TRIAL STATISTICAL ANALYSIS PLAN

BI Study No.:	1237.0073
Title:	Changes in health and functional status in patients with Chronic Obstructive Pulmonary Disease (COPD) during therapy with Spiolto® Respimat® [ELLACTO]
Investigational Product(s):	Spiolto® Respimat®
Responsible trial statistician(s):	
Date of statistical analysis plan:	26 July 2019
Version:	Final 1.1

1 TABLE OF CONTENTS

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2 LIST OF ABBREVIATIONS

Term	Definition / description
ADR	Adverse Drug Reaction
AE	Adverse Event
BI	Boehringer Ingelheim
CCQ	Clinical COPD Questionnaire
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case Report Form
CTP	Clinical Trial Protocol
ECG	Electrocardiogram
GOLD	Global Initiative for Chronic Obstructive Lung Disease
HH	HandiHaler Inhaler Device
ICF	Informed Consent Form
ICH	International Conference On Harmonisation
ICS	Inhalative Corticosteroides
LABA	Long-Acting Beta2 Adrenoceptor Agonist
LAMA	Long-Acting Muscarinic Antagonist
MCID	Minimal Clinically Important Difference
MedDRA	Medical Dictionary For Regulatory Activities
mMRC	Modified Medical Research Council
NIS	Non-Interventional Study
PASAPQ	Patient Satisfaction and Preference Questionnaire
PGE	Physician's Global Evaluation
PV	Protocol Violation
RMT	Respimat Inhaler Device
SAE	Serious Adverse Event
SAS	Statistical Analysis Software (System)

Term	Definition / description
SD	Standard Deviation
SmPC	Summary of Product Characteristics
SOC	System Organ Class
TSAP	Trail Statistical Analysis Plan
WHO DD	World Health Organization Drug Dictionary

3 INTRODUCTION

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 TSAP assumes familiarity with the Clinical Trial Protocol (CTP) version 2.0, dated 28 August 2018 and Case Report Form version Final 4.0 dated 01 Jun 2018. In particular, the TSAP is based on the planned analysis specification as written in CTP Section 9.8 "Data Analysis". Therefore, TSAP readers may consult the CTP 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.

SAS® Version 9.2 or higher will be used for all analyses.

The objective of this non-interventional study (NIS) is to measure changes in health and functional status by the clinical COPD questionnaire (CCQ), in COPD patients receiving treatment with Spiolto® Respimat® after approximately 6 weeks in routine clinical practice. Clinical studies investigating treatment with Spiriva® or with Striverdi® Respimat® and as well as with the combination Spiolto® Respimat®, have shown significant improvement in exercise capacity in patients with COPD. However, real life data with regards to the effects of a combination therapy with the approved brand Spiolto® Respimat® in COPD patients who need two long-acting bronchodilators are not yet available. This study aims to investigate functional status of COPD patients treated with Spiolto® Respimat® by means of the CCQ questionnaire, more specifically by its 'functional status' subdomain (CCQ-4).
Study results will be used to document the effectiveness of Spiolto® Respimat® in improving the functional status of COPD patients impaired in activity of daily living (ADL).

4 CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

As per amended protocol version 2.0, dated 28th Aug 2018, the statistical changes include change in CCQ score calculation (Section 9.8.3) and inclusion of secondary outcome "Treatment continuation of Spiolto® Respimat® after the study" (Section 9.3.2.2).

5 OUTCOMES

5.1 PRIMARY OUTCOME

- Proportion of patients achieving "therapeutic success" at visit 2 (i.e. approximately 6 weeks (± 10 days) after starting treatment) defined as ≥0.4 point of decrease in the total CCQ score between visit 1 (baseline) and visit 2.

5.2 SECONDARY OUTCOMES

5.2.1 Secondary outcomes

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

5.4 OTHER VARIABLES

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

Apart from the primary and secondary outcome variables, the following information will be collected during the study:

- **Visit 1 (Baseline):** Patients demographics, COPD and other relevant medical history, comorbidities, reported exacerbations based on medical history in the last 12 months and exacerbations leading to hospitalization in the last 12 months, GOLD patient groups (B, C, D) based on GOLD guidelines, GOLD spirometric classifications (1, 2, 3, 4) (when available), mMRC, smoking history, previous and concomitant pulmonary medication.Pregnancies at the beginning of the study.
- **Visit 2 (Next medical consultation approximately at 6 weeks ± 10 days):** Adverse events and safety reporting; adverse drug reactions (serious and non-serious), fatal AEs, pregnancies at the end of the study, withdrawal from treatment since visit 1 (baseline).

Baseline characteristics of eligible patients and provided informed consent, but were not treated in the study will also be collected.

6 GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENT

This is a self-controlled non interventional study enrolling consented COPD patients who will be treated with Spiolto® Respimat® according to approved Greek SmPC. Enrolled patients will undergo 2 study visits. Visit 1 (baseline visit) during screening and enrollment, visit 2 (follow up visit) at the end of 6 weeks (± 10 days) therapy with the product. A telephone contact will take place 2 weeks (± 10 days) after first day of therapy to check for compliance and safety issues.

All patients will receive LAMA/LABA combination treatment with Spiolto® Respimat® according to the Greek SmPC. 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 decision to treat will be taken independently of participation in this NIS and will be made before participation is considered.

6.2 IMPORTANT PROTOCOL VIOLATIONS

The following table 6.2: 1 defines the different categories of important protocol violations. The final column (i.e. excluded from) in the table 6.2:1 describes which PVs will be used to exclude the patients from the different patient analysis sets. In this example, patients are either excluded from "All" analysis sets or the “Treated set” or the “Full analysis set” or “None” of the patients analysis sets. The following table defines the different categories of important PVs but not limited to:

Table 6.2: 1 Important Protocol Violation

Category/ code		Description	Requirements	Detected by	Excluded From
A		**Entrance criteria not met**			
	A1	**Inclusion criteria not met**			
	A1.1	Patients with COPD diagnosis and therapeutic indication of two long-acting	Patient not diagnosed with COPD and/or do not	Manually	None

Category/ code		Description	Requirements	Detected by	Excluded From
		bronchodilators (LAMA + LABA) combination according to approved SmPC and guidelines, COPD GOLD 2017 groups B to D.	have any therapeutic indication of two long-acting bronchodilators (LAMA + LABA) combination according to approved SmPC and guidelines, COPD GOLD 2017 groups B to D.		
	A1.2	Female and male patients ≥ 40 years of age	Female and male patients < 40 years of age	Automated	None
	A1.3	Treatment with Spiolto ® Respimat® acc. to SmPC and at the discretion of the physician.	Treatment with Spiolto® Respimat® not acc. to SmPC and not at the discretion of the physician.	Manually	None
	A1.4	Written informed consent prior to participation	Informed consent not taken prior to participation or taken too late or missing informed consent date	Automated	All
	A2	**Exclusion criteria met**			
	A2.1	Patients with contraindications according to Spiolto® Respimat® SmPC	Patients with contraindications according to Spiolto® Respimat® SmPC	Manually	None
	A2.2	Patients treated with a LABA/LAMA combination (free and fixed dose) in the previous 6 weeks or patients already on a combination of LAMA and LABA therapy; either as a fixed combination	Patients who treated with a LABA/LAMA combination (free or fixed dose) in previous 6 weeks or patients already on a	Manually	None

Category/ code		Description	Requirements	Detected by	Excluded From
		product or as separate components Note: Patients previously treated with LABA or LAMA (with or without ICS) are eligible to be included in the study	combination of LAMA and LABA therapy; either as a fixed combination product or as separate components		
	A2.3	Patients continuing LABA-ICS treatment	Patients continuing LABA-ICS treatment during the study	Manually	None
	A2.4	Patients for whom further follow-up is not possible at the enrolling site during the planned study period of approximately 6 weeks	Patients for whom further follow-up is not possible at the enrolling site during the planned study period of approximately 6 weeks ± 10 days of window period	Automated	None
	A2.5	Pregnancy and lactation	Pregnancy and lactation (before participation and during the study)	Manually	None
	A2.6	Patients currently listed for lung transplantation	Patients currently listed for lung transplantation	Manually	None
	A2.7	Current participation in any clinical trial or any other non-interventional study of a drug or device.	Current participation in any clinical trial or any other non-interventional study of a drug or device.	Manually	None

KEY: IPV- Important Protocol Violation, TS- Treated set, FAS- Full analysis set

Note: Automated PVs are those detected via programmatically process. Manual PVs are those can not be detected through the data and it's picked up through other processes such as

site monitoring or IPV that is too complex to program which identified by the trial medical team. Important protocol violations will be defined and documented prior to clinical database lock. A strategy for dealing with data affected by protocol deviations will be agreed upon by the coordinator, Sponsor and Biostatistician before clinical database lock.
All the important protocol violations will be listed.

6.3 PATIENTS SET ANALYSED

- **Enrolled Set:**
  Enrolled set include all screened patients with the informed consent and date of registration.

- **Treated Set (TS):**
  Treated set include all screened patients with the informed consent, date of registration and at least one documented administration of Spiolto® Respimat®.

- **Full Analysis Set (FAS):**
  Full analysis set include all screened patients with informed consent, date of registration, at least one documented administration of Spiolto® Respimat® and available total CCQ score at visit 1 and visit 2.

If patients have missing values for an outcome, those patients will be excluded for that outcome's analysis as specified under section 6.6.
The below table 6.3:1 explains the patient analysis set to be used for each planned analysis

Table 6.3: 1 Patients sets analysed

Class of outcomes	Patient set		
	Enrolled set	Treated set	Full analysis set
Primary and key secondary outcomes	-	-	X
(Other) Secondary and further outcomes	-	-	X
Safety endpoints	-	X	-

Class of outcomes	Patient set		
	Enrolled set	Treated set	Full analysis set
Demographic/baseline outcomes	-	X	-
Disposition/inclusion exclusion criteria and important protocol violation	X	-	-

Note: No key secondary and further outcomes mentioned in CTP.

6.5 POOLING OF CENTRES

This section is not applicable because centre/country is not included in the statistical model .

6.6 HANDLING OF MISSING DATA AND OUTLIERS

The questions in Clinical COPD Questionnaire (CCQ) are divided into symptoms based, function state and mental state domains. Total CCQ score with missing data can not be calculated if domain specific CCQ score are not calculable as per the rule specified in TSAP section 7.4.

When a data is ambiguous (e.g. if patient fills in two answers on one question), the data should be considered as missing.

For example, when one question in mental state domain has missing or ambiguous score, then CCQ score for mental state domain can not be calculated. Hence, total CCQ score can not be calculated and will be considered as missing.

Other missing values will be considered as missing, no imputation will be done for the analysis purpose.

Missing or incomplete AE dates are imputed according to BI standards [2] (i.e. "Handling of missing and incomplete AE dates").

No outlier analysis is planned for this study.

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

Values observed at Visit 1 during screening and enrollment will be considered as baseline assessment.

Enrolled patients will undergo two study visits. Visit 1 (baseline visit) and visit 2 (follow up visit) approximately at the 6 weeks (± 10 days of window period) after therapy with the product. A telephone contact will take place 2 weeks (± 10 days of window period) after first day of therapy to check for compliance and safety issues.

7 PLANNED ANALYSIS

- All study data will be included in individual patient study data listings. In general, all data will be listed by visit, study site and patients (wherever applicable). All summary tables will be presented with descriptive statistics for the parameters being analyzed, wherever applicable.
- Numeric presentations:

- Non-integer numerical data should be presented with decimal point.
- If the non-formatted data that are received (e.g., from the clinical database) are inconsistently presented, a decision on how to present the final data will be made on a case-by-case basis.
- When rounding is required, number 5 or above will be rounded up.
- When deriving new variable(s) based on raw data, no rounding will be performed at intermediate calculation. Rounding will only be performed when displaying data.
- For End-Of-Text (EoT) tables, Descriptive analysis for continuous data will include number of non-missing observations (n), mean, standard deviation (SD), median, minimum and maximum. Means and medians will be rounded to 1 decimal place additional to the original data. Standard deviation will be rounded to 2 decimals place additional to the original data. Minimum and maximum will be displayed with the same decimal precision as the original data. Q1 and Q3 will be presented with 1 decimal additional to the original data.
- For tables that are provided for primary and secondary outcomes with some extreme data, median, quartiles and percentiles should be preferred to mean, standard deviation, minimum and maximum.
- Proportion and its confidence interval will be presented with 2 decimal places whenever applicable.

- Tabulations of frequencies for categorical data will include all possible categories and will display the number of observations in a category as well as the percentage (%) relative to the respective patient set whether they have non-missing values or not.
- Percentage should be displayed without the "%" sign within the data column. The precision for percentages should be one decimal point. The category missing will be displayed only if there are actually missing values.
- Zero count and percentage will be presented as '0' only.

- Missing data will not be imputed but will be analyzed as missing.
- Baseline assessments are the assessments taken at the visit 1 for all patients. If there are multiple assessments collected on the same scheduled time, the average of these assessments will be used.
- The change from baseline is defined as the post-baseline value minus the baseline value.
- Text column should be left justified.
- All the data analysis will be done using SAS® version 9.2 or higher.

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographic and other baseline characteristics at visit 1 (baseline) will be listed individually by study site and patients and only descriptive statistics are planned for the demographic and baseline characteristics.

Age, age at start of COPD, height, weight, number of exacerbation in the last 12 months, number of exacerbation leading to hospitalization in the last 12 months and number of pack-years will be summarized using descriptive statistics and gender (male and female), pregnancy status (pregnant, not pregnant and not applicable), number of exacerbation in last 12 months (0, 1 and ≥2), number of exacerbation leading to hospitalization in the last 12 months (0, 1 and ≥2), smoking status (smoker, ex-smoker, nonsmoker), Spirometric COPD severity (GOLD spirometric classification 1, 2, 3, 4), COPD severity (GOLD patients group B, C, D and mMRC score will be summarized using frequency counts and percentages.

Table 7.1: 1 Breathlessness based on mMRC scale

mMRC scale	**Breathlessness condition**
Grade 0	I only get breathless with strenuous exercise.
Grade 1	I get short of breath when hurrying on the level or walking up a slight
Grade 2	On level ground, I walk slower than people of the same age on the level because of breathlessness, or I have to stop for breath when walking on my own pace.
Grade 3	I stop for breath after walking about 100 yards (about 91 meters) or after a few minutes on the level ground.
Grade 4	I am too breathless to leave the house or I am breathless when dressing.

7.2 CONCOMITANT DISEASES AND MEDICATION

Relevant past and concomitant medical conditions/ diseases/ comorbidities and concomitant medication will be listed individually by site and patients.

All the past and concomitant medical conditions/ diseases/ comorbidities will be coded using MedDRA, version 20.1 or higher.

Patients used other COPD related therapeutics in last 6 months prior to treatment will be listed individually by site and patients separately.

Medication used before the first dose of Spiolto® Respimat® will be considered as prior medication and medication used after the first dose or medication used during the study duration will be recorded as concomitant medications.

All prior or concomitant medications will be coded using the World Health Organization Drug Dictionary (WHO DD), enhanced version September 2017 or later, and will be summarized using frequency counts and percentages as per ATC level 3 text.

7.3 TREATMENT COMPLIANCE

No analysis planned for compliance of treatment.

7.4 PRIMARY OUTCOME

The primary outcome is to measure the proportion of patients achieving the "therapeutic success" defined as a ≥0.4 point of decrease in the Clinical COPD Questionnaire (CCQ) score between visit 1 (baseline) and visit 2 (approximately 6 weeks ± 10 days after visit 1). A change of ≥0.4 points (decrease) is considered to be the minimal clinically important difference (MCID) for both CCQ score and CCQ-4.

CCQ is short questionnaire with 10 questions (regards to their symptoms, functional and mental state) and that is scored by the patient on a 7-point scale between 0 (very good health status) and 6 (extremely poor health status) at visit 1 (baseline) and visit 2 (end of the observation approximately 6 weeks ± 10 days after visit 1). A higher score is indicative of worse status.

CCQ questionnaire is subdivided into three domains and rules required to calculate CCQ score is given as below in table 7.4:1.

Table 7.4: 1 Rules to calculate the CCQ score

Domain	**Questions number***	**Number of questions in domain**	**Number of questions required**	**% Required questions**
Symptoms	1, 2, 5 and 6	4	3	75
Functional state	7, 8, 9 and 10	4	3	75
Mental state	3 and 4	2	2	100

*Refer annex.3 of protocol i.e. additional information of protocol for Clinical COPD Questionnaire.

Individual questions within the CCQ are equally weighted.

Total CCQ score can be calculated if the number of required questions per each domain is available and individual domain specific CCQ scores are calculable.

Suppose scores for all the domain specific questions are available except one question with missing score in the functional status domain and/or symptom domain. So, functional status domain and symptom domain specific CCQ score can be calculated as per the rule though it has missing data. Hence, total CCQ score also can be calculated.

Domain specific CCQ score is calculated as below:

$$\text{Domain specific CCQScore} = \frac{\text{Sum of available scores for domain specific questions}}{\text{Number of non} - \text{missing questions for specific domain}}$$

The total CCQ score is calculated by adding the score of the ten questions divided by 10 or by multiplying the domain specific score with the original amount of questions and adding these numbers and dividing by 10 as below:

$$\text{Total CCQScore} = \frac{[(\text{Symptom domain score} \times 4) + (\text{Functional state domain} \times 4) + (\text{Mental state domain} \times 2)]}{10}$$

For example, when question #5 is not completed or there are two answers, the scores will be calculating as follows:

For the symptom domain, add the score from questions 1, 2 and 6 and divide by 3. Calculate the other domain scores as usual. To calculate the total score use the following algorithm mentioned above i.e.

$$\text{Total CCQScore} = \frac{[(\text{Symptom domain score} \times 4) + (\text{Functional state domain} \times 4) + (\text{Mental state domain} \times 2)]}{10}$$

Handling of the missing value or ambiguous values will be handled as specified in TSAP section 6.6.

The proportion of patients with therapeutic success (≥0.4 point decrease in total CCQ score from visit 1 to visit 2) at visit 2 will be presented with the 95% confidence interval.

The 95% confidence interval will be estimated using Clopper Pearson Exact method.

The following SAS program or other relevant program can be used to estimate the proportion and its related confidence interval.

```
proc freq data=<data-set>;
by <variable>;
tables <variable>/ binomial;
exact binomial;
run;
```

Also prepared Bar Graph of Number and Percentage of subjects achieved therapeutic success.

Subgroup analysis will be performed for primary outcome as per mentioned in the TSAP section 6.4.

7.5 SECONDARY OUTCOMES

7.5.1 Secondary outcomes

- The CCQ scores and CCQ-4 scores at both the visits and absolute change in the CCQ and CCQ-4 score from visit 1 to visit 2 will be summarized with descriptive statistics (n, mean, SD, maximum, median, minimum). The summary for the same will be presented for the patients with therapeutic success (i.e. ≥0.4 point decrease in CCQ score between visit 1 and visit 2. Also prepared Bar Graph of Absolute change in Total CCQ and CCQ-4 Score.

  CCQ-4 is the functional status subdomain of CCQ. The functional status (CCQ-4) is calculated as sum of the 4 questions i.e. question number 7, 8, 9 and 10 divided by 4.

  Additionally, subgroup analysis will be performed as specified in section 6.4.
- The Physician's Global Evaluation (PGE) assesses the patients general condition using and eight-point scale ranging from 1 (poor) to 8 (excellent). The Physician's Global Evaluation (PGE) score at visit 1 and visit 2 will be listed indivually by site, patients and visit and summarize by frequency count and percentage. Additionally, the shift from baseline table will be prepared for the PGE score and also prepared the Bar graph.
- Patient satisfaction with Spiolto® Respimat® will be evaluated at visit 2 using seven point ordinal scale ranging from very dissatisfy to very satisfied of abbreviated PASAPQ Part-I questionnaire. Patients satisfaction with Spiolto® Respimat® at visit 2 (end of the study) will be listed individually by site and patients and summarize by frequency count and percentage also prepared Bar Graph of Patients Satisfaction Score (PASAPQ Part I) at Visit 2.
- Patient preference (PASAPQ part-II: Rating of preference and willingness to continue with inhaler) at visit 2 (end of the study) for the patients who have used the Spiriva HH prior to the study will be listed indivually by site and patients and summarize by frequency and percentage and also prepared Bar Graph of Patients'(who have used

Spiriva HH prior to the study) Preference and Willingness to Continue with Inhaler (PASAPQ Part II) at Visit 2.

- Patients' willingness score to continue using Spiolto® Respimat® inhaler device at visit 2 for the patient who have used Spiriva HH prior to the study will be listed individually by site and patients and summarize by descriptive statistics. Patients' willingness score will range from 0 to 100. 0 indicated patient would not be willing to continue using Spiolto® Respimat® inhaler and 100 indicates patient would definitely be willing to continue Spiolto® Respimat® inhaler.
- Treatment continuation of Spiolto® Respimat® after the study will be measured based on the Yes/No question if treatment with Spiolto® Respimat® is going to be continued after the study. Percentage of patients willing to continue with Spiolto® Respimat® after the study will be summarized.

All the analysis related to primary and secondary outcomes will be carried out on full analysis set (FAS).

7.7 EXTENT OF EXPOSURE

Exposure to LAMA/LABA combination treatment with Spiolto® Respimat® will be estimated as time from the day treatment is initiated till the last dose administrated by the patient or study completion. Days on treatment will be summarized using N, mean, SD, minimum, median and maximum. Frequency and percentage will be presented for extent of exposure in weeks.

7.8 SAFETY ANALYSIS

In general, safety analyses will be descriptive in nature and will focus on ADRs (serious and non-serious), fatal AEs and pregnancy at the beginning and at the end of the study. All safety analyses will be based on the treated set.

Listings for adverse events, serious adverse event, adverse drug reaction (serious and non-serious), fatal adverse events and adverse events leading to treatment discontinuation will listed separately by SOC and PT.

Listing of the pregnant patients will be prepared separately.

7.8.1 Adverse events

Adverse events will be collected at the time points or visits as specified in the study protocol table 9.1.1 . AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 20.1 or higher. All AEs occurring from signing of ICF onwards until end of the study will be collected.

An AE is considered to be an adverse drug reaction (ADR) if either the physician who has reported the AE or the sponsor assesses its causal relationship between event and drug checked as 'Yes'.

The frequency and percentage of AEs/SAEs, AE with fatal outcome and ADRs (serious and non-serious) will be tabulated by system organ class and preferred term.

Multiple overlapping or adjacent recordings (AE occurrence) of same AE are collapsed into one AE event if all AE attributes are identical (patient number, LLT, outcome, therapy, intensity, action taken, seriousness, reason for seriousness, causal relationship).

Two AE occurrences are considered to be time-overlapping if the start date of the second, later occurrence is earlier or equal to the end date of the first occurrence.

Two AE occurrences are considered to be time-adjacent if the start date of the second, later occurrence is one day later than the end date of first occurrence.

All AEs will be listed individually for each patients by system organ class (SOC) and preferred term (PT) assigned to the AEs.

No imputation is planned for missing AE data except for missing dates which will be handled according to BI standard[(2)].

An overall summary of adverse events will be presented with counts and percentages.

Summary of adverse events will be based on frequency and percentage of patients.

Summary will be presented for adverse event (AE), adverse drug reaction (ADR), serious adverse drug reaction, adverse events (including AE, SAE, ADR and serious ADR) leading to treatment discontinuation and serious adverse event with other seriousness criteria included fatal AEs.

The frequency of patients with adverse events will be summarized by primary system organ class and preferred term. The system organ classes will be sorted by default alphabetically preferred terms will be sorted by frequency (within system organ class) in descending order.

Duration of AE will be calculated as AE end date minus AE onset date +1. Both onset and end dates need to be present to calculate a duration. If AE end date is missing then AE duration will be set as missing.

7.8.2 Laboratory data

This section is not applicable as no laboratory data are planned to collect as per the CTP.

7.8.3 Vital signs

This section is not applicable as no vital signs data are planned to collect as per the protocol.

7.8.4 ECG

This section is not applicable as no ECG data are planned to collect as per the protocol.

7.8.5 Others

No other data is planned to collect as per protocol.

8 REFERENCES

1.	001-MCS-40-415_RD-02: "Trial Statistical Analysis Plan (TSAP) Template (annotated, PDF copy)",version: 1.0
2.	001-MCG-156_RD-01: "Handling of Missing and Incomplete AE Dates", version: 3.0
3.	001-MCS-90-140: "Post-Authorization Safety Studies", version: 3.0
4.	001-MCS-05-504: "Reconciliation of Adverse Events Information in BI studies, version: 7.0
5.	001-MCS-50-408: "Medical and Quality Review in Clinical Trials", version: 5.0
6.	001-MCG-156: “Analysis and Presentation of Adverse Event Data from Clinical Trials”, version 8.0
7.	User manual, Macro XAE, Document number: 4058.321.06, version: 3.0

10 HISTORY TABLE

Table 10: 1 History table

Version	Date	Author	Sections Changed	Brief description of change
Final 1.1	26-July-2019		•Section 4, Section 7.5.1	• Section 4 updated as per amended protocol and secondary objective description updated.
Final 1.1	14-May-2019		•Section 5.2, Section 7.5	• Added secondary objective "Treatment continuation of Spiolto® Respimat® after the study" as per updated protocol version 2.0.
Final 1.0	12-Feb-2019		•	
Draft 1.3	10-Oct-2018		•Section 1 •Section5.1 Section7.4 Section7.5.1 •Section 5.4 •Section 6.2 •Section 7.4 Section 7.5.1	• Updated TSAP the latest version of TSAP display template • >0.4 is replace by >=0.4 • Safety reporting text is repeated in section 5.5, so it was removed. • Added word "medical" for "Note: … such as site monitoring or IPV that is too complex to program which identified by the trial medical team • Added following figures for primary and secondary endpoints Figure 15.2.1 Bar Graph of Number and Percentage of subjects achieved therapeutic success(Full Analysis Set) Figure 15.2.2 Bar Graph of Absolute change in Total CCQ Score(Full Analysis Set) Figure 15.2.3 Bar Graph of PGE Score at visit 1 and visit 2(Full Analysis Set) Figure 15.2.4 Bar Graph of Patients Satisfaction Score (PASAPQ Part I) at Visit 2 (Full Analysis Set) Figure 15.2.5 Bar Graph of

Version	Date	Author	Sections Changed	Brief description of change
				Patients'(who have used Spiriva HH prior to the study) Preference and Willingness to Continue with Inhaler (PASAPQ Part II) at Visit 2 (Full Analysis Set)
Draft 1.2	20-Sep-2018		•Section 1 •Section 6.3 •Table 6.3: 1 • •Section 6.5 •Section 7.8.1 •Section 8	• Updated TSAP the latest version of TSAP display template • List of table added under table of contents • Definition of patient analysis set has updated • Updated the table 6.3: 1 for more clarification • • Updated text for pooling of centres • Other significant adverse event removed from the adverse event analysis • Removed section 8.0
Draft 1.1	22-Jun-2018		•Section 5.1 •Section 5.2 •Section 5.2.1 •Section 5.4 •Section 6.2 •Section 6.3 •Section 6.6 •Section 7 •Section 7.4 •Section 7.5.1 •Section 7.5.2 •Section 7.8.1	• Mentioned more specific primary and secondary outcomes under section 5.1 and 5.2 • Removed section 5.2.1 as not applicable • Updated section 5.4 • Updated analysis set to be excluded from for specific iPVs. • Updated patient analysis set under section 6.3 • Handling of missing data and ambiguous values for the calculation of CCQ score updated under section

Version	Date	Author	Sections Changed	Brief description of change
				6.6 • Section 7 updated for the numeric presentation of data • Section 7.4 updated for the method to calculate CCQ score • Section 7.5.1 removed as not applicable • More measurement details specified for secondary outcomes under section 7.5.2 • Added definition of other significant adverse event under section 7.8.1
Draft 1.0	03-April-2018		None	This is the initial TSAP with necessary information for trial conduct