Trial Statistical Analysis Plan

BI Trial No.:	1237.43
Title:	OTIVACTO - Assessment of physical functioning and handling of Spiolto® Respimat® in patients with chronic obstructive pulmonary disease (COPD) requiring long-acting dual bronchodilation in routine clinical practice
Investigational Product(s):	Spiolto® Respimat® 2.5 microgram/2.5 microgram, inhalation solution; tiotropium/olodaterol
Responsible trial statistician(s):	Phone: Fax
Date of statistical analysis plan:	19JUL2018
Version:	FINAL 1.0

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2. LIST OF ABBREVIATIONS

Term	Definition / description
AE	Adverse event
BI	Boehringer Ingelheim Pharma GmbH&Co. KG
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
PF-10	Physical functioning questionnaire
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 “Research Methods”. 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

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

5. ENDPOINT(S)

5.1 PRIMARY ENDPOINT

The primary endpoint of the presented study is "therapeutic success" at visit 2 i.e. approximately 6 weeks after starting treatment, defined as 10-point increase in the PF-10 score between visit 1 and visit 2.

5.2 SECONDARY ENDPOINTS

- Absolute changes in PF-10 score 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

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 (Age >=40 years)	Not met as specified in the protocol	None
	A1.2	Inclusion criterion 3 (Patients diagnosed with COPD and requiring long-acting dual bronchodilation (LAMA+LABA) treatment according to approved Spiolto® Respimat® SmPC)	Not met as specified in the protocol	TS, FAS
	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 who have been treated with a LABA/LAMA combination (free and fixed dose) in the previous 6 months)	Met as specified in the protocol	None
	A2.3	Exclusion criterion 3 (Patients continuing LABA-ICS treatment should not be additionally treated with Spiolto® Respimat® in order to avoid a double dosing of long-acting beta-agonists)	Met as specified in the protocol	None
	A2.4	Exclusion criterion 4 (Patients for whom further follow-up is not possible at the enrolling site during the planned study period of approx.. 6 weeks)	Met as specified in the protocol	None
	A2.5	Exclusion criterion 5 (Pregnancy and lactation)	Met as specified in the protocol	None
	A2.6	Exclusion criterion 6 (Patients currently listed for lung transplantation)	Met as specified in the protocol	None
	A2.7	Exclusion criterion 7 (Current participation in any clinical trial or any other non-interventional study of a drug or device)	Met as specified in the protocol	None
B		**Informed consent**		

Category/ Code		Description	Requirements	Excluded from
	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 ANALYSED

Full analysis set (FAS): All screened patients with informed consent, date of registration, at least one documented administration of Spiolto® Respimat® and available PF-10 score at visit 1 and visit 2.

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

Table 6.3.1 Patient sets analysed

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

6.4 SUBGROUPS

Not applicable.

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 PF-10 questionnaire, missing values will be replaced with the mean of the other values, if less than half of the questions are missing for a patient. If half or more than half of the questions are missing, no score will be calculated and the PF-10 score will be marked as missing. 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 PF-10 questionnaire at visit 1 and 2 as well as satisfaction survey at visit 2. In addition, the PGE is completed by the physician at visit 1 and 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. The number and percentage of patients with and without therapeutic success will be calculated for the whole FAS set.

The PF-10, represented by the physical functioning subscale of the Short Form 36 (SF-36), ranges from 0 to 100. A higher score indicates a better physical functioning. The score is calculated as followed:

Answer to questions 01- 10	Score
Yes, limited a lot	1
Yes, limited a little	2
No, not limited at all	3

Transformed scale = [(Sum of final item values – 10) * 100] / 20

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®, the number and percentage of patients within each category will be displayed. For absolute changes in PF-10 score, summary statistics, a frequency table and a normality test (Shapiro-Wilk test) will be provided.

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 between start of treatment and 21 days after permanently discontinuation of therapy or end of study 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. Serious events will be tabulated as well as adverse events (drug-related or serious ones) leading to treatment discontinuation. 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.

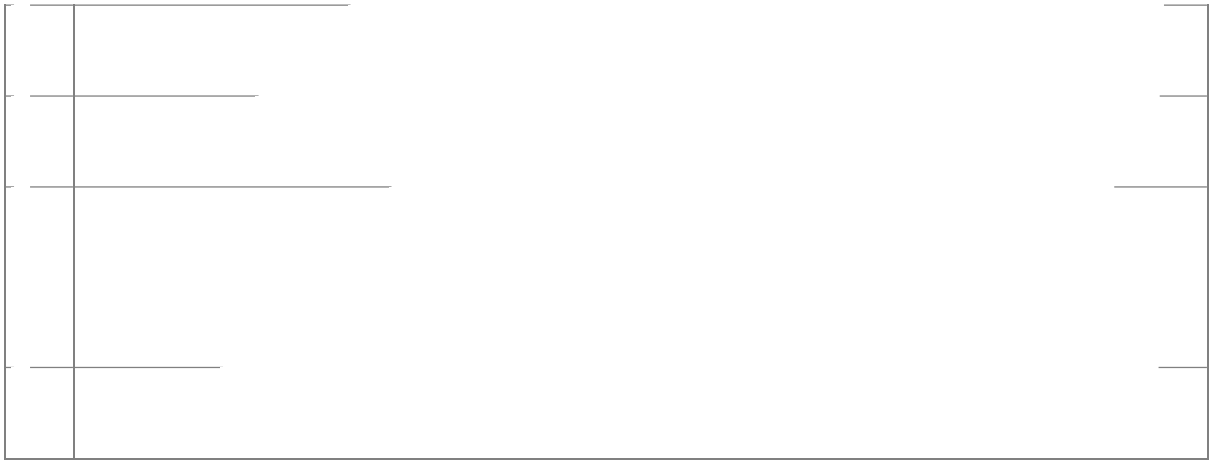
The frequency of patients with drug-related adverse events or events with fatal outcome will be summarised by primary system organ class and preferred term. Separate tables will be provided for patients with serious adverse events.

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, NCI-CTC grade, 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].



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	**20-JUN-2018**		None	This is the first Draft-Version without any modification
Draft v0.2	**29-JUN-2018**		3, 4, 5.2, 7, 7.4	Minor corrections and added additional analysis (frequency table, normality test) for absolute changes in PF-10 score
Draft v0.3	**12-JUL-2018**		4, 6.4, 7.3, 7.4	Deleted subgroup analysis
Draft v0.4	**13-JUL-2018**		6.2, 6.3	Patients who not met inclusion criterion 3 are excluded from all patient analysis sets
Draft v0.5	**16-JUL-2018**		6.2	Changed ‘All’ to ‘TS, FAS’
Draft v0.6	**18-JUL-2018**		6.2, 6.3	Changed ‘TS, FAS’ to ‘All’ for B1 and changed definition of FAS and TS
Final v1.0	**19-JUL-2018**		None	This is the first Final-Version without any modification