TRIAL STATISTICAL ANALYSIS PLAN

BI Trial No.:	0205-0541
Title:	A randomized, open-label, two-way crossover study to compare patient acceptability/preference of Tiotropium Respimat® with Tiotropium Handihaler® in patients with moderate to very severe chronic obstructive pulmonary disease (COPD).
Investigational Product(s):	Tiotropium Respimat® (Spiriva® Respimat®)
Responsible trial statistician(s):	[redacted] Phone: +[redacted]
Date of statistical analysis plan:	14JUL2021
Version:	Final

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[redacted]

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2. LIST OF ABBREVIATIONS

Term	Definition / description
AE	Adverse Event
AESI	Adverse Event of Special Interest
BI	Boehringer Ingelheim
[redacted]	
CI	Confidence Interval
COPD	Chronic Obstructive Pulmonary Disease
CRA	Clinical Research Associate
CRF	Case Report Form, paper or electronic (sometimes referred to as "eCRF")
CTM	Clinical Trial Manager
CTP	Clinical Trial Protocol
DBL	Database Lock
DPIs	Drypowder Inhalers
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
[redacted]	
eDC	Electronic Data Capture
EDTA	Ethylenediaminetetraacetic Acid
FC	Flow Chart
FEV	Forced Expiratory Volume
FUP	Follow Up
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
ICH	International Council on Harmonization
IEC	Independent Ethics Committee
IMPs	Investigational Medicinal Products
IPDs	Important Protocol Deviations
IRB	Institutional Review Board
ISF	Investigator Site File
IUD	Intrauterine Device

MC	Mean Completer
MedDRA	Medical Dictionary for Drug Regulatory Activities
MMRM	Mixed effect repeated measures model
PASAPQ	Patient satisfaction and preference questionnaire
PFT(s)	Pulmonary function test(s)
pMDIs	Pressurized Metered Dose Inhalers
PRN	As needed
REP	Residual Effect Period
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reactions
TEAE	Treatment-emergent adverse events
TMF	Trial Master File
TIC	Trial Identification Card
TIOSPIR	Tiotropium Safety and Performance in Respimat®
URI	Upper Respiratory Infection
WHO	World Health Organization
WOCBP	Woman of childbearing potential

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 7 “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 9.4 (or later) will be used for all analyses.

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

No change concerning statistical analysis has occurred since the CTP was finalized.

5. ENDPOINTS(S)

5.1 PRIMARY ENDPOINT(S)

The primary endpoint of the study is the performance domain of the Patient satisfaction and preference questionnaire (PASAPQ) after 4 weeks of treatment.

The PASAPQ is a two-part questionnaire. Part I consists of 14 questions. The first 13 questions generate the Performance domain (7 questions) and the Convenience domain (6 questions), which form a Total Score (all 13 questions). Question 14 asks for overall satisfaction with the device used in the study. Part II consists of stand-alone questions concerning a subject's device preference (question 15) and willingness to continue use (question 16). The first 14 questions in PASAPQ have Likert-type response options of 1 (very dissatisfied) to 7 (very satisfied). Question 15 asks for a response to indicate the preference for the trial device. Question 16 asks for a response between 0 and 100 with 0 indicating not willing to continue using the trial device and 100 indicating definitely willing to continue.

The performance domain score is the sum of 7 questions within the domain (Q1, Q2, Q3, Q4, Q5, Q10 and Q11) and then transformed to a 0 (least) to 100 (most) point scale.

Assessment of primary endpoints are described in section 5.1.1 of the CTP.

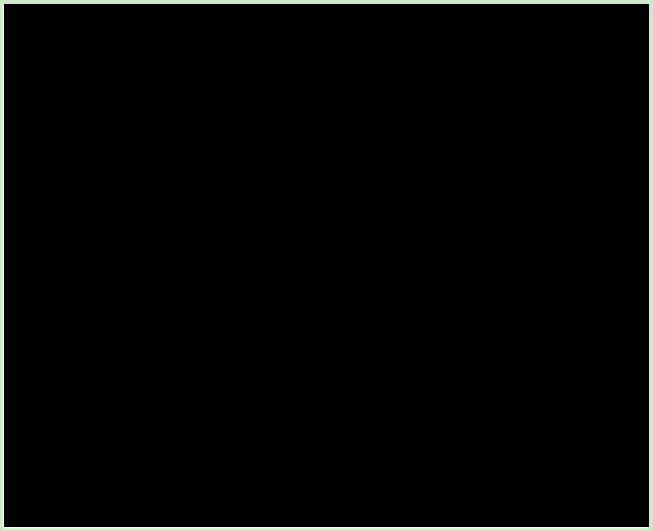
5.2 SECONDARY ENDPOINT(S)

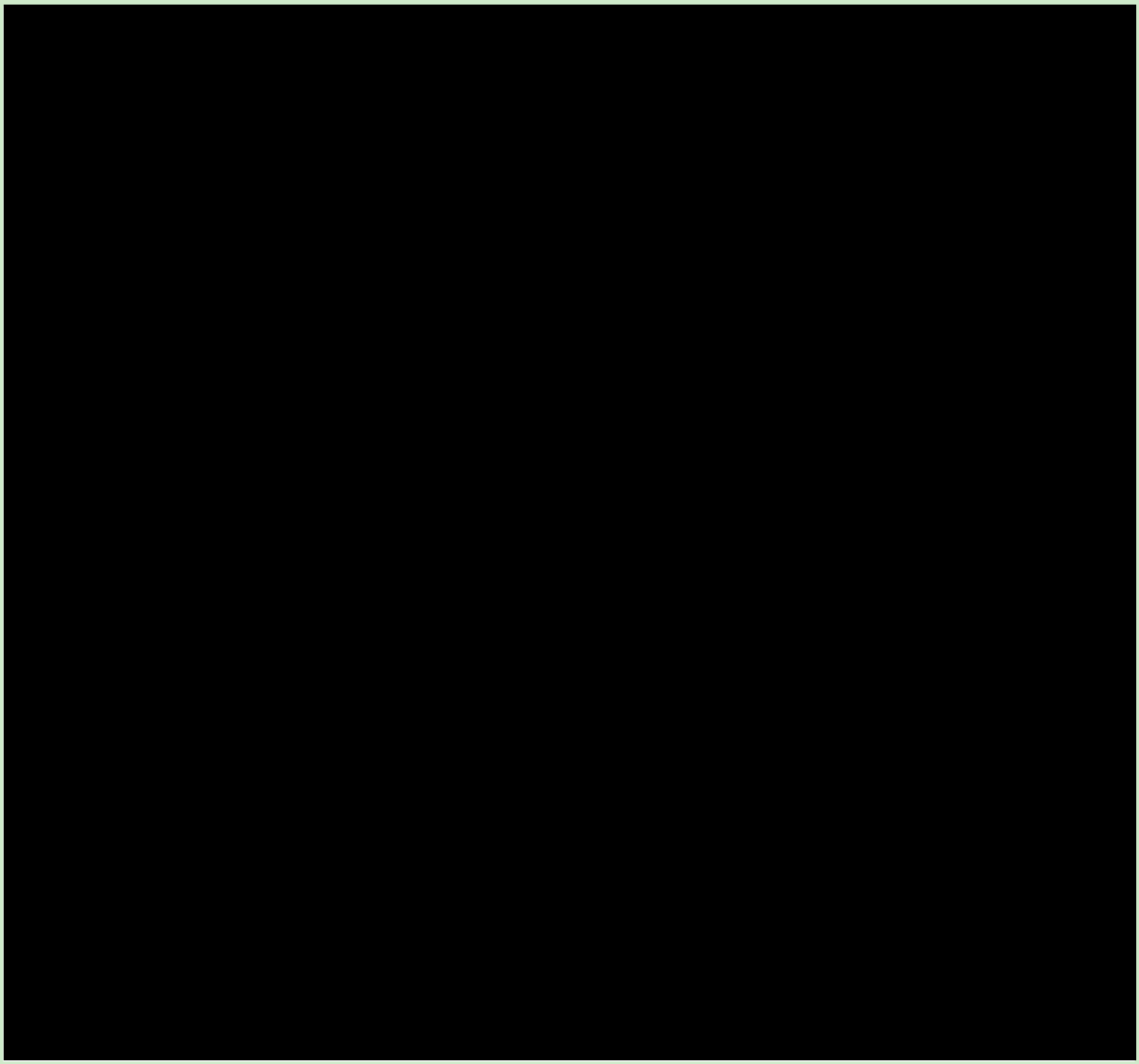
5.2.1 Key secondary endpoint(s)

Not applicable, since there are no key secondary endpoints specified in the protocol.

5.2.2 Secondary endpoint(s)

1. PASAPQ total score after 4 weeks of treatment. Total score is the sum of 13 questions (Q1-Q13) and then transformed to a 0 (least) to 100 (most) point scale.
2. Proportion of patients indicating preference which will be administered at Week 8.
3. Overall Satisfaction Question Score from PASAPQ will be administered at week 4 and 8.
4. Score on willingness to continue will be administered at week 8.
   Assessment of secondary endpoints are described in section 5.1.2 of the CTP.





6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENT(S)

This is a crossover trial consisting of a one-week screening period followed by two four-week treatment periods and a four-week follow-up period. In this study, there will be no theorical washout between treatment periods.

The definition below is the analyzing treatment. The same labels and sort order as for the randomized treatment groups will be used.

Table 6.1: 1 Definition of analyzing treatments

Label	Sort order	Start date	Stop date
Screening		Date of informed consent	Date of first administration
Treatment	1	Date of first received Respimat®	Date of last received Respimat®
Treatment	2	Date of first received Handihaler®	Date of last received Handihaler®
Follow-up		Date of last administration + 1 days	Date of last contact

For the main safety analysis, data occurring before the first drug intake date is assigned to "screening". Data occurring during the treatment periods and within 4 weeks of stop of study drug will be assigned to the respective treatment for that period.

6.2 IMPORTANT PROTOCOL DEVIATIONS

All subjects with important deviations from the protocol will be listed (Appendix 16.2 of the CTR). The IN/EX numbers refer to the definition given in the CTP and CRF.

Subjects with potentially important protocol deviations (iPDs) will be identified based on Table 6.2: 1 and documented. The table defines the different categories of important PDs. The final column describes which PDs will be used to exclude subjects from the different subject analysis sets.

The list of PDs in Table 6.2: 1 is considered a ‘working’ list, which is expected to be updated throughout the trial and finalized prior to the Database Lock (DBL). In any case, all important PDs will be tracked during the study at Medical Quality Review Meetings (MQRMs) or Blinded Reported Plan Meeting (BRPM) to verify the quality of the inclusion and the conduct of the study.

Table 6.2: 1 Important protocol deviations

Category / Code		Description	Requirements	Excluded from
A		**Entrance criteria not met**		
	A1	Inclusion criteria not met	Inclusion criteria 5 not met as specified in the protocol.	None
	A2	Exclusion criteria not met	Exclusion criteria 1, 2, 3 not met as specified in the protocol	None
B		**Informed consent**		
	B1	Informed consent not available/not done	Informed consent date missing	All
	B2	Informed consent too late	Informed consent date was after Visit 2 date	None
C		**Trial medication**		
	C1	Incorrect trial medication taken during study	Incorrect trial medication taken during study Incorrect rescue medication taken during study	None
	C2	Randomization not followed	Not following randomized treatment sequence or randomized treatment devices	None
D		**Concomitant medication**		
		Prohibited medication use during study	According to CTP section 4.2.2.1 Restrictions regarding concomitant treatment	None
E		**Missing critical data**		
	E1	Primary endpoint related data missing	Patients missed PASAPQ both in Visit 3 and Visit 4	FAS

6.3 SUBJECT SETS ANALYSED

The analysis will be based on the following populations (Table 6.3:1):

Treated set (TS) is defined as all patients who were dispensed study medication and were documented to have at least one dose of investigational treatment.

Full analysis set (FAS) is defined as all patients who were randomized to treatment sequence and received at least one dose of one study drug and providing at least one PASAPQ score measurement.

Table 6.3: 1 Subject sets analyzed

Class of endpoint	Treated set (TS)	Full analysis set (FAS)
Primary endpoint		primary analysis
Secondary endpoints		X
Safety endpoints	X	

Demographic/baseline endpoints	X

The number of subjects with available data for an endpoint may differ. For details, see Section 6.6.

[redacted]

6.5 POOLING OF CENTRES

Not applicable.

6.6 HANDLING OF MISSING DATA AND OUTLIERS

Every effort should be made to collect the complete data at the planned time points for this trial.
For PASAPQ, imputation of responses to individual questions will follow the "half-scale rule". If a patient missed less than four of the seven questions in the Performance domain or less than four of the six questions in the Convenience domain in the PASAPQ, then the missing item in this domain is imputed using the observed mean from the same domain(Mean Completer), and then the Total score is calculated as the sum of the 13 items after substitution for missing items at the domain level has taken place. If a patient missed more than three items in either domain, then the domain and the Total score are set to missing and will not be imputed. The number of patients who cannot be included in the FAS will be summarised by treatment group and period. If a patient missed a visit due to reasons unrelated to the patient's response to the treatment, the missing data will not be imputed. The MMRM will handle data missing at random based on the likelihood method. Sensitivity analyses will be conducted to compare imputed data and un-imputed data in primary endpoint only if imputation happens. Missing or incomplete AE dates are imputed according to BI standards.

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

'Baseline' is defined as the non-missing last available pre-treatment assessment.

Planned and actual study day will be included in the analysis data sets. These will both be calculated relative to the beginning of the study and to the beginning of respective study periods in the crossover design as indicated in the following table.

Table 6.7: 1 Planned and actual study days, and time windows

	Relative to period start		Relative to study start	
Visit	Planned day	Actual day (visit window)	Planned day	Actual day (Visit window)
2	1	1 (NA)	1	1 (NA)
3	28	Visit 3 date − Visit 2 date + 1 (±1 day)	28	Visit 3 date − Visit 2 date + 1 (±1 day)
4	28	Visit 4 date − Visit 3 date + 1 (±1 day)	56	Visit 4 date − Visit 3 date + 1 (±1 day)
5	28	Visit 5 date − Visit 4 date + 1 (±2 day)	84	Visit 5 date − Visit 4 date + 1 (±2 day)

7. PLANNED ANALYSIS

For End-Of-Text (EoT) tables, the set of summary statistics is: N / Mean / Standard deviation (SD) / Min / Median / Max.

For tables that are provided for endpoints with some extreme data, median, quartiles and percentiles should be preferred to mean, SD, minimum and maximum.

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 treatment group (unless otherwise specified, all patients in the respective patient set whether they have non-missing values or not).

The precision for percentages should be one decimal point, unless the denominator is smaller than 100 (in all treatment columns), in which case percentages are given in integer numbers. The category missing will be displayed only if there are actually missing values.

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Only descriptive statistics are planned for this section of the report. Demographic and baseline characteristics will be displayed for TS by treatment group and for the total.

7.2 CONCOMITANT DISEASES AND MEDICATION

Concomitant diseases and medication on-treatment period will be displayed for TS population. Only descriptive statistics are planned for this section of the report.

Concomitant therapy medication will be displayed by Anatomical Therapeutic Chemical level 3 (ATC3) and Preferred Term (PT) respectively by treatment group and for the total.

7.3 TREATMENT COMPLIANCE

Only descriptive statistics are planned for this section of the report. Summary statistics will be given for percent compliance along with the number (%) of patients with compliance in the categories 80% - 120%, <80% or >120%. Treatment compliance will be displayed for the TS population.

7.4 PRIMARY ENDPOINT(S)

In the primary analysis, comparisons between treatment groups for the performance domain of PASAPQ will be based on a mixed effect repeated measures model (MMRM). This model will include treatment and period as fixed effects and patient as a random effect. Compound symmetry will be used as a covariance structure for within-patient variation. The SAS procedure MIXED will be used involving the restricted maximum likelihood estimation and the Kenward-Roger approximation for denominator degrees of freedom. Adjusted mean values as well as treatment contrasts will be presented together with the 95% confidence intervals (CI) and p-values.

7.5 SECONDARY ENDPOINT(S)

Continuous secondary endpoints will be analyzed using a similar MMRM model as for the primary endpoint. Chi-squared test will be performed to analysis proportion of patients indicating preference.

7.5.1 Key secondary endpoint(s)

Not applicable.

7.5.2 (Other) Secondary endpoint(s)

Not applicable.

[redacted]

7.7 EXTENT OF EXPOSURE

Extent of exposure will be summarized using descriptive statistics for the total treatment exposure in days.

7.8 SAFETY ANALYSIS

All treated patients will be included in the safety analysis. In general, safety analyses will be descriptive in nature and will be based on BI standards. No hypothesis testing is planned.

7.8.1 Adverse events

The analyses of AEs will be descriptive in nature and will be based on BI guideline 'Handling and summarization of AE data for CTRs and integrated summaries'. All analyses of AE will be based on the number of patients with AEs and NOT on the number of AEs. For this purpose, AE data will be combined in a 2-step procedure into AE records.
In the first step, AE occurrences, i.e. AE entries collected in the eCRF, will be collapsed into AE episodes provided that all the following applies:

- The same MedDRA lowest level term was reported for the occurrences
- The occurrences are 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)
- Treatment did not change between the onset of the occurrences or treatment changed between the onset of the occurrences, but no deterioration was observed for the later occurrence.

In the second step, AE episodes will be condensed into AE records provided that the episodes were reported with the same term on the respective MedDRA level and that the episodes are assigned to the same treatment. For further details on summarization of AE data, please refer to BI guideline 'Handling and summarization of AE data for CTRs and integrated summaries'.

Analyses of AEs are based on the concept of treatment emergent adverse events. This means that all AEs occurring between first drug intake and 28 days after last drug intake are assigned to the respective analyzing treatment. All AEs occurring before first drug intake are assigned to 'screening', AEs starting after trial completion date are assigned to 'post-study'. Screening and post-study AEs are presented in subject data listings only. For details on the treatment definition, see Section 6.1.

An overall summary of AEs will be presented.

The frequency of patients with AEs will be summarized by treatment, primary SOC and PT. Separate tables will be provided for patients with other significant adverse events according to ICH E3, for patients with AEs leading to treatment discontinuation, for patients with AEs leading to death, for patients with investigator determined drug-related adverse events, for patients with SAEs and for patients with AESI.

According to ICH E3, AEs classified as 'other significant' include those non-serious and non-significant adverse events with
(i) 'action taken = discontinuation' or 'action taken = reduced', or
(ii) marked haematological and other lab abnormalities or that lead to significant concomitant therapy as identified by the Clinical Monitor/Investigator and confirmed at a BRPM.

The system organ classes will be sorted according to the standard sort order specified by the European Medicines Agency, PTs will be sorted by frequency (within SOC).

7.8.2 Laboratory data

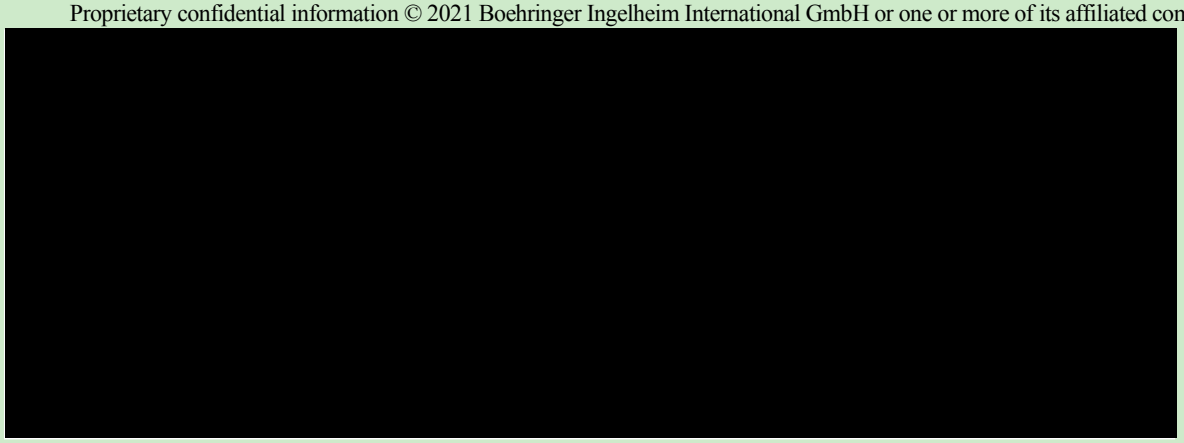
Laboratory data will be calculated both quantitatively as well as qualitatively. The latter will be done via comparison of laboratory data to their reference ranges. Values outside the reference range as well as values defined as clinically relevant will be summarized. Treatment groups will be compared descriptively with regard to distribution parameters as well as with regard to frequency and percentage of patients with abnormal values or clinically relevant abnormal values.

7.8.3 Vital signs and ECG data

Vital signs and ECG data observed at screening, during the course of the trial and at the end-of-trial evaluation will be assessed with regard to possible changes compared to findings before start of treatment.

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 36-472*: "Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics", current version; IDEA for CON.
3.	*001-MCG-156_RD-01:* "Handling of missing and incomplete AE dates", current version; 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.
5.	*CPMP/ICH/137/95*: “Structure and Content of Clinical Study Reports”, ICH Guideline Topic E3; Note For Guidance on Structure and Content of Clinical Study Reports, current version



10. HISTORY TABLE

Table 10: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
Initial				
Final				