Trial Statistical Analysis Plan

BI Trial No.:	1237.44
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):	[redacted] Phone: [redacted] Fax: [redacted]
Date of statistical analysis plan:	29MAY2017
Version:	FINAL 1.0
	Page 1 of 16

1. TABLE OF CONTENTS

LIST OF TABLES

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 “Statistical Methods and Determination of Sample Size”. 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 9.3 or higher will be used for all analyses.

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

- [redacted]

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

- [redacted]

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 10-point increase in the PF-10 score between visit 1 and visit 2.

5.2 SECONDARY ENDPOINT(S)

- 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

5.3 FURTHER ENDPOINT(S)

None.

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 and COPD GOLD guideline recommendation)	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 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**		
	B1	Informed consent not available/not done	IC 01 not met as specified in the protocol	All

Category/ Code		Description	Requirements	Excluded from
		(Inclusion criterion 1)	or informed consent date missing	

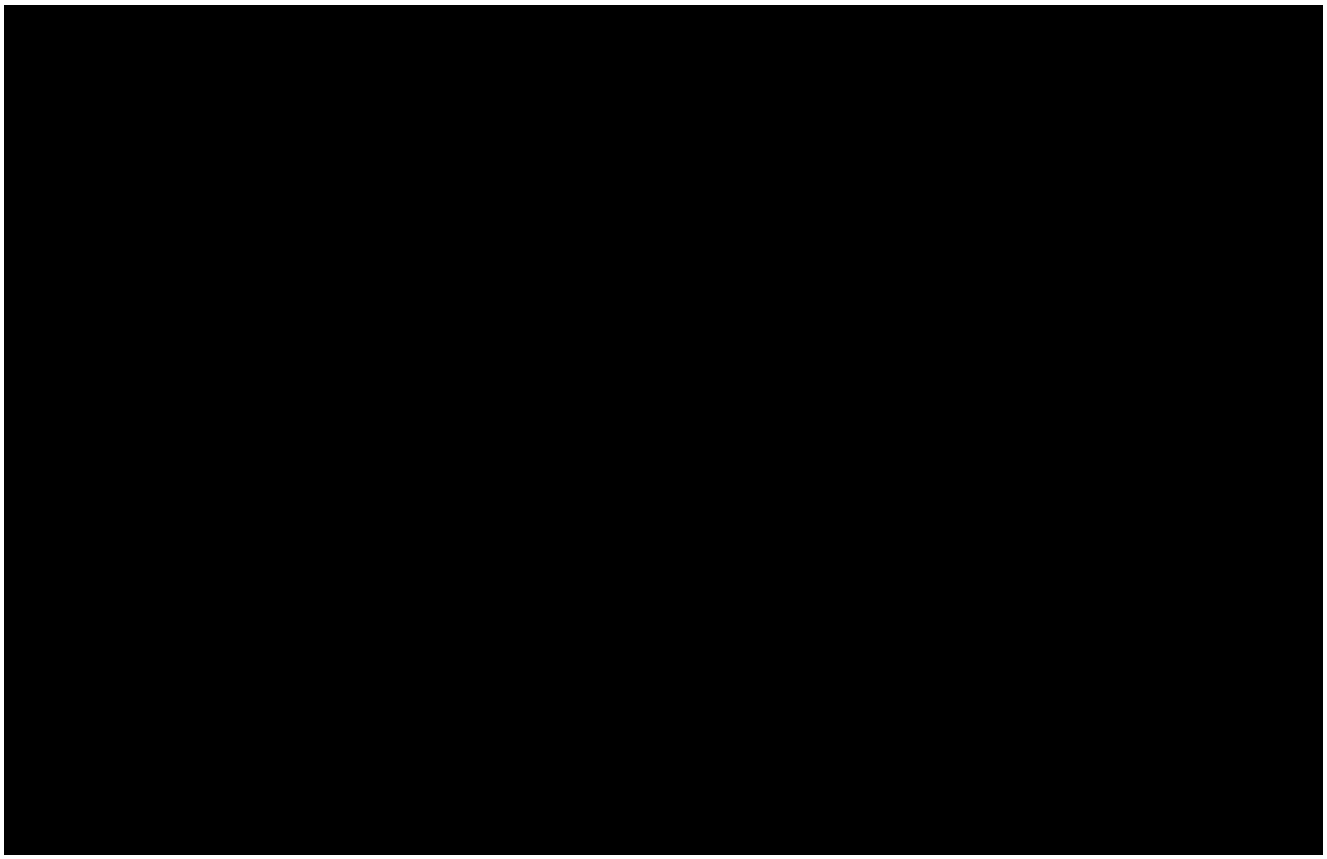
6.3 PATIENT SETS ANALYSED

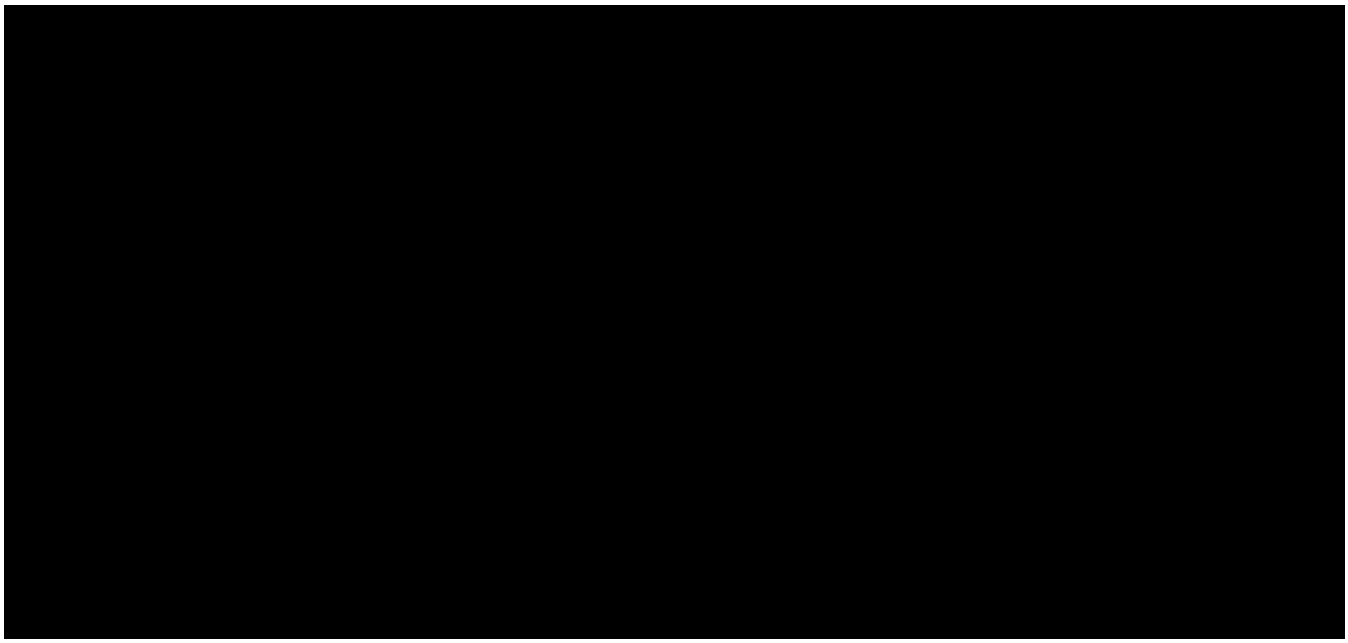
Full analysis set (FAS): All screened patients with informed consent, date of registration, at least one documented administration of Spiolto® Respimat® and available PF-10 score at visit 1 and visit 2.

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	





6.5 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. Incidence 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 [redacted]

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 will be provided.

[redacted]

[redacted]

7.5 FURTHER ENDPOINT(S)

Not applicable.

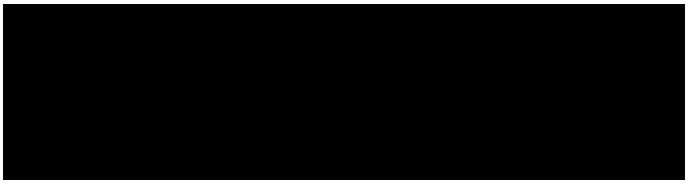
7.6 EXTENT OF EXPOSURE

Not applicable.

[redacted]

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.
2	*001-MCS-50-413*: "Handling of Protocol Violations in Clinical Trials and Projects", current version; group: Study Conduct; IDEA for CON.
3	*001-MCG-156_RD-01:* "Handling of missing and incomplete AE dates", current version; IDEA for CON. *001-MCG-156_RD-01:* "Handling of missing and incomplete AE dates", version 5; IDEA for CON.
4	*001-MCG-156*: "Handling and summarization of adverse event data for clinical trial reports and integrated summaries", current version; IDEA for CON.



10. HISTORY TABLE

Table 10: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
Draft v1.0	**27-JUL-2016**	[redacted]	None	This is the first Draft-Version of TSAP without any modification
Draft v1.1	**11-AUG-2016**		4-8	This is the second Draft-Version of TSAP. Besides adjustments in [redacted] analyses sets, documentation of AE was adapted
Draft v1.2	**17-AUG-2016**		7.3, 7.4, 8	This is the third Draft-Version of TSAP. Besides adjustments in planned statistical test, references were added
Draft v1.3	**29-SEP-2016**		3, 6.2, [redacted] 8	This is the fourth Draft-Version of TSAP. References have been updated.
Draft v1.4	**14-OCT-2016**		6.2	This is the fifth Draft-Version of TSAP. Display of ECadapted
Draft v1.5	**19-OCT-2016**		7.3, 7.4	This is the sixth Draft-Version. [redacted]
Draft v1.6	**21-OCT-2016**		7.4	This is the seventh Draft-Version. Pooling of PGE and Satisfaction was added.
Draft v1.7	**31-OCT-2016**		7.4	This is the seventh Draft-Version. [redacted]
Final 1.0	**22-NOV-2016**		[redacted]	[redacted]
Final 1.1	**29-May-2017**		3, 4	This is the first modification of the final version. References to CTP and TSAP were corrected