Trial Statistical Analysis Plan

BI Trial No.:	1237-0072
Title:	NIS 1237-0072: Changes in clinical control of COPD patients measured by the Clinical COPD Questionnaire during therapy with Spiolto® Respimat® in routine clinical practice
Investigational Product(s):	Spiolto® Respimat® 2.5 microgram/2.5 microgram per puff inhalation solution
Responsible trial statistician(s):	
Date of statistical analysis plan:	19 July 2019
Version:	Final 2.0

1. TABLE OF CONTENTS

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2. LIST OF ABBREVIATIONS

Term	Definition / description
AE	Adverse event
BI	Boehringer Ingelheim Pharma GmbH&Co. KG
CCQ	Clinical COPD Questionnaire
CR	Complete Response
COPD	Chronic obstructive lung disease
GOLD	Global Initiative for Chronic Obstructive Lung Disease
LABA	Long-acting beta2-adrenoceptor agonist
LAMA	Long-acting anticholinergic bronchodilator
Max	Maximum
MedDRA	Medical Dictionary for Drug Regulatory Activities
Min	Minimum
mMRC	Modified Medical Research Council Scale
NIS	Non-interventional study
PGE	Physician’s global Evaluation
SAE	Serious Adverse event
TEAE	Treatment-emergent AE
TSAP	Trial Statistical Analysis Plan

3. INTRODUCTION

As per ICH E9[1], 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), including Protocol Amendments. In particular, the TSAP is based on the planned analysis specification as written in CTP Section 9.7 “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, randomization.

SAS® Version 9.4 or higher will be used for all analyses.

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

    - In addition to the protocol, subgroup analyses will be performed for all secondary endpoints, i.e. for changes from baseline in CCQ scores (symptom, functional state (CCQ-4), mental state and total scale), patient's satisfaction and willingness to continue treatment as well as PGE

- New analyses set, which is not mentioned in the protocol (Details are displayed in TSAP Section 6.3):
    - Full analysis set (FAS)

5. ENDPOINT(S)

5.1 PRIMARY ENDPOINT(S)

The primary endpoint of the presented study is "therapeutic success" at visit 2 i.e. approximately 6 weeks after starting treatment, defined as 0.4-point decrease in the total CCQ score between visit 1 and visit 2.

5.2 SECONDARY ENDPOINT(S)

- Absolute changes in CCQ scores (symptom, functional state (CCQ-4), mental state and total scale) from visit 1 to visit 2
- General condition of the patient, evaluated by the physician (PGE score) at visit 1 and visit 2
- Patient satisfaction with Spiolto® Respimat® at visit 2
- Patients' willingness to continue with Spiolto® Respimat® at visit 2

5.4 OTHER VARIABLE(S)

Other variables will be baseline characteristics and patient's characteristics such as age, gender, height and weight. Additionally information about concomitant medication, diseases, therapy data, further therapies and comorbidities will be collected as well as about smoking status, exacerbation history, mMRC and GOLD group.

6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENT(S)

In the presented study, treatment with Spiolto® Respimat® will be according to product information.

6.2 IMPORTANT PROTOCOL VIOLATIONS

Table 6.2: 1 defines the different categories of important protocol violations (PVs). The final column describes which PVs will be used to exclude subjects from the different patient analysis sets[2].

Table 6.2: 1 Important protocol violations

Category/ Code		Description	Requirements	Excluded from
A		**Entrance criteria not met**		
	A1.1	Inclusion criterion 2 (Female or male patients >=40 years of age)	Not met as specified in the protocol	None
	A1.2	Inclusion criterion 3 (Patients diagnosed with COPD and requiring a combination of two long-acting bronchodilators according to Spiolto® Respimat® SmPC, GOLD COPD strategy document 2018 (GOLD COPD groups B to D) and local COPD guidelines)	Not met as specified in the protocol	None
	A2.1	Exclusion criterion 1 (Patients with contraindications according to Spiolto® Respimat® SmPC)	Met as specified in the protocol	None
	A2.2	Exclusion criterion 2 (Patients already on a LABA/LAMA or LABA/LAMA/ICS combination (free and fixed dose) in the last 6 weeks before study entry)	Met as specified in the protocol	None
	A2.3	Exclusion criterion 3 (Patients continuing LABA/ICS treatment after study enrolment)	Met as specified in the protocol	None
	A2.4	Exclusion criterion 4 (Current participation in any clinical trial or any other non-interventional study of a drug or device)	Met as specified in the protocol	None
	A2.5	Exclusion criterion 5 (Pregnancy or lactation)	Met as specified in the protocol	None
B		**Informed consent**		
	B1	Informed consent not available/not done (Inclusion criterion 1)	IC 01 not met as specified in the protocol or informed consent date missing	All

6.3 PATIENT SETS ANALYZED

Full analysis set (FAS): All screened patients with informed consent, date of registration (date of creation of screening form in the eCRF), and at least one documented administration of Spiolto® Respimat® and available total CCQ score at visit 1 and visit 2.

Treated set (TS): All screened patients with informed consent, date of registration (date of creation of screening form in the eCRF), and at least one documented administration of Spiolto® Respimat®.

Table 6.3: 1 Patient sets analyzed

	Patient set	
Class of endpoint	TS	FAS
Primary and secondary endpoints		X
Safety endpoints	X	
Demographic/baseline	X	

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

In context of CCQ, missing values will be replaced according to the corresponding manual (details are displayed in TSAP Section 7.3). No other missing data will be imputed.

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

Baseline visit (Visit 1) will include historical and demographic data as well as registration and initial examination. Treatment with Spiolto® Respimat® will be documented at visit 2 after approximately 6 weeks of treatment. The mMRC breathlessness scale is completed by the patient at visit 1 and CCQ at visit 1 and 2. In addition, the PGE is completed by the physician at visit 1 and visit 2 as well as satisfaction survey at visit 2.

7. PLANNED ANALYSIS

All analyses in this study are descriptive.

For categorical variables summary tabulations of the number and percentage within each category (with a category for missing data) of the parameter will be presented. For continuous variables number of values, mean, standard deviation, minimum, median, maximum and number of missing values will be presented. Proportion rates and 95% CI will be given when appropriate.

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Only descriptive statistics are planned for this section of the report. All baseline analyses will be done for the treated set.

7.2 CONCOMITANT DISEASES AND MEDICATION

Only descriptive statistics are planned for this section of the report. All analyses will be done for the treated set.

7.3 PRIMARY ENDPOINT

For the primary endpoint, the percentage of patients with therapeutic success will be presented together with the 95% confidence interval, whereupon therapeutic success is defined as 0.4-point decrease in CCQ score from visit 1 to visit 2. The number and percentage of patients with and without therapeutic success will be calculated for the whole FAS set and the above mentioned subgroups.
For comparison of subgroups, χ^2-Test or Fisher's Exact test, if χ^2-Test is not valid, will be used and p-values will be interpreted nominally. Additionally, 95% confidence intervals for the percentage of patients with therapy success will be calculated for each subgroup analyzed.

The total CCQ score ranges from 0 to 6. A higher score is indicative of worse status. If a patient fills in two answers on one question the data will be considered as missing. Missing values will not be imputed, one answer in the subscales "symptom" and "CCQ-4" might be missing, respectively, in order to calculate the total score. The total CCQ score and the corresponding subscales are calculated as followed, in case that at least the number of required answers is available:

Scale	Items	Items required	Scoring (For details see www.ccq.nl)
Symptom	1; 2; 5; 6	3	$\frac{Sum\ of\ answered\ questions}{Number\ of\ answered\ questions}$
Functional state (CCQ-4)	7-10	3	$\frac{Sum\ of\ answered\ questions}{Number\ of\ answered\ questions}$
Mental state	3; 4	2	$\frac{Item\ 3+4}{2}$
Total CCQ score	All subscales must be calculable		$\frac{(Symptom\ +Functional\ state)*4+(Mental\ state)*2}{10}$

7.4 SECONDARY ENDPOINT(S)

All analysis will be descriptive and will be performed on FAS. For general condition of patients and patient's satisfaction with Spiolto® Respimat® as well as the willingness to continue the treatment, the number and percentage of patients within each category will be displayed. For absolute changes in CCQ scores (symptom, functional state (CCQ-4), mental state and total scale) summary statistics will be provided.

7.6 EXTENT OF EXPOSURE

Not applicable.

7.7 SAFETY ANALYSIS

The analysis of adverse events will be descriptive and conducted according to Boehringer Ingelheim standards. The main focus will be on treatment emergent events. All AE that occurred after signing the informed consent until the end of study (visit 2) will be considered as treatment emergent and will be displayed in frequency tables. Non treatment-emergent events will be assigned to “screening” or “post-treatment” and only be displayed in listings. All analyses will be based on the treated set.

In context of the presented study, only drug-related adverse events or events with fatal outcome (i.e., serious adverse events) will be documented. Their frequency and severity will be tabulated according to MedDRA-SOC and PT. Additionally adverse events (drug-related or serious ones) leading to treatment discontinuation will be presented. Moreover, the causality of events with fatal outcome will be displayed.

Unless otherwise specified, the analyses of drug-related adverse events and events with fatal outcome will be descriptive in nature. All analyses will be based on the number of patients with AEs and not on the number of events.

An overall summary of drug-related adverse events and events with fatal outcome will be presented.

The frequency of patients with drug-related adverse events or events with fatal outcome will be summarised by primary system organ class and preferred term. Separate tables will be provided for patients with serious adverse events.

The system organ classes will be sorted alphabetically, preferred terms will be sorted by frequency (within system organ class).

For analysis multiple AE occurrence data on the CRF will be collapsed into an AE event provided that all of the following applies:

- All AE attributes are identical (PT, severity, action taken, therapy required, seriousness, reason for seriousness, relationship, outcome**)**
- The occurrences were time-overlapping or time-adjacent (time-adjacency of 2 occurrences is given if the second occurrence started on the same day or on the day after the end of the first occurrence). For classification into TEAE or Non-TEAE, the first documented start of event will be used.

For further details on summarization of AE data, please refer to [3] and [4].

8. REFERENCES

1	*CPMP/ICH/363/96:* "Statistical Principles for Clinical Trials", ICH Guideline Topic E9, Note For Guidance on Statistical Principles for Clinical Trials, current version.

9. ADDITIONAL SECTIONS

Not applicable.

10. HISTORY TABLE

Table 10: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
Draft v0.1	**18-JUL-2018**		None	This is the first Draft-Version of TSAP without any modification
Draft v0.2	**31-AUG-2018**		6.2	Violation of A1.2 does not lead to exclusion of any analysis set
			6.3	Definition of analysis sets changed, i.e. “diagnosis of COPD in whom treatment with two long acting bronchodilators is indicated” no longer necessary to be analyzed
			6.4	Definition of “maintenance naïve” added
Draft v0.3	**03-DEC-2018**		4, 6.2, 6.3	Comments added, that have to be discussed
Draft v0.4	**17-JAN-2019**		4., 6.4	Subgroups adapted
Draft v0.5	**22-FEB-2019**		4., 6.4	Definition of treatment naïve added
Final 1.0	**27-FEB-2019**		6.3	Date of registration specified
Final 2.0	**19-JUL-2019**		7.7	Corrected “NCI-CTC grade” to “severity”