TRIAL STATISTICAL ANALYSIS PLAN

c27526629-04

BI Trial No.:	1237-0095
Title:	A randomized, double blind, placebo-controlled, multi-center, parallel group study to compare the efficacy of inhaled tiotropium + olodaterol, fixed dose combination (5µg/5µg) vs. placebo delivered by Respimat® inhaler in patients with moderate to severe COPD, stratified by peak inspiratory flow rate [TRONARTO®]. Including Protocol global amendment 3 [c27526629-04]
Investigational Product(s):	Tiotropium + Olodaterol Respimat® fixed dose combination or matching placebo delivered via Respimat® inhaler.
Responsible trial statistician(s):	[redacted] Telephone: [redacted]
Date of statistical analysis plan:	29 SEP 2020 SIGNED
Version:	Final

1. TABLE OF CONTENTS

LIST OF TABLES

2. LIST OF ABBREVIATIONS

See Medicine Glossary:
http://glossary

Term	Definition / description
ADS	Analysis Data Set
AE	Adverse event
ANCOVA	Analysis of Covariance
ATC	Anatomical Therapeutic Classification
AUC	Area Under the Curve
BRPM	Blinded report planning meeting
CD	Concomitant diagnosis
CML	Clinical Monitor Local
COPD	Chronic Obstructive Pulmonary Disease
CRA	Clinical Research Associate
CT	Concomitant treatment
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
DBL	Data Base Lock
DH	Digital Health
DM&SM	Boehringer Ingelheim Data Management and Statistics Manual
DRA	Drug Regulatory Affairs
eCRF	electronic Case Report Form
EoT	End of Text
EMEA	European Agency for the Evaluation of Medicinal Product
FAS	Full analysis set
FDC	Fixed Dose Combination
FEV_1	Forced Expiratory Volume in One Second
FVC	Forced Vital Capacity
ICF	Informed Consent Form
ICH	International Conference on Harmonisation

Term	Definition / description
(I)PD	(Important) Protocol Deviation
(I)PV	(Important) Protocol Violation
IVRS	Interactive Voice Response System
LOCF	Last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed effects model repeated measures
MQRM	Medical Quality Review Meeting
PEF	Peak Expiratory Flow
PFT	Pulmonary Function Test
PIFR	Peak Inspiratory Flow Rate
PK	Pharmacokinetics
PPS	Per protocol set
PRN	Pro re nata (when necessary)
PSTAT	Project Statistician
PT	Preferred term
Q1	Lower quartile
Q3	Upper quartile
REML	Restricted maximum likelihood
RS	Randomised set
SABA	Short-acting beta agonist
SAE	Serious Adverse Event
SAMA	Short-acting muscarinic antagonist
SD	Standard deviation
SMQ	Standardised MedDRA query
SOC	System organ class
TS	Treated set
TSAP	Trial statistical analysis plan
TTM	Termination of trial medication

3. INTRODUCTION

As per International Conference on Harmonisation (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 Trial Statistical Analysis Plan (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, randomisation.

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

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

Sensitivity analyses were added for primary and key secondary analyses in section 7.4.2 and 7.5.1. The analysis of further endpoint includes MMRM analysis.

5. ENDPOINTS(S)

5.1 PRIMARY ENDPOINT(S)

The primary endpoint is change from baseline in FEV_1 $AUC_{0\text{-}3h}$ after 4 weeks of treatment.

Analyses will be performed in PIFR optimal (≥60 L/min) group and PIFR sub-optimal (<60 L/min) group separately.

5.2 SECONDARY ENDPOINT(S)

5.2.1 Key secondary endpoint(s)

The key secondary endpoint is change from baseline in trough FEV_1 after 4 weeks of treatment.

Analyses will be performed in PIFR optimal (≥60 L/min) group and PIFR sub-optimal (<60 L/min) group separately.

5.2.2 Secondary endpoint(s)

There are no additional secondary endpoints in this trial.

[redacted]

5.4 OTHER VARIABLE(S)

Safety

All adverse events (including those identified during the physical examination): Details can be found in section 7.8.1.

Treatment exposure/Time to discontinuation from study drug

Treatment exposure will be calculated as drug stop date minus drug start date plus 1. Time to discontinuation of study drug is defined as discontinuation date minus drug start date plus 1.

Treatment compliance

- Percent compliance
- Percent missing compliance information

Treatment compliance (80% to 120%) will be based on data recorded in the eCRF.

6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENT(S)

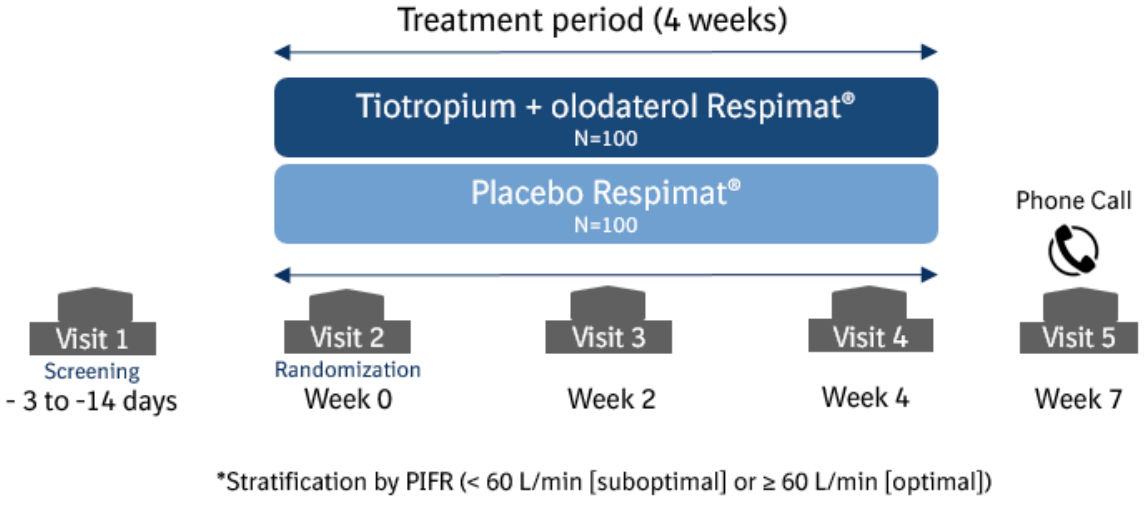
As described in Section 4 of the CTP, the following treatments are planned to be investigated in this study:

Table **Error! No text of specified style in document.**: 1 Treatment and labels

Treatment	Label
Tiotropium + Olodaterol FDC (5 µg / 5 µg) inhalation solution	T+O 5/5
Matching Placebo inhalation solution	PBO

This trial is a randomized, double-blind, placebo-controlled, multicenter, parallel study designed to assess efficacy of tiotropium + olodaterol delivered by Respimat® on FEV_1 $AUC_{0\text{-}3h}$, and trough FEV_1 in patients with moderate to severe COPD, stratified by optimal and sub-optimal PIFR. The study will consist of a screening period of up to 2 weeks, a 4-week randomized treatment period and a three week follow-up period. An overview of the trial design is presented in Figure 6.1: 1

Figure 6.1: 1 Trial Design



The residual effect period is defined as 21 days.

Approximately 200 patients will be randomized (1:1) to either the active arm (tiotropium + olodaterol, FDC) or the placebo arm. The randomization will be stratified by optimal (≥60 L/min) or sub-optimal (< 60 L/min) PIFR as measured with the [redacted] set

at med/low resistance. Each strata will be capped to a total of approximately 100 patients. An interactive response technology (IRT) will be used for randomization and stratification.

After signing informed consent and completing the screening visit, patients will enter a screening period of 3 to 14 days. During the screening period, patients will continue to receive their COPD maintenance treatment, except for the medication washout requirements required before the randomization visit. Patients will be randomized into the 4-week treatment period in which they will be randomly assigned to one of two treatments: tiotropium + olodaterol FDC or matching placebo. The randomization visit (visit 2) will be followed by a clinic visit in 2 weeks (visit 3) and end of treatment (EOT) visit (visit 4) will be 4 weeks (28 days) after randomization. A follow-up visit by telephone will be scheduled three weeks after the last dose of study medication.

6.2 IMPORTANT PROTOCOL DEVIATIONS

A patient's deviation (PD) from the trial protocol is considered "important" if it can be expected that the deviation had a distorting influence on the assessment of the treatment effect on the primary endpoint of the trial or could affect the patient's safety or rights.

Table 6.2:1 gives the important PDs for this trial. The final decision with regard to important PVs and exclusion from the PPS will be made at the final review meeting. Some important PVs will be set automatically; others will need a decision at a Medical Quality Review Meeting (MQRM) team review of the manual PD log.
The IQRMP addresses the risks of items related to COVID-19. The DV domain contains all iPD and relevant information regarding COVID-19. All iPD will be listed.

Table 6.2: 1 Handling of iPDs

iPD code	iPD Category & Brief Description	Requirement	Excluded from which analysis set
A1	Inclusion criteria not met	IN #2-7 (per protocol)	None
A2	Exclusion Criteria not met	EX #1-24 (per protocol)	None
B1	Informed consent not available/not done	IN #1. Verify that the subject has been properly consented and has signed re consent when applicable	All
B2	Informed consent too late	Verify that the subject has been properly consented and has signed re consent when applicable	None
C1	Incorrect trial medication taken	Incorrect trial medication taken	None
C2	Randomization order not	Verify correct dispensing of IMP by	None

	followed and incorrect trial medication taken	comparing IRT records against IMP Accountability Log	
C3.2	Non-compliance with study medication as defined in protocol section 4.3 Treatment Compliance	Serious non-compliance with study medication as defined in protocol 4.3 Treatment Compliance	None
C4	Medication code broken inappropriately	Medication code broken inappropriately	None
D1	Improper medication washout at baseline visit or at primary endpoint visit 4.	Verify that patients have complied with medication washout requirements prior to PFT measurements during V2 (baseline), V3 and V4 (primary endpoint) (protocol table 4.2.3.1.1 and footnotes)	None
D2	Prohibited medication use during the study	Prohibited medication use during study as per protocol section 4.2.3.1.1	None
F3.1	PFT measurement at 3-hour time point performed more than 4 hours after dosing	At visit 2, the PFTs should begin between 07: 00 a.m. and 10:00 a.m. At visits 3 and 4, PFTs should begin within ± 30 minutes of the time it started at visit 2.	None
F3.2	PFT measurement at 3:00 planned time performed earlier than 2 hours after dosing at primary endpoint visit(s)	At visit 2, the PFTs should begin between 07: 00 a.m. and 10:00 a.m. At visits 3 and 4, PFTs should begin within ± 30 minutes of the time it started at visit 2.	None
F4.1	Trial medication taken prior to pre-dose measurement at baseline visit	Verify that the visit has been rescheduled and the site has retrained the subject to dose only after the trough PFT measurement during V2.	None
F4.2	Trial medication taken prior to pre-dose measurement at primary endpoint visit(s)	Verify that the visit has been rescheduled and the site has retrained the subject to dose only after the trough PFT measurement during V4.	None
F4.4	Drug administration outside time window at randomization visit and primary endpoint visit.	Verify that the subject dosed 5 minutes prior to the first PFT measurement during V2 and V4.	None
Q1	Missed examinations; Non-COVID-19 related		None

Q2	Missed visit; Non-COVID-19 related		None
Q3	Drug shipment; Non-COVID-19 related		None
…	…		…

6.3 SUBJECT SETS ANALYSED

The following subject sets are defined in this trial:

- Randomized Set (RS): This patient set includes all patients who signed the informed consent form and were randomized, regardless whether the patient was treated with trial medication or not.
- Treated Set (TS): All randomized patients who were dispensed trial medication and were documented to have taken any dose of trial medication.
- Full Analysis Set (FAS): This patient set is nested within the TS and includes patients who had baseline and at least one post-baseline measurement for at least one efficacy endpoint(either a baseline and post-baseline primary endpoint or a baseline and a post-baseline key secondary endpoint) The FAS will be used for the primary analyses of the primary efficacy endpoint and for all other efficacy endpoints.

Table 6.3: 1 Subject sets analysed

	Subject set		
Class of endpoint	Treated set	FAS	RS
Primary and key secondary endpoints		primary analysis	
(other) Secondary and further endpoints		X	
Safety endpoints & treatment exposure	X		
Demographic/baseline endpoints	X		
Disposition			X

[redacted]

6.5 POOLING OF CENTERS

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

6.6 HANDLING OF MISSING DATA AND OUTLIERS

Every effort should be made to collect complete data for each time point on each test day.

The REML-based MMRM model described in Sections 7.4.1 and 7.5.1 will handle missing data due to early drop outs or missing data in between visits which are assumed to be missing at random.

Adjusted multiple imputation will be used to handle missing data in a sensitivity analysis. Details are described in Section 7.4.1 and 7.5.1.2.

FEV_1 measurements

FEV_1 measurements at individual time points that are flagged as unacceptable by the vendor will be set to missing prior to applying any missing data imputation rules. Missing FEV_1 measurements at a given in-clinic visit will be imputed by the available data from the patient at that visit except for trough FEV1. Completely missing visits will not be imputed and will be handled through the MMRM statistical model expect for cases where a patient discontinues due to an AE indicative of worsening of COPD. For the case of discontinuing due to an AE indicative of worsening of COPD, completely missing visits, missing data points will be imputed with the worst observation observed before discontinuation.

Discontinuation due to an AE indicative of worsening of COPD will be determined as follows.

- Check that the reason for discontinuation on the termination of trial medication is adverse event.
- Get the AE flagged by the investigator as the primary reason for discontinuation of trial medication.
- Check whether this AE belongs to the group of AEs identified as corresponding to either COPD exacerbation or lower respiratory disorders. This will be based on the BI system in place for grouping MedDRA preferred terms into medical concepts (currently referred to as pharmacovigilance endpoints).

Additional details on the imputation of missing data for specific cases are provided below:

- Any visit occurring more than one day after discontinuation of study medication which has non-missing data will not be used in the analysis.

- For patients taking a salbutamol (SABA) as rescue medication during Visit 2 and 4, any subsequent FEV_1 measurements from the time of rescue use until time of rescue plus 8 hours (e.g., 2:17 to 10:17) will be set to missing and imputed by the worst non-missing (either observed or imputed) observation for that visit strictly prior to the administration of the rescue medication (even if it is a pre-dose value, either observed or imputed). If there are FEV_1 measurements after the 8-hour window they will be considered valid and not imputed provided that they are not in the 8-hour window for a subsequent rescue medication use. If rescue medication is taken at any on-treatment in-clinic visit and there is no rescue medication time given, data for the entire visit will be considered missing and it will be handled the same way as the case where all measurements after rescue use are set to missing.

Missing safety data will not be imputed with the exception of missing AE dates which will be imputed according to BI standards (see Boehringer Ingelheim Data Management and Statistics Manual (DM&SM) “Handling of missing and incomplete AE dates.

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

The baseline value will be the measurement made prior to the first dosing at Visit 2. If there are more than one measurement of FEV1 available prior to randomization, the mean of the two pre-dose pulmonary function test measurements at Visit 2, prior to the administration of the first dose of the randomized treatment, is used as the baseline FEV1. Planned and actual study day will be included in the analysis data sets. These will both be calculated relative to the beginning of study as indicated in the following table (nominal visits). See Table 6.7:1.

Time windows will not be used but rather planned visits.

Table 6.7:1 Planned and actual study days

Visit	Planned Study Day	Actual Study Day
2	1	1
3	15	Visit 3 date – Visit 2 date + 1
4	29	Visit 4 date – Visit 3 date + 1

7. PLANNED ANALYSIS

For End-of-Text (EoT) tables, the set of summary statistics for descriptive displays of continuous variables is: N / Mean / SD / Min / Median / Max.

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). Percentages will be rounded to one decimal place. The category missing will be displayed only if there are actually missing values.

The efficacy analysis will be performed in FAS.

For efficacy and safety analyses, patients will be analysed according to their planned treatment group.

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Only descriptive statistics are planned for this section of the report. COPD background characteristics will be summarized.

Body plethysmography will be analyzed descriptively for visit 2.

7.2 CONCOMITANT DISEASES AND MEDICATION

Only descriptive statistics are planned for this section of the report. A table of number (%) of patients with concomitant diagnoses (CDs) by system organ class (SOC) and preferred term (PT) will be included along with a supporting listing. Concomitant diagnoses will be coded with the most recent version of the Medical Dictionary for Regulatory Activities (MedDRA) in effect at database lock.

Frequency tables (%) will be presented for medical history and COPD background characteristics.

Pulmonary medication will be summarized as the number (%) of patients taking pulmonary medications within the last three months before visit 1 and during the treatment periods.

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% or >120%, 80% - 120%.

7.4 PRIMARY ENDPOINT(S)

The primary endpoint is change from baseline in FEV_1 $AUC_{0\text{-}3h}$ after 4 weeks of treatment.

Analyses will be performed in PIFR optimal (≥60 L/min) group and PIFR sub-optimal (<60 L/min) group separately.

7.4.1 Primary analysis of the primary endpoint(s)

The primary endpoint will be analyzed using an ANCOVA model including the fixed, categorical effect of treatment and the fixed continuous effect of baseline. The data is collected at baseline (visit 2) and at visit 4.

Significance tests will be based on adjusted means using a two-sided $\alpha = 0.05$ (two-sided 95% confidence intervals).

The primary analysis will be performed on the FAS within the optimal and sub-optimal PIFR groups, respectively. Patients will be analyzed according to the PIFR stratum to which they belong (regardless of any miss-assignment to treatment based on identification of the wrong stratum), as such an error occurs before randomization and is therefore consistent with regulatory guidance.

The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors. Significance tests will be based on least-squares means using a two-sided $\alpha = 0.05$ (two-sided 95% confidence intervals).

The following SAS code will be used for the analysis.

```
PROC MIXED DATA=alldat method=reml order=formatted;
  CLASS trtp (ref=last);
  MODEL chg = base trtp ;
  LSMEANS trtp / cl diff om cov;
RUN;
```

Here the endpoint is chg (change from baseline), baseline value of the endpoint is base and the treatment group is trtp. The data set alldat will be set to the optimal and sub-optimal PIFR subgroups, respectively. The data set should only include post baseline visits since change from baseline will be identical to zero for the baseline visit.

7.4.2 Sensitivity analysis, subgroup analysis, exploratory analysis of the primary endpoint(s)

Sensitivity analysis

Additional models will include covariates such as severity (e.g. GOLD stage), gender and age. These models will be analyzed separately for each PIFR subgroup.

Missing data analysis

The ANCOVA primary analysis only accounts for missing observations under the MCAR (missing completely at random) assumption. The robustness of the primary analysis to the

MAR (missing at random) assumption will therefore be assessed by performing a multiple imputation (MI) sensitivity analysis with an extended covariate set. Data from Trough FEV1 will also be included in the imputation procedure as it is measured at both visits 3 and 4. It therefore may provide information about patient state prior to discontinuation that is not available directly for the primary endpoint and hence reduce any biases caused by missing data.

Missing data will be multiply imputed 100 times using the MCMC (Markov Chain Monte Carlo) method. The imputation will be performed separately for each combination of treatment and PIFR subgroup. Separate chains will be used for each imputation, with 1000 burn-in iterations. Jeffrey's prior will be used. The seed number will be set to 123795. The following variables will be included in the multiple imputation model: treatment (Tio+Olo vs placebo), continuous baseline FEV1, continuous age, gender (male or female) and disease severity (GOLD group 2 or 3), smoking (yes/no), previous exacerbation (yes/no), country (US, Germany), change from baseline Trough FEV1 at visit 3 and 4 and change from baseline FEV_1 $AUC_{0\text{-}3h}$ at visit 4.

For each imputed complete data set, the primary endpoint will be analyzed at visit 4 using the primary ANCOVA analysis model. The 100 estimates and standard errors will then be combined using Rubin's rules (16,17) to produce a single estimate with standard error, confidence interval and nominal p-value.

The following SAS code will be used for multiple imputation step.

```
PROC MI data=midat seed=123795 nimpute=100 out=miout;
   VAR var;
   MCMC chain=multiple nbiter=1000 prior=jeffreys;
   BY pifr trtp;
RUN;
```

Here the data set is midat, var are all the variables to be entered into model, trtp is the treatment group and pifr is the PIFR sub group. The data set midat must have one record per patient with all variables for each visit arranged horizontally. The variable chg4 is the change from baseline for the endpoint of interest to be analyzed below.

An ANCOVA model will be used on the result of the imputations using the SAS code as follows.

```
PROC SORT data=miout;
  BY _imputation_ pifr;
RUN;

ODS OUTPUT diffs=mixdiff ;
ODS LISTING CLOSE;

PROC MIXED DATA=miout method=reml order=formatted;
```

```
 BY _imputation_ pifr;
 CLASS trtp (ref=last);
 MODEL chg4 = trtp var / solution cl covb ddfm=KR s;
 LSMEANS trtp / cl diff om cov;
RUN;

ODS LISTING;
```

Finally the results of the 100 ANCOVA analyses will be combined using the SAS code below.

```
PROC SORT data=mixdiff ;
 BY pifr _imputation_;
RUN;

PROC MIANALYZE data=mixdiff;
  BY pifr;
  MODELEFFECTS estimate;
  STDERR stderr;
run;
```

Homogeneity of treatment effect

To assess the homogeneity of the treatment effect on the primary endpoint across the levels of PIFR subgroups, the same ANCOVA model as in the primary analysis will be fitted in the overall population but replacing the treatment term by a treatment-by-PIFR subgroup term. A descriptive p-value of treatment effect homogeneity at week 4 will be calculated. No overall treatment effect will be estimated from this model as it is not interpretable. The analysis will be done separately for population before and after COVID-19.

Similarly, the same ANCOVA model as in the primary analysis will be fitted in the overall population but replacing the treatment term by a treatment-by-continuous baseline PIFR term. A descriptive p-value of treatment effect homogeneity at week 4 will be calculated. No overall treatment effect will be estimated from this model as it is not interpretable. The analysis will be done separately for population before and after COVID-19.

The results of the analysis of the primary endpoints for tiotropium + olodaterol FDC within the optimal and sub-optimal PIFR groups will be presented in a forest plot and the treatment by PIFR subgroup interaction p-value will be provided. Sensitivity analysis will be performed by including additional covariates such as severity, gender and age in the model to adjust for potential differences in prognostic factors between sub-optimal and optimal PIFR subgroups.

7.5 SECONDARY ENDPOINT(S)

7.5.1 Key secondary endpoint(s)

The key secondary endpoint is change from baseline in trough FEV_1 after 4 weeks of treatment.

Analyses will be performed in PIFR optimal (≥60 L/min) group and PIFR sub-optimal (<60 L/min) group separately.

7.5.1.1 Primary analysis of the key secondary endpoint(s)

The key secondary endpoint will be analyzed using the restricted maximum likelihood (REML) based approach using a mixed model with repeated measurements (MMRM). The analysis will be performed on the FAS within the optimal and sub optimal PIFR groups, respectively. The data is collected at baseline (visit 2), visit 3 and visit 4.

The analysis will include the fixed, categorical effect of treatment at each visit and the fixed continuous effect of baseline at each visit. Visits will be treated as repeated measures with an unstructured covariance structure used to model the within-patient measurements.

The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors. Significance tests will be based on least-squares means using a two-sided $\alpha = 0.05$ (two-sided 95% confidence intervals).

If a patient misses a visit, the missing data will not be imputed. The mixed effect model will handle missing data based on a likelihood method under the “missing at random” assumption.

The following SAS code will be used for the analysis.

```
PROC MIXED DATA=alldat cl method=reml order=formatted;
  CLASS usubjid trtp (ref=last) tptno;
  MODEL chg = trtp*tptno base*tptno / ddfm=kr solution;
  REPEATED tptno / subject=usubjid type=un r rcorr;
  LSMEANS tptno*trtp / pdiff=all om cl alpha=0.05 slice=tptno;
RUN;
```

Here tptno is the planned analysis day number for each visit, the endpoint is chg, baseline value of the endpoint is base and the treatment group is trtp.
The data set alldat will be set to the optimal and sub-optimal PIFR subgroups, respectively. The data set should only include post baseline visits since change from baseline will be identical to zero for the baseline visit.

In the event of non-convergence, the following methods will be attempted (in order) to overcome it:

1. Add the 'singular=1e-10' option in the model statement – This raises the threshold at which columns are declared linearly dependent (from typically 1e-12).
2. Set 'maxiter=100' in the PROC MIXED statement – This increases the number of convergence iterations used from a default of 50.
3. Set 'scoring=4' to specify use of the Fisher scoring algorithm in the first 4 iterations.
4. Include the statement 'performance nothread' – this removes multi-threading from the calculations.

7.5.1.2 Sensitivity analysis, subgroup analysis, exploratory analysis of the key secondary endpoint(s)

Sensitivity analysis

Additional models will include covariates such as disease severity (e.g. GOLD stage), gender and age. These models will be analyzed separately for each PIFR subgroup.

Missing data analysis

A multiple imputation analysis will be performed on the key secondary endpoint similar to that of the primary endpoint described in section 7.4.2.

Homogeneity of treatment effect

To assess the homogeneity of the treatment effect on the key secondary endpoint across the levels of PIFR subgroups, the same MMRM model as in the key secondary analysis will be fitted in the overall population but replacing the treatment term by a treatment-by-PIFR subgroup term. A descriptive p-value of treatment effect homogeneity at week 4 will be calculated. No overall treatment effect will be estimated from this model as it is not interpretable. The analysis will be done separately for population before and after COVID-19.

Similarly, the same MMRM model as in the key secondary analysis will be fitted in the overall population but replacing the treatment term by a treatment-by-continuous baseline PIFR term. A descriptive p-value of treatment effect homogeneity at week 4 will be calculated. No overall treatment effect will be estimated from this model as it is not interpretable. The analysis will be done separately for population before and after COVID-19.

The results of the analysis of the key secondary endpoints for tiotropium + olodaterol FDC within the optimal and sub-optimal PIFR groups will be presented in a forest plot and the treatment by PIFR subgroup interaction p-value will be provided. Sensitivity analysis will be performed by including additional covariates such as severity, gender and age in the model to adjust for potential differences in prognostic factors between sub-optimal and optimal PIFR subgroups.

7.5.2 Other Miscellaneous endpoint(s)

For the FVC data descriptive statistics at screening are planned for this section of the report.

The analyses will be done separately for each PIFR sub group.

7.7 EXTENT OF EXPOSURE

Extent of exposure will be summarized using descriptive statistics for days of exposure as well as number (%) of patients whose total exposure falls in the categories of <2weeks and 2-<4weeks and more than 4 weeks.

7.8 SAFETY ANALYSIS

All safety analyses will be performed on the treated set.

7.8.1 Adverse Events

Unless otherwise specified, the analyses of adverse events will be descriptive in nature. All analyses of AEs will be based on the number of subjects with AEs and NOT on the number of AEs.

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

- All AE attributes are identical (LLT, intensity, 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 further details on summarization of AE data, please refer to (13,14).

The analysis of adverse events will be based on the concept of treatment emergent adverse events. That means that all adverse events occurring between first drug intake till last drug intake + residual effect period (21 days) will be assigned to the randomized treatment. All adverse events occurring before first drug intake will be assigned to 'screening' and all adverse events occurring after the residual effect period will be assigned to 'post-treatment' (for listings only). Adverse events that start before first drug intake and deteriorate under treatment will also be considered as 'treatment-emergent . For details on the treatment definition, see Section 6.1.

According to ICH E3 AEs classified as 'other significant' needs to be reported and will 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 lead to significant concomitant therapy as identified by the Clinical Monitor/Investigator at a Medical Quality Review Meeting.

An overall summary of adverse events will be presented.

The frequency of subjects with adverse events will be summarized by treatment, primary system organ class and preferred term (mention MedDRA levels to be displayed in the tables). Separate tables will be provided for subjects with other significant adverse events according to ICH E3 and for subjects with serious adverse events.

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

7.8.2 Laboratory data

Clinically relevant findings in laboratory data will be reported as AEs and will be analyzed as part of the AE analysis.

7.8.3 Vital signs

Only descriptive statistics are planned for this section of the report. Clinically relevant findings in vital signs will be reported as AEs and will be analyzed as part of the AE analysis.

7.8.4 ECG

Abnormal findings in ECGs will be reported either as baseline conditions (if identified at the screening visit) or as AEs if judged clinically relevant by the investigator.

7.8.5 Others

Not applicable since there were no additional endpoints.

8. REFERENCES

1.	*001-MCS-50-415_RD-02:* "Project Analysis Dataset (PADS) Template (template) ", current version, Group "Biostatistics & Data Sciences", IDEA for CON.
2.	*CPMP/ICH/363/96:* "Statistical Principles for Clinical Trials", ICH Guideline Topic E9, Note For Guidance on Statistical Principles for Clinical Trials, current version.
3.	*001-MCS-50-415_RD-03:* "Clinical Trial Analysis Decision Log (template) Decision Log", current version, Group "Biostatistics & Data Sciences", IDEA for CON.
4.	*001-MCS-36-472:* "Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics", current version, Group "Biostatistics & Data Sciences", IDEA for CON.
5.	*001-MCS-40-106_RD-03:* "Clinical Trial Protocol general template for Phase I-IV", current version, Group "Clinical Operations", IDEA for CON.
6.	*001-MCS-80-606*: "Management of Non-Compliances", current version, Group "Quality Medicine", IDEA for CON.
7.	*001-MCS-40-413:* Identify and Manage Important Protocol Deviations (iPD)", current version, Group "Clinical Operations", IDEA for CON.
8.	*001-MCS-40-135_RD-01:* "Integrated Quality and Risk Management Plan", current version, Group "Clinical Operations", IDEA for CON.
9.	REGULATION (EU) No 536/2014 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC, European Commission webpage.
10.	*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, EMA webpage.
11.	*001-MCS-80-606*: "Handling of Non-Compliances in Clinical Development, Medicine and QRPE", current version; IDEA for CON.
12.	*001-MCG-156_RD-01*: "Handling of missing and incomplete AE dates", current version; IDEA for CON.
13.	*001-MCG-156*: "Handling and summarization of adverse event data for clinical trial reports and integrated summaries", current version; IDEA for CON.
14.	*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.
15.	*BI Statistical Position Paper- Standards for Inferential Analyses v1.1(April 2019)*

16.	*Rubin D.B. Inference and missing data. Biometrika 63, 581-592 (1976).*
17.	*R12-2094 Little, R.J. & Rubin, D.B. Statistical Analysis with Missing Data, 2nd ed. New York: John Wiley & Sons (2002)*

10. HISTORY TABLE

Table 10: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
Initial	01-JUL -2020	[redacted]	None	This is the initial TSAP with necessary information for trial conduct
Final	29-SEP-2020	[redacted]	None	This is the final TSAP

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