnaires: the COPD Assessment Test for the evaluation of patient's health status, the EQ-5D-5L to measure patient's QoL, SMAQ for the assessment of treatment adherence, and PASAPQ to assess patient's satisfaction with treatment and the inhaler. Not all these tools are routinely used in real world practice. However, according to the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) document "Considerations on the definition of non-interventional trials under the current legislative framework" (2011), the following are general principles for interviews and questionnaires to still be seen as non-interventional: "they should not lead to a change in behaviour or influence treatment and should be as short as needed to reach the objectives of the non-interventional trial".

In this study, the inclusion of QoL and satisfaction questionnaires as well as subjects willing to complete them might increase compliance with drug and thus overestimate QoL. This limitation will be recognized in the potential study publications.

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. Also, to be able to discuss the extend of selection bias in the publication, a screening log will be completed to describe the number of non-recruited subjects who need to start tiotropium bromide plus olodaterol (Spiolto® Respimat®) after using Spiriva® Handihaler® and the reasons.

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.

There is also a risk of limited internal validity due to the absence of a control group. This could lead to overestimation of drug effect due to the "regression to the mean" effect sometimes observed in patients with already impaired clinical status. However, the requirement of a minimum exposure period with the previous treatment and the collection of exacerbations during the previous 12 months can help discussing from a clinical point of view any change observed during the follow-up period. Additionally, the use of different tools and scales for the measurements of clinical outcomes provides additional validation to the study, if results are consistent among them. [redacted]

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 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. Answers to the convenience questionnaires will be directly noted in the eCRF.

The following documents can be regarded as source data/documents:

- [redacted]
- Informed Consent forms
- Other medical reports
- Source worksheets

It is expected to have the following information including the source data/documents (National legislation regarding the content of subject notes should be followed):

- [redacted]
- Medical history and physical examination details
- AEs and concurrent treatment(s)
- Visit dates
- Subject ID
- Study Number
- Date when subject signed informed consent
- Information on the subject's treatment

9.10.2.2 Direct access to source data and documents

The investigator / institution will permit study-related monitoring, audits, IEC review and regulatory inspection, providing direct access to all related source data / documents.

Electronic 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 Trial Manager (CTM) and auditor may review all eCRFs, and written informed consents. The accuracy of the data will be verified by reviewing the documents described in Section 9.10.2.1.

9.10.2.3 Completion of study

The 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.

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) (33), Guidelines for Good Pharmacoepidemiology Practice (GPP) (34), 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.

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 Independent Ethics Committee (IEC) according to current national 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 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 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 drug reaction

An adverse drug reaction (ADR) 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 authorisation. 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 eCRF from first dose of Spiolto® Respimat® until the end of the study, once informed consent is obtained:

- all adverse drug reactions (ADRs) (serious and non-serious) associated with Spiolto® Respimat®
- all AEs with fatal outcome

All ADRs associated with Spiolto® Respimat®, 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 according to the previous criteria and recorded 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 first dose of Spiolto® Respimat®, 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 the first dose of Spiolto® Respimat®until the end of the study, once informed consent is obtained:

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	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 eCRF 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 Spiolto® Respimat®(e.g. Spiriva)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.

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ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

Not applicable.

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Doc.Ref. EMA/540136/2009

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

ENCePP Checklist for Study Protocols (Revision 3)

Adopted by the ENCePP Steering Group on 01/07/2016

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology, which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the section number of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example, in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post- authorisation safety studies). The Checklist is a supporting document and does not replace the format of the protocol for PASS as recommended in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title: Quality of life and p**R**eference of COPD pati**E**nts after **S**witching from Tiotropium monother**A**py (Spiriva® Handihaler®) to dual therapy with Tiotropium bromide plus Olodaterol (Spiolto® Respimat®) under real life **C**ondi**T**i**O**ns in Greece (ELLACTO II study)

Study reference number: 1237-0098

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	6
1.1.2 End of data collection[2]	☒	☐	☐	6
1.1.3 Study progress report(s)	☐	☐	☒	
1.1.4 Interim progress report(s)	☐	☐	☒	
1.1.5 Registration in the EU PAS register	☒	☐	☐	6
1.1.6 Final report of study results.	☒	☐	☐	6

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	8
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	7
2.1.2 The objective(s) of the study?	☒	☐	☐	8
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	8
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☒	☐	☐	9.5

Comments:

The study is not designed to confirm (or refute) any pre-defined hypotheses.

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
[2] Date from which the analytical dataset is completely available.

Section 3: Study design		**Yes**	**No**	**N/A**	**Section Number**
3.1	Is the study design described? (e.g. cohort, case-control, cross-sectional, new or alternative design)	☒	☐	☐	9.1
3.2	Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.1; 9.4
3.3	Does the protocol specify measures of occurrence? (e.g. incidence rate, absolute risk)	☒	☐	☐	9.3.3
3.4	Does the protocol specify measure(s) of association? (e.g. relative risk, odds ratio, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☐	☐	☒	
3.5	Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☒	☐	☐	11

Comments:

Statistical analyses will be of exploratory and descriptive in nature.

Section 4: Source and study populations		**Yes**	**No**	**N/A**	**Section Number**
4.1	Is the source population described?	☒	☐	☐	9.2.2
4.2	Is the planned study population defined in terms of:				
	4.2.1 Study time period?	☒	☐	☐	9.2.3
	4.2.2 Age and sex?	☒	☐	☐	9.2.2
	4.2.3 Country of origin?	☒	☐	☐	9.2.2
	4.2.4 Disease/indication?	☒	☐	☐	9.2.2
	4.2.5 Duration of follow-up?	☒	☐	☐	9.2.2
4.3	Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	9.2.2-4

Comments:

Section 5: Exposure definition and measurement		**Yes**	**No**	**N/A**	**Section Number**
5.1	Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	9.3.2
5.2	Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☒	☐	☐	9.3.2; 9.9

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☒	☐	☐	9.3.2
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☒	☐	☐	9.3.2

Comments:

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	9.3.3
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.3.3
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☒	☐	☐	9.9
6.4 Does the protocol describe specific endpoints relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease, disease management)	☐	☐	☒	

Comments:

There are no Health Technology Assessments planned for this study.

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol describe how confounding will be addressed in the study?	☒	☐	☐	9.9
7.1.1. Does the protocol address confounding by indication if applicable?	☐	☐	☒	
7.2 Does the protocol address:	☐	☐	☐	
7.2.1. Selection biases (e.g. healthy user bias)	☐	☒	☐	
7.2.2. Information biases (e.g. misclassification of exposure and endpoints, time-related bias)	☐	☒	☐	
7.3 Does the protocol address the validity of the study covariates?	☒	☐	☐	9.7.2; 9.8

Comments:

Section 8: Effect modification	**Yes**	**No**	**N/A**	**Section Number**

Section 8: Effect modification	**Yes**	**No**	**N/A**	**Section Number**
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☐	☐	☒	

Comments:

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	9.3.2
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.3.3
9.1.3 Covariates?	☒	☐	☐	9.3.1
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	9.3.2
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.3.3
9.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	9.3.1
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	9.3.2
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD)-10, Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	9.3.3
9.3.3 Covariates?	☒	☐	☐	9.3.1
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Is the choice of statistical techniques described?	☒	☐	☐	9.7
10.2 Are descriptive analyses included?	☒	☐	☐	9.7
10.3 Are stratified analyses included?	☒	☐	☐	9.7

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.4 Does the plan describe methods for adjusting for confounding?	☐	☒	☐	
10.5 Does the plan describe methods for handling missing data?	☒	☐	☐	9.7.3
10.6 Is sample size and/or statistical power estimated?	☒	☐	☐	9.5

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	9.8
11.2 Are methods of quality assurance described?	☒	☐	☐	9.8
11.3 Is there a system in place for independent review of study results?	☒	☐	☐	9.8

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	9.9
12.1.2 Information bias?	☒	☐	☐	9.9
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☒	☐	☐	9.9
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	9.2

Comments:

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	9.10.1
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	10

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	5

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	12
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12

Comments:

ANNEX 3. ADDITIONAL INFORMATION

COPD Assessment Test (CAT) (9)

[redacted]

Your name:

Today's date:

How is your COPD? Take the COPD Assessment Test™ (CAT)

This questionnaire will help you and your healthcare professional measure the impact COPD (Chronic Obstructive Pulmonary Disease) is having on your wellbeing and daily life. Your answers, and test score, can be used by you and your healthcare professional to help improve the management of your COPD and get the greatest benefit from treatment.

For each item below, place a mark (X) in the box that best describes you currently. Be sure to only select one response for each question.

Example: I am very happy 0 X 2 3 4 5 I am very sad

			SCORE
I never cough	0 1 2 3 4 5	**I cough all the time**	
I have no phlegm (mucus) in my chest at all	0 1 2 3 4 5	**My chest is completely full of phlegm (mucus)**	
My chest does not feel tight at all	0 1 2 3 4 5	**My chest feels very tight**	
When I walk up a hill or one flight of stairs I am not breathless	0 1 2 3 4 5	**When I walk up a hill or one flight of stairs I am very breathless**	
I am not limited doing any activities at home	0 1 2 3 4 5	**I am very limited doing activities at home**	
I am confident leaving my home despite my lung condition	0 1 2 3 4 5	**I am not at all confident leaving my home because of my lung condition**	
I sleep soundly	0 1 2 3 4 5	**I don't sleep soundly because of my lung condition**	
I have lots of energy	0 1 2 3 4 5	**I have no energy at all**	
		TOTAL SCORE	

COPD Assessment Test and the CAT logo is a trade mark of the [redacted]
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Last Updated: February 24, 2012

EQ-5D-5L questionnaire (23,24)

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

- I have no problems in walking about ❑
- I have slight problems in walking about ❑
- I have moderate problems in walking about ❑
- I have severe problems in walking about ❑
- I am unable to walk about ❑

SELF-CARE

- I have no problems washing or dressing myself ❑
- I have slight problems washing or dressing myself ❑
- I have moderate problems washing or dressing myself ❑
- I have severe problems washing or dressing myself ❑
- I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

- I have no problems doing my usual activities ❑
- I have slight problems doing my usual activities ❑
- I have moderate problems doing my usual activities ❑
- I have severe problems doing my usual activities ❑
- I am unable to do my usual activities ❑

PAIN / DISCOMFORT

- I have no pain or discomfort ❑
- I have slight pain or discomfort ❑
- I have moderate pain or discomfort ❑
- I have severe pain or discomfort ❑
- I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

- I am not anxious or depressed ❑
- I am slightly anxious or depressed ❑
- I am moderately anxious or depressed ❑
- I am severely anxious or depressed ❑
- I am extremely anxious or depressed ❑

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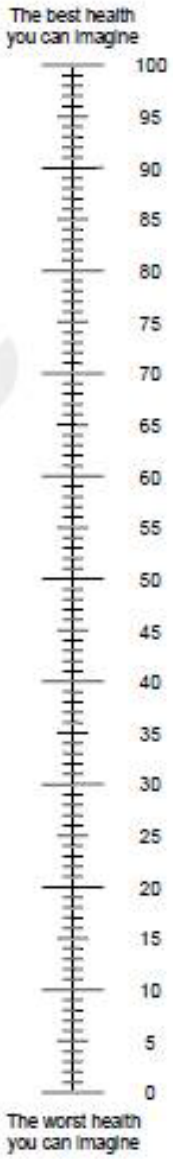
- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



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Simplified Medication Adherence Questionnaire (SMAQ) (25)

1. Do you ever forget to take the medication?	Yes…No
2. Do you always take the medication at the specified time?	Yes….No
3. Do you ever stop taking the medication if you feel ill?	Yes….No
4. Did you forget to take the medication during the weekend?	Yes….No
5. In the last week, How many times did you not take a dose?	A: None of the above B: 1-2 C: 3-5 D: 6-10 E: Greater than 10
6. Since the last medical visit, how many full days did you not take the medication?	Number of days:

Modified Medical Research Council (mMRC) questionnaire (26)

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 and preference questionnaire (PASAPQ) (29)

PATIENT SATISFACTION
AND PREFERENCE QUESTIONNAIRE

PASAPQ

Direct version

PART 1: 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 overall feeling of inhaling your medicine?	Inhaler	☐	☐	☐	☐	☐	☐	☐
2.	With the feeling that the inhaled dose goes to your lungs?	Inhaler	☐	☐	☐	☐	☐	☐	☐
3.	That you can tell the amount of medication left in your inhaler?	Inhaler	☐	☐	☐	☐	☐	☐	☐
4.	That the inhaler works reliably?	Inhaler	☐	☐	☐	☐	☐	☐	☐
5.	With the ease of inhaling a dose from the inhaler?	Inhaler	☐	☐	☐	☐	☐	☐	☐
6.	With the instructions for use?	Inhaler	☐	☐	☐	☐	☐	☐	☐
7.	With the size of your inhaler?	Inhaler	☐	☐	☐	☐	☐	☐	☐
8.	That the inhaler is durable (hard wearing)?	Inhaler	☐	☐	☐	☐	☐	☐	☐

▼ ***Please go to the next page***

			Very Dissatisfied	Dissatisfied	Somewhat Dissatisfied	Neither Satisfied nor Dissatisfied	Somewhat Satisfied	Satisfied	Very Satisfied
9.	With the ease of cleaning your inhaler?	Inhaler	☐	☐	☐	☐	☐	☐	☐
10.	With using the inhaler?	Inhaler	☐	☐	☐	☐	☐	☐	☐
11.	With the speed at which medicine comes out of the inhaler?	Inhaler	☐	☐	☐	☐	☐	☐	☐
12.	With the ease of holding the inhaler during use?	Inhaler	☐	☐	☐	☐	☐	☐	☐
13.	With the overall convenience of carrying the inhaler with you?	Inhaler	☐	☐	☐	☐	☐	☐	☐
14.	Overall, how satisfied are you with your inhaler?	Inhaler	☐	☐	☐	☐	☐	☐	☐

▼ *Please go to the next page*

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

Comparing the two inhalers that you have used, 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 ☐

How would you feel about continuing to use the inhaler?

Please indicate your willingness to continue using the inhaler that you used during the study by providing a value between 1 and 100.

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

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

Inhaler ☐

THANK YOU VERY MUCH FOR COMPLETING THIS SURVEY.

PLEASE RETURN THIS SURVEY TO THE STUDY COORDINATOR.