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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
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1. TABLE OF CONTENTS

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
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events CTP
DMRP	Data management and review plan
DMP	Data Management Plan
eCRF	Electronic Case Report Form
EMA	European Medicines Agency
ENCePP	European Network of Centers for Pharmacoepidemiology and Pharmacovigilance
EQ-5D-5L	EuroQoL-5D-5L questionnaire EU
FDA	Food and Drug Administration
FDC	Fix Dose Combination
FEV1	Forced expiratory volume in one second GCP
GEP	Good Epidemiological Practice
GPP	Good Pharmacoepidemiology Practice
GVP	Good Pharmacovigilance Practices
GOLD	Global Initiative for Chronic Obstructive Lung Disease HCPs
IB	Investigator's Brochure
ICH	International Conference on Harmonization
ICS	Inhaled Corticosteroids
IEC	Independent Ethics Committee
ISF	Investigator Site File
IQR	Interquartile range
LABA	Long-acting $beta_2$ adrenoceptor agonist LAMA
MedDRA	Medical Dictionary for Drug Regulatory Activities mMRC
NIS	Non-Interventional Study
PASAPQ	Abbreviated Patient Satisfaction Questionnaire PASS
PGE	Physician's Global Evaluation
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SEAP	Statistical and epidemiological analysis plan
SD	Standard Deviation
SDV	Source data verification
SMAQ	Simplified Medication Adherence Questionnaire SmPC
WHO	World Health Organization

3. RESPONSIBLE PARTIES

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- [redacted] (When BI NIS [redacted] is not [redacted]; in all cases)

4. PURPOSE AND SCOPE

As per ICH E9, the purpose of this document is to provide a more technical and detailed elaboration of the principal features of the analysis described in the protocol, and to include detailed procedures for executing the statistical analysis of the primary and secondary variables and other data.
This SEAP assumes familiarity of the SEAP reviewers with the NIS protocol. In particular, the SEAP is based on the planned analysis specification as written in NIS protocol Section 9.7 "Data Analysis". Therefore, SEAP readers may consult the NIS protocol for more background information on the study, e.g., on study objectives, study design and population, treatments, definition of measurements and variables, planning of sample size.

5. AMENDMENTS AND UPDATES

5.1 Changes form protocol analysis

Additional modifications from the CTP made in this SEAP:

- It was stated in CTP to exclude patients with missing values. Missing values will be treated in a different way according to their nature. Missing values due to Intercurrent Event (IE) are taken care at the estimands definitions, on the other hand, missing values not related to IE will be multiple imputed if missingness is greater than 25% for a specific variable.
- It was suggested in the CTP, [redacted]
- To assess the potential associations between patient characteristics, treatment, preference [redacted] ing

to health status assessed with CAT will not be assessed via univariate methods, however the applicable [redacted] are included to the statistical models in the primary and the first secondary endpoint analysis. [redacted]

6. RESEARCH QUESTION AND OBJECTIVE

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.

7. RESEARCH METHODS

7.1 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 centre.

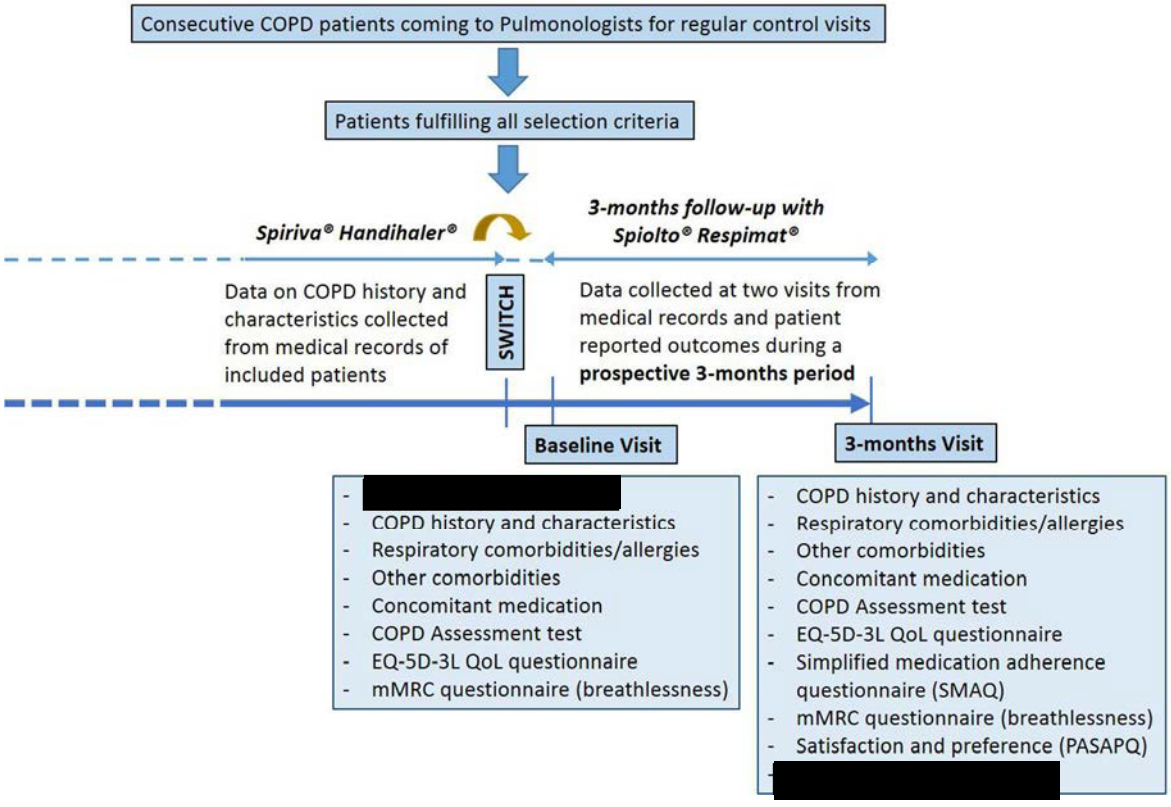
The intended Health Care Professionals (HCPs) are office-based pulmonologists and practice physicians from Hospital pulmonary clinics, who are treating symptomatic COPD patients every day, being aware that most of their patients suffer from the physical restrictions induced by the disease per se.

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 6 months. All centers will stop recruitment once the total sample size of 1500 patients is achieved or, alternatively, at the end of the 6-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

Figure 1. Study scheme



7.2 SETTING

It is planned that data of approximately 1500 COPD patients from approximately 150 sites (around 143 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.

7.3 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 143 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.

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.

7.4 STUDY VISITS

The enrolment period of the study will last for a maximum of 6 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.

Visit windowing will be performed as described in Table 7.4:1, in order to assign data to the relevant study visit based on the actual day of the assessment. However, in the listings, all visits performed will be displayed (even if outside time-window).

Table 7.4:1 Analysis Visit Window

Analysis visits	Target Day	Analysis visit window [days]
Baseline	1	<=1
3 Months	92	63-121

Safety data are excluded from analysis visit mapping window and the investigator may enter data as needed.
Post baseline: Any assessment after the baseline visit.

8. VARIABLES

COPD history and clinical characteristics at baseline and changes up to 3-months visit:

- Months since COPD diagnosis, defined as: (Date at enrolment – Date of diagnosis)/30.5
- Gold group (A, B, C, D)

- COPD type (Chronic, bronchitis, Emphysema, Other)
- Number of exacerbations in the year before baseline (None, 1, 2, >2)
- Number of hospitalizations in the year before baseline (None, 1, 2, >2)
- Smoking Status (Never, Past, Current, Unknown)
- Packyears
- Presence of Eosinophilia (Yes, No)
- Months since PFTs performed, defined as: (Date of enrolment-Date of PFTS performed)/30.5
- FEV1/FVC % predicted ratio
- FEV1% predicted.

Respiratory comorbidities and allergies at baseline and changes up to 3-months visit:

- Pneumonia (Yes, No, Not evaluated)
- Allergic rhinitis (Yes, No, Not evaluated)
- Bronchiectasis (Yes, No, Not evaluated)
- Lung diseases due to external agents (Yes, No, Not evaluated)

Comorbidities:

- Diabetes mellitus (Yes, No, Unknown)
- Osteoporosis (Yes, No, Unknown)
- Cardiovascular diseases (Yes, No, Unknown) (including heart failure, atrial fibrillation and other arrhythmias)
- Malignancies (Yes, No, Unknown)
- Anxiety/depression (Yes, No, Unknown)
- Insomnia (Yes, No, Unknown)
- Pulmonary artery hypertension (Yes, No, Unknown)
- Sleep apnea (Yes, No, Unknown)
- Gastroesophageal reflux disease (Yes, No, Unknown)
- Hemolytic anemia (Yes, No, Unknown)

- Atopy (Yes, No, Unknown)
- Sinusitis (Yes, No, Unknown)
- Emphysema (Yes, No, Unknown)
- Duration of each Comorbidity(months) is defined as: (Stop Date/ICF Date- Start Date)/30.5

Current and past COPD therapies (in the period of one year before enrolment)

- Short Acting β2-agonists (Yes, No)
- Long Acting β2-agonists (LABA) (Yes, No)
- Short Acting anticholinergics (Yes, No)
- Short Acting anticholinergics (LAMA) (Yes, No)
- Inhaled corticosteroids (ICS) (Yes, No)
- PDE4 inhibitors (Yes, No)
- Methylaxnthines (Yes, No)
- LABA/ICS Combinations (Yes, No)
- LAMA/LABA Combinations (Yes, No)
- Duration of treatment (months) defined as: (Stop Date-Start Date)/30.5

Relevant concomitant medications at baseline and changes up to 3-months visit:

- Use of concomitant inhalers (Yes, No)
- Other concomitant medications

[redacted]

COPD Assessment Test (CAT): 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. 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 is five units. No target score represents the best achievable outcome, however, CAT scores <10 corresponding to mild impact on patient's life are usually considered those representing patients without impaired health status

EQ-5D-5L questionnaire : a well-established and commonly used tool for the measurement of patients QoL. The EQ-5D-5L consists of two parts: the EQ-5D descriptive system and the EQ visual analogue scale (EQ VAS). The EQ-5D-5L descriptive system comprises five dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression). Each dimension has five levels (no problems, slight problems, moderate problems, severe problems and extreme problems) 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 digits for the five dimensions can be combined into a 5-digit number that describes the patient's health state. 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): 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. 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.

SMAQ questionnaire is dichotomic (yes, no), any answer in the sense of non-adherent groups, assigns patient to the non-adherent category. Thus, patient is considered non-adherent if at least one answer to the SMAQ questionnaire is the following:

1: YES.
2: No
3: YES
4: YES
5: C, D or E
6: more than two days.

Modified British Medical Research Council (mMRC) Dyspnea Scale: it 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.

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

[redacted]

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

8.1 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 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.

8.2 Outcomes

8.2.1 Primary outcomes

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.

8.2.2 Secondary outcomes

The secondary outcomes of the current study 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]

8.3 Covariates

The following variables will be considered, among others, as covariates and will be examined in terms of their association with the primary outcome measure.

- Patient's age at baseline (<65 years, ≥65 years)
- Sex (female, male)
- Obesity (i.e. BMI ≥30 kg/m^2) (yes, no)
- Smoking habits (current smoker, past smoker).
- Packyears
- Gold group (A, B, C and D).

9. DATA SOURCES

Patient [redacted] 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 must be completed: To be completed by the physician:

- [redacted] (only at Visit 1)
- Patient medical files (including comorbidities and concomitant medications)
- Assessment of inhaler handling in daily use (only at Visit 2)

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

- 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-months visit):

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

10. DATA MANAGEMENT AND SOFTWARE/TOOLS

A data management and review plan (DMRP) was created to describe all functions, processes, and specifications for data collection, cleaning, and validation. The electronic Case Report Forms (eCRFs) 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 DMRP. 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.

10.1 Software/Tools

Stata V13.0 and R V4.0.2 will be used for the entire analysis.

10.2 Handling of Missing Values

If missingness is more than 25% for a specific outcome [redacted] methodologies will be examined. More specific information is provided in Section

11.3.1

10.3 Handling of Inconsistencies in Data and Outliers

To identify the possible outliers, Z-score and IQR (interquartile range) methods will be used. An observation will be considered as an outlier if it is not included in the following interval for the primary and secondary continuous variables: (Q_1-1.5*IQR, Q_3+1.5IQR). In order to visualise the outliers, histograms and/or scatterplots will be generated with the rest of the data. If the effect of the outliers is strong, delete or replace will be examined.

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

11. DATA ANALYSIS

11.1 Analysis Sets

Enrolled set (ES): Defined as all patients screened.

Treated Set (TS): All patients who were enrolled in the study and have received at least one dose of Spiolto® Respimat®.

Per Protocol Set (PPS): All patients of the TS who have completed the study with no major protocol violation.

11.2 Main analysis

Baseline data analysis will be carried out. Comorbidities, [redacted] information, and clinical characteristics will be described for the TS.

All categorical variables will be summarized as relative and absolute frequencies. Proportion and 95% CI will be given 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.

Summary statistics will be provided for all primary and secondary endpoints throughout the study.

11.2.1 Analysis of primary outcome.

11.2.1.1 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®.

The primary estimand is defined as follows:

A. Population: Is defined through inclusion/exclusion criteria of the study protocol to reflect the target population.
B. Variable: Continuous variable response.

C. Intercurrent Event (IE): Include death, drop-out due to any adverse event (AE) and treatment discontinuation. For patients experiencing an IE, the most extreme unfavourable value will be assigned (CAT score at 3 Months equals to 40).
D. Population level summary: The change from Baseline of total CAT score within 3 Months.

Mixed model for repeated measurements (MMRM) assuming random missingness will be fitted. The dependent variable will be the CAT score at each visit. Visit, GOLD group, smoking habits, packyears, sex, age, and comorbidities appearing at a rate greater than 5% will be entered as covariates. Patients will be fitted at random and an unstructured covariance matrix will be used, allowing adjustment for correlations between study visits within the study patients. The Kenward- Roger degrees of freedom approximation will be used in the model (ddfm=kr).

Summaries of the estimated mean change from baseline of CAT score at 3 Months will be provided with 95% confidence interval. Model information will be provided as footnote under the corresponding table.

11.2.2 Analysis of Secondary outcomes.

11.2.2.1 Change in the proportion of patients with COPD Assessment Test (CAT) $\geqslant$10 (representing impaired health status) within three months after the switch

Estimand:

A. Population: Is defined through inclusion/exclusion criteria of the study protocol to reflect the target population.
B. Variable: Binary variable response. Response is defined as having CAT score $\geq$ 10.
C. Intercurrent Event (IE): Include death, drop-out due to any adverse event (AE) and treatment discontinuation. For patients experiencing an IE, the most extreme unfavourable value will be assigned (patient CAT score $\geq$ 10).
D. Population Level Summary: Odds ratio of response within 3 Months.

This endpoint will be analysed with a logistic GEE model with CAT response as dependent variable. Visit, GOLD group, smoking habits, packyears, sex, age, and comorbidities appearing at a rate greater than 5% will be entered as covariates and unstructured covariance matrix will be used.

Summaries of the estimated OR will be provided with 95% confidence interval. Model information will be provided as footnote under the corresponding table.

11.2.2.2 Mean change from baseline in the total EQ VAS within three- months after the switch

Estimand:

A. Population: Is defined through inclusion/exclusion criteria of the study protocol to reflect the target population.
B. Variable: Continuous variable response.

C. Intercurrent Event (IE): Include death, drop-out due to any adverse event (AE) and treatment discontinuation. For patients experiencing an IE, the most extreme unfavourable value will be assigned (EQ-VAS equals to 0).

D. Population level summary: The change from Baseline of EQ-VAS score within 3 Months.

This endpoint will be analysed with a Mixed Model for Repeated Measures (MMRM) with EQ-VAS score as dependent variable. Visit, GOLD group, smoking habits, packyears, sex, age, and comorbidities appearing at a rate greater than 5% will be entered as covariates. Patients will be fitted at random and an unstructured covariance matrix will be used, allowing adjustment for correlations between study visits within the study patients. The Kenward- Roger degrees of freedom approximation will be used in the model (ddfm=kr).

Summaries of the estimated mean change from baseline of EQ-VAS score at 3 Months will be provided with 95% confidence interval. Model information will be provided as footnote under the corresponding table

11.2.2.3 Proportion of patients that change (improve/worsen) each of the 5 dimensions of the EQ-5D-5L within three-months after the switch

Estimand:

A. Population: Is defined through inclusion/exclusion criteria of the study protocol to reflect the target population.

B. Variable: Ordinal variable response.

C. Intercurrent Event (IE): Include death, drop-out due to any adverse event (AE) and treatment discontinuation. For patients experiencing an IE, the most extreme unfavourable value will be assigned

D. Population level summary: Odds ratio of improvement.

This endpoint will be analysed with an ordinal logistic GEE model with EQ-5D-5L response as dependent variable. Visit, GOLD group, smoking habits, packyears, sex, age, and comorbidities appearing at a rate greater than 5% will be entered as covariates and an unstructured covariance matrix will be used. This model will be repeated for each of the 5 dimensions.

Summaries of the estimated OR will be provided with 95% confidence interval. Model information will be provided as footnote under the corresponding table.

11.2.2.4 Rate of adherence to medication of COPD patients according to the SMAQ three-months after the switch

Estimand:

A. Population: Is defined through inclusion/exclusion criteria of the study protocol to reflect the target population.

B. Variable: Binary variable response.

C. Intercurrent Event (IE): Include death, drop-out due to any adverse event (AE) and treatment discontinuation. For patients experiencing an IE, the most extreme unfavourable value will be assigned (Patient not adhered).

D. Population level summary: Proportion of adhered and not adhered patients.

For this endpoint frequency tables will be provided.

11.2.2.5 Mean total score in abbreviated Q (first 13 questions of Part 1) (patient satisfaction with the inhaler device) approximately three-months after the switch

Estimand:

A. Population: Is defined through inclusion/exclusion criteria of the study protocol to reflect the target population.

B. Variable: Continuous variable response.

C. Intercurrent Event (IE): Include death, drop-out due to any adverse event (AE) and treatment discontinuation. For patients experiencing an IE, the most extreme unfavourable value will be assigned (Total score equals to 13).

D. Population level summary: Mean total score of abbreviated Questionnaire three months after the switch

For this endpoint summary statistics tables will be provided.

11.2.2.6 Mean score of overall satisfaction according to Question 14 of PASAPQ (Part 1) three-months after the switch.

Estimand:

A. Population: Is defined through inclusion/exclusion criteria of the study protocol to reflect the target population.

B. Variable: Continuous variable response.

C. Intercurrent Event (IE): Include death, drop-out due to any adverse event (AE) and treatment discontinuation. For patients experiencing an IE, the most extreme unfavourable value will be assigned (Score of Question 14 equals to 1)

D. Population level summary: Mean score of overall satisfaction three months after the switch.

Estimand will be assessed by summary statistics.

11.2.2.7 Proportion of preference (Spiriva® Handihaler® vs Spiolto® Respimat®) according to PASAPQ (Part 2) three-months after the switch

Estimand:

A. Population: Is defined through inclusion/exclusion criteria of the study protocol to reflect the target population.

B. Variable: Binary variable response.

C. Intercurrent Event (IE): Include death, drop-out due to any adverse event (AE) and treatment discontinuation. For patients experiencing an IE, the most extreme unfavourable value will be assigned (Preference of Spiriva Handihaler®)

D. Population level summary: Proportion of patients preferring Spiriva® Handihaler® and proportion of preferring Spiolto® Respimat®.

Estimand will be assessed by summary statistics.

11.2.2.8 Mean score of willingness to continue with inhaler (Spiolto® Respimat®) according to PASAPQ (Part 2) three-months after the switch.

Estimand:

A. Population: Is defined through inclusion/exclusion criteria of the study protocol to reflect the target population.

B. Variable: Coninuous variable response.

C. Intercurrent Event (IE): Include death, drop-out due to any adverse event (AE) and treatment discontinuation. For patients experiencing an IE, the most extreme unfavourable value will be assigned (Willingness to continue equals to 0)

D. Population level summary: Mean score of willingness to continue with the inhaler Spiolto® Respimat®.

Estimand will be assessed by summary statistics.

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

Estimand:

A. Population: Is defined through inclusion/exclusion criteria of the study protocol to reflect the target population.

B. Variable: Continuous variable response.

C. Intercurrent Event (IE): Include death, drop-out due to any adverse event (AE) and treatment discontinuation. For patients experiencing an IE, the most extreme unfavourable value will be assigned (Dyspnea status equals to 4)

D. Population level summary: Mean change of Baseline of Dyspnea status within 3 months

This endpoint will be analysed with a Mixed Model for Repeated Measures (MMRM) with mMRC score as dependent variable. Visit, GOLD group, smoking habits, packyears, sex, age, and comorbidities appearing at a rate greater than 5% will be entered as covariates. Patients will be fitted at random and an unstructured covariance matrix will be used, allowing adjustment for correlations between study visits within the study patients. The Kenward- Roger degrees of freedom approximation will be used in the model (ddfm=kr).

Summaries of the estimated mean change from baseline of mMRC at 3 Months will be provided with 95% confidence interval. Model information will be provided as footnote under the corresponding table

11.2.3 COVID-19 IMPACT

The COVID-19 pandemic started before first patient first visit; it is necessary to analyse the possible impact of the pandemic to this NIS. Separated tables will capture the number of patients dropped-out due to COVID-19, the frequencies of deaths, AEs and SAEs related to COVID-19 and the number of visits delayed/not done due to the pandemic.

[redacted]

[redacted]

11.4 Safety Analysis

All safety analyses will be performed on TS.

11.4.1 Adverse events

All treatment emergent adverse events recorded during the trial will be presented in listings for AEs / SAEs. Especially the Adverse Drug Reactions (ADR), these might be followed up after the study completion and until they are resolved. As treatment emergent adverse events are considered all the AEs following ICF signature providing the patient has already received treatment with Spiolto® Respimat®. Initially, an AE overview table will be created summarizing the total number of AEs, patients with at least one: AE, SAE, SAE leading to death, SAE leading to drug discontinuation and the number of pregnant patients with at least one AE. A separate table showing the overview of AE occurred during the study will be presented by SOC and PT. SOC terms will be sorted alphabetically; PTs will be sorted within each SOC term by decreasing frequency. In such tables if a patient reported more than one AE within the same PT or SOC, the patient will be counted only once for this PT/SOC. AEs will be coded based on the MedDRA terminology. The existing version at the time of the database lock will be used.

12. 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.

13. REFERENCES

13.1 PUBLISHED REFERENCES

13.2 UNPUBLISHED REFERENCES

ANNEX 1. ADDITIONAL INFORMATION

TABLE 1.1 DISPOSITION OF PATIENTS

	N	%
Subjects entered the study		
Subjects discontinued		
Discontinuation reasons		
Treatment Discontinuation for any reason		
Patients decision/ICF withdrawal		
Patient is lost to follow-up		
Non-compliance to study requirements (exclusion criterion is met)		
Protocol violation		
Treatment with Spiolto Respimat discontinuation		
Adverse Event		
Investigators decision		
Other Cause		

TABLE 1.2 PREMATURE DISCONTINUATION FROM STUDY DUE TO COVID-19

	N	%
Subjects entered the study		
Subjects discontinued due to COVID-19		
Subjects Treated		
Prematurely discontinued from study		
AE SARS-CoV-2 infection		
COVID-19 related, not due to AE		

TABLE 1.3 NUMBER OF VISITS DELAYED/NOT DONE DUE TO COVID-19

	N	%
Visits completed on time		
Visits delayed due to COVID-19		
Visits not done due to COVID-19		

TABLE 1.4 ANALYSIS SETS

	N	%
Enrolled Set (ES)		
Treated Set (TS)		
Per Protocol Set (PPS)		

[redacted]

	N=xxx
Gender n (%)	
Male	
Female	
Missing	
Occupation n (%)	
Employee	
Manager	
Part timer	
Self Employed	
Public Service	
Student	
Without Occupation	
Other	
Missing	
Education n (%)	
Less than high school diploma	
High school degree or equivalent	
Bachelor’s degree	
Master’s degree	
Doctorate	
Other	
Missing	
Marital Status n (%)	
Single	
Married	
Divorced	
Widow	
Missing	
Weight (kg)	
n	
Mean	
Median	
SD	
Minimum	
Maximum	
Q1	
Q3	
Missing	
Height (cm)	

	N=xxx
n	
Mean	
Median	
SD	
Minimum	
Maximum	
Q1	
Q3	
Missing	
BMI (kg/m^2)	
n	
Mean	
Median	
SD	
Minimum	
Maximum	
Q1	
Q3	
Missing	
Obesity (BMI>30kg/m^2)	
Yes	
No	
Missing	
Smoking status	
Never	
Past	
Current	
Unknown	
Missing	
Pack years for Past and Current smokers	
n	
Mean	
Median	
SD	
Minimum	
Maximum	
Q1	
Q3	
Missing	

TABLE 2.2 COPD HISTORY AND CLINICAL CHARACTERISTICS

	Baseline N=xxx	3 Months N=xxx
Months since COPD diagnosis		
n		
Mean		
Median		
SD		
Minimum		
Maximum		
Q1		
Q3		
Missing		
COPD type n (%)		
Chronic bronchitis		
Emphysema		
Other COPD		
Presence of Eosinophilia in the peripheral blood n (%)		
Yes		
No		
Missing		

TABLE 2.2.1 COPD HISTORY AND CLINICAL CHARACTERISTICS

	12 months before baseline N=xxx	Baseline to 3 months N=xxx
Number of exacerbations n (%)		
None		
1		
2		
>2		
Missing		
Number of hospitalisations due to COPD exacerbations n (%)		
None		
1		
2		
>2		
Missing		

TABLE 2.3 PFT MEASUREMENTS BY VISIT.

	Baseline	3 Months

	N=xxx	N=xxx
PFT performed		
Yes		
No		
Unknown		
Missing		
Time since PFTs performed		
n		
Mean		
Median		
SD		
Minimum		
Maximum		
Q1		
Q3		
Missing		

TABLE 3.1 SUMMARY TABLE OF COMORBIDITIES

	n	%
Presence of at least 1 comorbidity		
Yes		
No		
Missing		
Diabetes mellitus		
Yes		
No		
Not evaluated		
Osteoporosis		
Yes		
No		
Not evaluated		
Cardiovascular diseases (including heart failure, atrial fibrillation and other arrythmias)		
Yes		
No		
Not evaluated		
Malignancies		
Yes		
No		
Not evaluated		

	n	%
Anxiety/Depression		
Yes		
No		
Not evaluated		
Insomnia		
Yes		
No		
Not evaluated		
Pulmonary artery hypertension		
Yes		
No		
Not evaluated		
Sleep apnoea		
Yes		
No		
Not evaluated		
Gastroesophageal reflux disease		
Yes		
No		
Not evaluated		
Hemolytic anemia		
Yes		
No		
Not evaluated		
Atopy		
Yes		
No		
Not evaluated		
Sinusitis		
Yes		
No		
Not evaluated		
Emphysema		
Yes		
No		
Not evaluated		

TABLE 4.1 CURRENT COPD TREATMENT*.

	n	%
Any Short acting β2-agonists		
Salbutamol		
Terbutaline sulfate		
Any Long acting β2-agonists		
Salmeterol		
Fumaric formoterol		
Vilanterol		
Olodaterol		
Indacaterol		
Any Short-acting anticholinergics		
Bromide ipartropium		
Any Long-acting anticholinergics (LAMA)		
Bromide tiotropum		
Bromide aclidine		
Bromide glucuronide		
Bromide umecline		
Any Inhaled corticosteroids (ICS)		
Fluticasone propionate		
Voudessonide		
Furometic mometazone		
Siklesonide		
Any PDE 4 inhibitors		
Roflumilast		
Any Methylxathines		
Aminophyline		
Theophyline		
Any LABA/ICS Combinations		
Salmeterol-Fluticazone		
Formoterol-Budesonide		
Βιλαντερόλη-Fluticazone		
Formoterol-Beclomethazone		
Formoterol-Budesonide		
Formoterol-Fluticazone		
Any LAMA/LABA Combinations		
Aclidine-Formoterol		
Glycopyrronium-Indacaterol		
Tiotoprium-Olodaterol		
Umeclidine-Vilanterol		

*one year before enrolment

TABLE 4.2 PAST COPD TREATMENT*.

	n	%
Any Short acting β2-agonists		
Salbutamol		
Terbutaline sulfate		
Any Long acting β2-agonists		
Salmeterol		
Fumaric formoterol		
Vilanterol		
Olodaterol		
Indacaterol		
Any Short-acting anticholinergics		
Bromide ipartropium		
Any Long-acting anticholinergics (LAMA)		
Bromide tiotropum		
Bromide aclidine		
Bromide glucuronide		
Bromide umecline		
Any Inhaled corticosteroids (ICS)		
Fluticasone propionate		
Voudessonide		
Furometic mometazone		
Siklesonide		
Any PDE 4 inhibitors		
Roflumilast		
Any Methylxathines		
Aminophyline		
Theophyline		
Any LABA/ICS Combinations		
Salmeterol-Fluticazone		
Formoterol-Budesonide		
Βιλαντερόλη-Fluticazone		
Formoterol-Beclomethazone		
Formoterol-Budesonide		
Formoterol-Fluticazone		
Any LAMA/LABA Combinations		
Aclidine-Formoterol		
Glycopyrronium-Indacaterol		

	n	%
Tiotoprium-Olodaterol		
Umeclidine-Vilanterol		

TABLE 6.1.1 SUMMARY OF CAT TOTAL SCORE DURING THE TRIAL BASED ON OBSERVED DATA.

Visit		n	Mean	Median	SD	Min	Max	Q1	Q3	Missing
Baseline	Base									
Month 3	Base									
	Post									
	Change									

Footnote: at 3 months only subjects with both baseline and post baseline value will be included.
Footnote: CAT: COPD Assessment Test.

TABLE 6.1.2 SUMMARY OF CAT TOTAL SCORE DURING THE TRIAL BASED ON [redacted]
TABLE 6.1.3 SUMMARY OF CAT TOTAL SCORE DURING THE TRIAL BASED ON [redacted]
TABLE 6.1.4 SUMMARY OF CAT TOTAL SCORE DURING THE TRIAL BASED ON [redacted]
Same shells as Table 6.1.1

TABLE 6.2.1 CHANGE FROM BASELINE TOTAL CAT SCORE ESTIMATES DURING THE TRIAL BASED ON [redacted]

Visit	LS Mean	95%CI
Month 3 Change from Baseline		
Covariate 1...n		

Footnote: CAT: COPD Assessment Test. LS: Least Square
Footnote: adjusted for covariates

TABLE 6.2.2 CHANGE FROM BASELINE TOTAL CAT SCORE ESTIMATES DURING THE TRIAL BASED ON [redacted]
TABLE 6.2.3 CHANGE FROM BASELINE TOTAL CAT SCORE ESTIMATES DURING THE TRIAL BASED ON [redacted]
Same shell as Table 6.2.1

TABLE 7.1.1 SHIFT CHANGES OF IMPAIRED HEALTH PATIENTS BASED ON OBSERVED DATA

	Baseline		3 Months							
			>10		<10		Missing		Total	
CAT Score	n	%	n	%	n	%	n	%	n	%
>10										
<10										
Missing										
Total										

TABLE 7.1.2 SHIFT CHANGES OF IMPAIRED HEALTH PATIENTS BASED ON [redacted]

TABLE 7.1.3 SHIFT CHANGES OF IMPAIRED HEALTH PATIENTS BASED ON [redacted]

Same shells as Table 7.1.1

TABLE 7.2.1 CHANGE FROM BASELINE OF THE IMPAIRED HEALTH PATIENTS DURING THE TRIAL BASED ON [redacted]

Visit	OR	95%CI for OR
Month 3 Change from Baseline		
Covariate 1...n		

Footnote: CAT: COPD Assessment Test. OR: Odds Ratio
Footnote: adjusted for covariates

TABLE 7.2.2 CHANGE FROM BASELINE OF THE IMPAIRED HEALTH PATIENTS DURING THE TRIAL BASED ON [redacted]

TABLE 8.1.1 MEAN EQ VISUAL ANALOGUE SCALE BY VISIT BASED ON OBSERVED DATA.

Visit		n	Mean	Median	SD	Min	Max	Q1	Q3	Missing
Baseline	Base									
Month 3	Base									
	Post									
	Change									

Footnote1: at 3 months only subjects with both baseline and post baseline value will be included.
Footnote2: EQ-VAS's range is 0-100 where zero represents the worst state the patient can imagine and 100 the best.

TABLE 8.1.2 MEAN EQ VISUAL ANALOGUE SCALE BY VISIT BASED ON [redacted]

TABLE 8.1.3 MEAN EQ VISUAL ANALOGUE SCALE BY VISIT BASED ON [redacted]

Same shell as Table 8.1.1

TABLE 8.2.1 MEAN CHANGE FROM BASELINE OF EQ-VAS BASED ON [redacted]

Visit	LS Mean	95%CI
Month 3		
EQ-VAS		

*EQ-VAS: EQ visual analogue scale.
Footnote: adjusted for covariates

TABLE 8.2.2 MEAN CHANGE FROM BASELINE OF EQ-VAS BASED ON [redacted]

TABLE 9.1.1 SHIFT CHANGES OF MOBILITY DIMENSION OF EQ-5D-5L BASED ON OBSERVED DATA

	Baseline N=xxx		3 Months N=xxx									
			I have no problems in walking about		I have some problems in walking about		I am confined to bed		Missing		Total	
Mobility Statements	n	%	n	%	n	%	n	%	n	%	n	%
I have no problems in walking about												
I have some problems in walking about												
I am confined to bed												
Missing												
Total												

TABLE 9.1.2 SHIFT CHANGES OF MOBILITY DIMENSION OF EQ-5D-5L BASED ON [redacted]
TABLE 9.1.3 SHIFT CHANGES OF MOBILITY DIMENSION OF EQ-5D-5L BASED ON [redacted]
TABLE 9.2.1 SHIFT CHANGES OF SELF-CARE DIMENSION OF EQ-5D-5LBASED ON OBSERVED DATA.
TABLE 9.2.2 SHIFT CHANGES OF SELF-CARE DIMENSION OF EQ-5D-5L BASED ON [redacted]
TABLE 9.2.3 SHIFT CHANGES OF SELF-CARE DIMENSION OF EQ-5D-5L BASED ON [redacted]
TABLE 9.3.1 SHIFT CHANGES OF USUAL ACTIVITIES DIMENSION OF EQ-5D-5L BASED ON OBSERVED DATA.
TABLE 9.3.2 SHIFT CHANGES OF USUAL ACTIVITIES DIMENSION OF EQ-5D-5L BASED ON [redacted]
TABLE 9.3.3 SHIFT CHANGES OF USUAL ACTIVITIES DIMENSION OF EQ-5D-5L BASED ON [redacted]
TABLE 9.4.1 SHIFT CHANGES OF PAIN/DISCOMFORT DIMENSION OF EQ-5D-5L BASED ON OBSERVED DATA.
TABLE 9.4.2 SHIFT CHANGES OF PAIN/DISCOMFORT DIMENSION OF EQ-5D-5L BASED ON [redacted]
TABLE 9.4.3 SHIFT CHANGES OF PAIN/DISCOMFORT DIMENSION OF EQ-5D-5L BASED ON [redacted]
TABLE 9.5.1 SHIFT CHANGES OF ANXIETY/DISPERSION DIMENSION OF EQ-5D-5L BASED ON OBSERVED DATA.
TABLE 9.5.2 SHIFT CHANGES OF ANXIETY/DISPERSION DIMENSION OF EQ-5D-5L BASED ON [redacted]
TABLE 9.5.3 SHIFT CHANGES OF ANXIETY/DISPERSION DIMENSION OF EQ-5D-5L BASED ON [redacted]
Same shells as 9.1.1

TABLE 9.6.1.1 CHANGE FROM BASELINE ON THE MOBILITY DIMENSION DURING THE TRIAL BASED ON [redacted]

Visit	OR of improvement	95%CI for OR
Month 3		
Covariate 1…n		

Footnote: adjusted for covariates OR: Odds Ratio

TABLE 9.6.1.2 CHANGE FROM BASELINE ON THE MOBILITY DIMENSION DURING THE TRIAL BASED ON [redacted]
TABLE 9.6.2.1 CHANGE FROM BASELINE ON THE SELF-CARE DIMENSION DURING THE TRIAL BASED ON [redacted]
TABLE 9.6.2.2 CHANGE FROM BASELINE ON THE SELF-CARE DIMENSION DURING THE TRIAL BASED ON [redacted]
TABLE 9.6.3.1 CHANGE FROM BASELINE ON THE USUAL ACTIVITIES DIMENSION DURING THE TRIAL BASED ON [redacted]
TABLE 9.6.3.2 CHANGE FROM BASELINE ON THE USUAL ACTIVITIES DIMENSION DURING THE TRIAL BASED ON [redacted]
TABLE 9.6.4.1 CHANGE FROM BASELINE ON THE PAIN/DISCOMFORT DURING THE TRIAL BASED ON [redacted]
TABLE 9.6.4.2 CHANGE FROM BASELINE ON THE PAIN/DISCOMFORT DURING THE TRIAL BASED ON [redacted]
TABLE 9.6.5.1 CHANGE FROM BASELINE ON THE ANXIETY/DEPRESSION DIMENSION DURING THE TRIAL BASED ON [redacted]
TABLE 9.6.5.2 CHANGE FROM BASELINE ON THE ANXIETY/DEPRESSION DIMENSION DURING THE TRIAL BASED ON [redacted]
Same shells as 9.6.1.1

TABLE 10.1.1 SUMMARIES OF SMAQ QUESTIONNAIRE BASED ON OBSERVED DATA.

	N=xxx
Forget to take the medication for IPF	
Yes	
No	
Missing	
Always take your medication for IPF at the indicated time.	
Yes	
No	
Missing	
If feel worse, do you stop taking the medication for IPF?	
Yes	
No	
Missing	
At the last week, How often did you miss the medication for IPF?	
Never	
1-2 times	
3-5 times	
6-10 times	
More than 10 times	
At the past 3 Months	

	N=xxx
Days of missed medication for IPF	
n	
Mean	
Median	
SD	
Minimum	
Maximum	
Q1	
Q3	
Missing	
Days of missed one of the two daily doses of medication for IPF	
n	
Mean	
Median	
SD	
Minimum	
Maximum	
Q1	
Q3	
Missing	

TABLE 10.1.2 SUMMARIES OF SMAQ QUESTIONNAIRE BASED ON [redacted]

Same Shell as 10.1.1

TABLE 10.2.1 PROPORTION OF ADHERED AND NOT ADHERED PATIENTS BASED ON OBSERVED DATA.

Adherence	n	%
Yes		
No		
Missing		

*EQ-VAS: EQ visual analogue scale.

TABLE 10.2.2 PROPORTION OF ADHERED AND NOT ADHERED PATIENTS BASED ON [redacted]

Same shell as Table 10.2.1

TABLE 10.2.3 CHANGE FROM BASELINE OF CAT SCORE BY ADHERENCE

Adherence	n	Mean	Median	SD	Min	Max	Q1	Q3	Missing	Sig.
Yes										
No										
Difference										

TABLE 11.1.1 MEAN SCORE OF PASAPQ QUESTIONNAIRE BASED ON OBSERVED DATA

How satisfied are you with the:	n	Mean	Median	SD	Min	Max	Q1	Q3	Missing
Overall feeling of inhaling.									
Feeling that the inhaled dose goes to your lungs.									
Amount of medication left in your inhaler									
Reliability of inhaler									
Ease of inhaling a dose from the inhaler									
Instructions of use									
Size of inhaler									
Durability of inhaler									
Ease of cleaning the inhaler									
Using of inhaler									
Speed at which medicine comes out of the inhaler									
Ease of holding the inhaler during the use									
Convenience of carrying the inhaler									
Total score 1-13 Question									
Overall satisfaction of inhaler									

TABLE 11.1.2 MEAN SCORE OF PASAPQ QUESTIONNAIRE BASED ON [redacted]

Same shell as 11.1.1

TABLE 12.2.1 PASAPQ QUESTIONNAIRE PART II BASED ON OBSERVED DATA.

	n	%
Preference of inhaler		
Spiriva® Handihaler®		
Spiolto® Respimat®		
No preference		
Missing		
Willingness to continue using the inhaler		
n		
Mean		
Median		
SD		
Minimum		
Maximum		
Q1		
Q3		
Missing		

Footnote: Willingless' range is 0-100, where 100 indicates that the patient would definitely be willing to continue using the inhaler and 0 indicates that the patient would definitely not be willing to continue using the inhaler

TABLE 12.2.2 PASAPQ QUESTIONNAIRE PART II BASED ON [redacted]

Same shell as 12.2.1

TABLE 10.2.3 CORRELATION OF CAT CHANGE FROM BASELINE WITH WILLINGNESS TO CONTINUE WITH THE INHALLER

		R correlation	Sig.
CAT change from baseline	Willingness to continue		

TABLE 13.1.1 MMRC SCORE BY VISIT BASED ON OBSERVED DATA.

Visit		n	Mean	Median	SD	Min	Max	Q1	Q3	Missing
Baseline	Base									
Month 3	Base									
	Post									
	Change									

TABLE 13.1.2 MMRC SCORE BY VISIT BASED ON [redacted]

TABLE 13.1.3 MMRC SCORE BY VISIT BASED ON [redacted]

Same shell as Table 13.1.1

TABLE 13.2.1 SHIFT CHANGES OF MMRC DURING THE TRIAL BASED ON OBSERVED DATA.

	Baseline		3 Months													
			0		1		2		3		4		Missing		Total	
mMRC Grade	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
0																
1																
2																
3																
4																
Missing																
Total																

TABLE 13.2.2 SHIFT CHANGES OF MMRC DURING THE TRIAL BASED ON [redacted]

TABLE 13.2.3 SHIFT CHANGES OF MMRC DURING THE TRIAL BASED ON [redacted]

Same shell as Table 13.2.1

TABLE 13.3.1 CHANGE FROM BASELINE OF MMRC BASED ON [redacted]

	LS Mean	95%CI
Month 3 Change from Baseline		

mMRC: Modified British Medical Research Council ranged in (0-4).LS : Least Square
Footnote: adjusted for covariates

TABLE 13.3.2 CHANGE FROM BASELINE OF MMRC BASED ON [redacted]

[redacted]

[redacted]

TABLE 15.1 CONTINUATION OF THERAPY

	n	%
Continuation with Spiolto Respimat during the study		
Yes		
No		
Missing		
Reason for discontinuation		
Not work well enough		
Stopped working well		
Side effects		
Illness unrelated to treatment development		
Symptoms improved and prefer not to continue the treatment		
Too inconvenient		
Cannot afford treatment		
Other reason		
Continuation with Spiolto Respimat after the study		
Yes		
No		
Missing		

[redacted]

TABLE 17.1 SMOKING STATUS CHANGES

Has the smoking status changed from Baseline visit?	n	%
Yes		
No		
Unknown		
Missing		

TABLE 17.2 CHANGE FROM BASELINE OF FVC (%) PREDICTED.

Visit		n	Mean	Median	SD	Min	Max	Q1	Q3	Missing
Baseline	Base									
Month 3	Base									
	Post									
	Change									

TABLE 17.3 CHANGE FROM BASELINE OF FEV1/FVC (%) PREDICTED.
TABLE 17.4 CHANGE FROM BASELINE OF TROUGHFEV1 (%) PREDICTED.
*Trough FEV1 is the morning pre dose FEV1
Same shells as Table 17.2

TABLE 17.5 SHIFT CHANGES OF PNEUMONIA

	Baseline	3 Months									
		Yes		No		Not Evaluated		Missing		Total	
Pneumonia	n %	n	%	n	%	n	%	n	%	n	%
Yes											
No											
Not Evaluated											
Missing											
Total											

TABLE 17.6 SHIFT CHANGES OF ALLERGIC RHINITS

TABLE 17.7 SHIFT CHANGES OF BRONCHIECTASIS

TABLE 17.8 SHIFT CHANGES OF LUNG DISEASES DUE TO EXTERNAL AGENTS

Shame shells as 17.5

TABLE 17.9 SHIFT TABLE OF GOLD GROUP

	Baseline	3 Months											
		A		B		C		D		Missing		Total	
Gold group	n %	n	%	n	%	n	%	n	%	n	%	n	%
A													
B													
C													
D													
Missing													
Total													

TABLE17.10 LISING OF OUTLIERS

Patient Code	Variable	Value	Visit	Procedure Taken*

*If applicalbe

TABLE17.11.1 OVERVIEW OF ADVERSE EVENTS

	n (%)
Subjects treated	
Subjects with at least one:	
AE	
ADR	
Serious AE	
Serious AE leading to drug discontinuation	
Serious AE Leading to Death	
Number of pregnant patients with at least one AE	

TABLE17.11.2 OVERVIEW OF ADVERSE EVENTS RELATED TO COVID-19

	n (%)
Subjects treated	
Subjects with at least one:	
AE related to COVID-19	
Serious AE related to COVID-19	
Serious AE leading to drug discontinuation related to COVID-19	
Serious AE Leading to Death related to COVID-19	

TABLE 17.12 SUMMARY OF ADVERSE EVENTS BY SYSTEM ORGAN CLASS AND PREFERRED TERM

System Organ Class (SOC) Preferred Term (PT)	n (%)
Subjects treated	
System Organ Class 1	
Preferred Term 1	
:: ::	
:: ::	
Preferred Term N	
: :: ::	
System Organ Class N	
Preferred Term 1	
:: ::	
:: ::	
Preferred Term N	

Footnote: SOC terms are sorted alphabetically; PTs are sorted within each SOC term by decreasing frequency.
If a subject reported more than one AE within the same PT, the subject is counted only once for this PT.
If a subject reported more than one AE within the same SOC, the subject is counted only once for this SOC.
MedDRA xx.x was used for reporting.

LISTING 17.13 PREMATURE DISCONTINUATION OF STUDY DRUG

Patient Code	Age (yrs) / Sex	Date of ICF	Discontinuation Reason	Date of discontinuation

LISTING 17.14 ADVERSE EVENTS IN THE STUDY

Subject ID	SOC/ PT	Start Date / End Date	Causal Relationship of BI med/product	Serious (Y/N)/	SAE criteria fulfilled	Action Taken	Outcome	Treatment Administered

ANNEX 2. REVIEWERS AND APPROVAL SIGNATURES

The NIS SEAP must be sent for review to the following individuals **prior to approval**.

Reviewer	NIS involving BI product(s)	NIS not involving BI product(s)	
		Global NIS	Local NIS
[redacted]	X	X	X
[redacted]	X	X	X
[redacted]	X	X	X
[redacted]	X	X	X
[redacted]	X	X	

** When BI NIS lead is not TM Epi*

Study 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)

Study Number: 1237-0098

Protocol Version: 3.0

I herewith certify that I agree to the content of the study SEAP and to all documents referenced in the study SEAP.

Position: NIS [redacted] Name/Date: [redacted] Signature**:** _____

Position: [redacted] Name/Date: Signature**:** _____

Position: [redacted] Name/Date: Signature**:** _____

Position: [redacted] Name/Date Signature**:** _____