# Trial Statistical Analysis Plan

**c23758242-01**

| | |
|---|---|
| **BI Trial No.:** | 1237-0063 |
| **Title:** | A randomized, double-blind, double-dummy, active-controlled, multi-center, parallel group study to show the superiority in lung function of 12 weeks once daily treatment with orally inhaled tiotropium+olodaterol fixed dose combination delivered by the Respimat® inhaler vs. 12 weeks twice daily treatment with orally inhaled fluticasone propionate+salmeterol fixed dose combination delivered by the Diskus® in patients with Chronic Obstructive Pulmonary Disease (COPD) [ENERGITO® 2]<br><br>Including Protocol global amendment 2 [c13020187-03] |
| **Investigational Product:** | Stiolto®, Tiotropium+olodaterol fixed dose combination – Respimat® |
| **Responsible trial statistician:** | Telephone: |
| **Date of statistical analysis plan:** | 14 May 2018 SIGNED |
| **Version:** | Final |

# 1. TABLE OF CONTENTS

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## 2. LIST OF ABBREVIATIONS

Include a list of all abbreviations used in the TSAP

| Term | Definition / description |
|---|---|
| ADS | Analysis Data Set |
| AE | Adverse event |
| ANCOVA | Analysis of Covariance |
| ATC | Anatomical Therapeutic Classification |
| AUC | Area Under the Curve |
| BDI | Baseline Dyspnoea Index (Mahler) |
| 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 Products |
| FAS | Full analysis set |

| Term | Definition / description |
|---|---|
| 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 |
| (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 |
| 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 |
| SGRQ | Saint George's Respiratory Questionnaire |
| SMQ | Standardised MedDRA query |
| SOC | System organ class |
| TDI | Transitional Dyspnoea Index |
| TS | Treated set |

| Term | Definition / description |
|---|---|
| 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

In addition to the further endpoints described in the protocol, the following further endpoints will be added.

- FEV1 AUC 0-12 h response (change from baseline) [L] after 6 weeks treatment
- FVC AUC0-24h response (change from baseline) [L] after 6-weeks treatment
- FVC AUC0-12h response (change from baseline) [L] after 6-weeks treatment
- FVC AUC 12-24h response (change from baseline) [L] after 6-weeks of treatment

# 5. ENDPOINTS

## *5.1 PRIMARY ENDPOINTS*

Primary endpoint of efficacy will be used as described in the clinical trial protocol, section 5.1.1.

## *5.2 SECONDARY ENDPOINTS*

### 5.2.1 Key secondary endpoints

There are no key secondary endpoints in this trial.

#### 5.2.1 (Other) Secondary endpoints

Secondary endpoints of efficacy will be used as described in the clinical trial protocol, Section 5.1.2.

# 6. GENERAL ANALYSIS DEFINITIONS

## *6.1 TREATMENTS*

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

Table 6.1: 1 Treatment and labels

| **Treatment** | **Label** |
|---|---|
| Tiotropium + olodaterol FDC (5 µg / 5 µg) inhalation solution | T+O 5/5 |
| Fluticasone propionate + salmeterol FDC (250 µg / 50 µg) inhalation powder | F+S 250/50 |

This is a parallel-group trial consisting of a screening and run-in period of at least 4 four week duration, a 12-week randomised treatment period and a three week (21 days) follow up period

For the main safety analysis, data occurring during the treatment period between first double-blind drug intake date and within 21 days after the last drug intake date is assigned to and analysed under the respective treatment. Data occurring before the first drug intake date is assigned to screening/run-in period. Data more than 21 days after the end of the last treatment period and up to and including the date of the study termination will be assigned to follow-up.

Any cases of patient being treated with the wrong study medication will be identified and summarized as an important protocol violation.

- If a patient was treated with a study medication different from the randomized treatment throughout the on-treatment period, this patient will be included in the treated set and will be analysed as treated under the initial study medication received on Day 1 for both efficacy and safety analyses. Such a case will be reported as an important protocol violation and this patient will be excluded from the per-protocol set (PPS)
- If a patient was treated with incorrect study medication during part of the on-treatment period, this patient will be included in the treated set and will be analysed under the initial study medication received on Day 1 for both efficacy and safety analyses. For safety analyses, the actual incorrect study medication is listed as the actual treatment at onset of any adverse event in the subject data listings. Such a case will be reported as an important protocol violation and a decision will be made whether to exclude this patient from the PPS at the blinded report planning meeting (BRPM) on a case-by case basis before unblinding.

## *6.2 IMPORTANT PROTOCOL VIOLATIONS*

A patient's deviation 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 PVs for this trial. The final decision with regard to important PVs and exclusion from the PPS will be made at the final BRPM. Some important PVs will be set automatically; others will need a decision at a Medical Quality Review Meeting (MQRM) or BRPM or through team review of the manual PV log.

In the case that a patient is randomized in both this trial and another trial or is randomized at two different sites in this study the patient will be indicated as having IPV A2 (see Table 6.2: 1). The following process will be followed with regards to the patient's data.

- All efficacy data will be excluded from the analysis and the patient will be excluded from the Full Analysis Set (FAS) (this trial or both trials as appropriate).

- The only safety data which will be reported is exposure and serious adverse events (SAEs). These will be analysed according to the treatment which the patient actually received. If the patient is randomized twice in this study and both treatments are the same, the patient's data will be combined (i.e., the patient is only counted once). If the patient participates in two different trials in the project, he/she will be reported separately for each trial. As well, care will be taken with regard to the SAE narratives as to whether data for one patient number is relevant for an SAE under the other patient number.

- For disposition, demographics and baseline characteristics the patient will be analysed as treated. If the patient is randomized twice in this study and the treatments are different, the patient will be counted under each treatment. A footnote will be included in the disposition table identifying the situation and noting that the patient is counted twice for disposition as well as baseline data and important protocol violations.

The final decision with regards to important protocol violations and exclusion from the PPS will be made at the final BRPM or database lock meeting before unblinding.

Table 6.2: 1 Important Protocol Violations

| Category Code | | Description | Requirement | Excluded from |
|---|---|---|---|---|
| **A** | | **Entrance criteria not met** | | |
| | **A1** | **Inclusion Criteria not met** | Any of inclusion criteria 2 through 6 not met as specified in the protocol. | PPS |
| | **A2** | **Exclusion Criteria not met** | Any of exclusion criteria 2, 3, 9, 12,13, 15, 16, 17, 19, 20, 24, 25 not met as specified in the protocol<br><br>Any of exclusion criteria 1,4, 5, 6, 7, 8, 10, 11, 12, 14, 18, 21, 22, 23 not met as specified in the protocol | PPS<br><br>None |
| **B** | | **Informed Consent** | | |
| | **B1** | **Informed consent not available /not done** | Informed consent date missing; no signature on ICF | All |
| | **B2** | **Informed consent too late** | Date of informed consent was after the date of any study related procedure. If the date of informed consent equals to date of Visit 1, such cases are discussed at MQRM/ BRPM/DBL meetings. Patient signed the wrong version of ICF and then signed correct version with date after randomisation | None |
| **C** | | **Trial medication and randomisation** | | |
| | **C1** | **Incorrect trial medication taken** | Not throughout study; could be at a clinic visit or between clinic visits | PPS (decision at BRPM ) |
| | **C2** | **Randomisation order not followed and incorrect trial medication taken** | Throughout the study, check IVRS | PPS |
| | **C3** | **Non-compliance with study medication** | | |
| | **C3.2** | Serious non-compliance with study medication as reported in monitoring report | Decision at MQRM/BRPM<br>If at visit 4 | PPS |
| | **C4** | **Medication code broken inappropriately** | To be discussed and decided during MQRM/BRPM.<br>Only inappropriate code breaks are IPVs (e.g. unblinding by Global Pharmacovigilance is not). | PPS |

Table 6.2: 1 (cont.) Important protocol violations

| Category Code | | Description | Requirement | Excluded from |
|---|---|---|---|---|
| **D** | | **Concomitant medication** | | |
| | **D1** | **Improper medication washout at baseline visit or at primary endpoint visits** | Visit 2 and Visit 4, refer to Section 4.2.2.2 and Table 4.2.2.1:1 in CTP. Decision at BRPM | PPS |
| | **D2** | **Prohibited medication use during the study** | Refer to Table in 4.2.2.1:1 in CTP. Decision at BRPM if in week prior to Visit 2 or Visit 4. | PPS |
| **F** | | **Incorrect timing** | | |
| | **F3** | **Primary endpoint recorded outside time window** | | |
| | F.3.1 | PFT measurement at 12-hour time point performed more than 13 hours after dosing | Visit 4<br>Decision at BRPM | PPS |
| | F3.2 | PFT measurement at 23:00 or 24:00 planned time performed earlier than 22 hours after dosing at primary endpoint visit(s) | Visit 4<br>Decision at BRPM | PPS |
| | **F4** | **Trial medication** | | |
| | F4.1 | Trial medication taken prior to pre-dose measurement at baseline visit | Visit 2<br>Decision at BRPM | PPS |
| | F4.2 | Trial medication taken prior to pre-dose measurement at primary endpoint visit(s) | Visit 4<br>Decision at BRPM | PPS |
| | F4.3 | Evening dose of trial medication taken prior to 12h measurements | Visit 4<br>Decision at BRPM | PPS |
| | F4.4 | Drug administration outside time window at randomisation visit and primary endpoint visit. | Visit 2 and Visit 4 start times are both outside 0600 to 1100 inclusive OR<br>(One of Visit 2/Visit 4 start times is outside 6 am to 11 am inclusive AND<br>Visit 2 and 4 morning doses are more than 30 min apart) OR<br>(Visit 4 morning and evening doses do not meet the 12 hours+/- 30 minutes criterion)<br>Decision at BRPM | PPS |
| **Z** | | **Other** | | |
| | **Z1** | **Serious GCP non-compliance** | Manual PVs reported by CML/CRA. Carefully reviewed, described and documented in the DBL meeting minutes<br>Decision at BRPM | PPS |
| | **Z2** | **Other PV affecting efficacy and possible safety** | Additional PV identified through monitoring which impacts the primary analysis and possibly patient's rights or safety. Carefully reviewed and documented in BRPM minutes and comment field of IPV ADS. | PPS |

Table 6.2: 1 (cont.) Important protocol violations

| | | | | |
|---|---|---|---|---|
| | Z3 | Other PV affecting safety only | Additional PV identified through monitoring which impacts patient's rights or safety. Carefully reviewed and documented in BRPM minutes and comment field of IPV ADS. | None |

**Note:** Missing visits, evaluations, and tests will be considered missing data, not protocol deviations.

IPV categories B2, C1, C2, C3.2, C4, D1, D2, Z1, Z2 and Z3 cannot be checked programmatically and need to be done manually

### *6.3 PATIENT SETS ANALYZED*

There are four patient sets defined in this trial:

- Randomised Set (RS)
  This patient set includes all patients who signed the informed consent form and were also randomised, 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. The FAS will be used for the primary analyses of the primary efficacy endpoint and for all other efficacy endpoints.
- Per Protocol Set (PPS)
  This patient set is nested within the FAS and only includes patients who had no important PVs which are specified to be excluded from the efficacy analysis. (see Table 6.2: 1).
- The final decision regarding which patients are included in PPS will be made at BRPM prior to data unblinding.

If the number of patients in PPS is less than 90% of the number of patients in FAS, the primary analysis for the primary endpoint will also be performed on the PPS as supportive analyses.

The analysis will be compliant with ICH guideline (5)

Table 6.3: 1 Patient sets analyzed

| | | Patient set | |
|---|---|---|---|
| Class of endpoint | Treated set | FAS | PPS |
| Primary endpoint | | primary analysis | *supportive analysis |
| Key secondary, (other) secondary and further endpoints | | X | |
| Safety | X | | |
| Demographic/baseline | X | | |

* If the number of patients in PPS is less than 90% of the number of patients in FAS, the primary analysis for the primary endpoint will also be performed on the PPS as supportive analyses.

## *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*

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

### 6.6.1 Spirometry data

The REML-based MMRM model described in Section 7.3.1 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.

**$FEV_1$ and FVC measurements**

$FEV_1$ and FVC 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 $FEV_1$ and FVC measurements at a given in-clinic visit will be imputed by the available data from the patient at that visit. 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 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 short-acting beta agonist (SABA) or short-acting anticholinergic (SAMA) as rescue medication during Visit 3 and 4, any subsequent $FEV_1$ and FVC 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 $FEV_1$ and FVC 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.

- For randomly missing data (not due to worsening of study disease or rescue medication use), the following rules will be applied:

  - If one of the two pre-dose measurements at Visit 2 is missing, it will be imputed with the other predose measurement.

  - Missing 10 minute pre-dose measurement at Visits 3 and 4 will be imputed with the average of the 23h and 24h post-dose measurements at the same visit if both 23h and 24h time points have non-missing values, or will be imputed with the non-missing measurement at 23h or 24h.
  - If one of the post-dose 23h and 24h measurements is missing at a visit, then impute the missing post-dose measurement with the non-missing one.

- If both of the post-dose 23h and 24h measurements are missing and the 10-min pre-dose measurement is non-missing at a visit, then impute missing 23h and 24h measurements with the non-missing 10-min pre-dose measurement from the same visit.

### 6.6.2 SGRQ and CAT data

Missing answers for COPD Assessment Test (CAT) and St. George's Respiratory Questionnaire (SGRQ) will be handled based on related manuals [R12-1915R12-2870].

If the baseline SGRQ and CAT is missing the patient will be excluded from all SGRQ and CAT analyses, respectively.

Completely missing visits will not be imputed and will be handled through the MMRM statistical model.

In cases where an entire on-treatment visit is missing after a patient discontinues due to an AE indicative of worsening COPD, all SGRQ component scores and the SGRQ total score as well as CAT score will be imputed using the least favorable prior values for the respective scores.

If SGRQ total score and the CAT score is missing at a visit, the patient will be counted as non-responder for the SGRQ and CAT responder analysis, respectively, at that visit.

### 6.6.3 Safety data

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" (2),(3),(4).

## *6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS*

The definition of baseline values for $FEV_1$ can be found in Section 5 of the CTP. The mean of the two pre-dose pulmonary function test measurements at Visit 2, 1 hour prior and 10 minutes prior to the administration of the first dose of the randomised treatment, is used as the baseline $FEV_1$ and FVC, respectively. For CAT and SGRQ the measurements at Visit 2 is defined as baseline.

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

Table 6.7: 1 Planned and actual study days

| Visit | Planned Study Day | Actual Study Day |
|---|---|---|
| 2 | 1 | 1 |
| 3 | 42 | Visit 3 date – Visit 2 date + 1 |
| 4 | 84 | Visit 4 date – Visit 3 date + 1 |
| 5 | 105 | Visit 5 date – Visit 4 date + 1 |

# 7. PLANNED ANALYSIS

For End-of-Text (EoT) tables, the set of summary statistics for descriptive displays 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.

## 7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

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

GOLD A-D 2017 classifications will be summarized by treatment group.

## 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 0 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

In the primary analyses, comparisons between treatment groups for the primary endpoint will be based on a mixed effects model repeated measures (MMRM). Change from baseline in $FEV_1$ $AUC_{0\text{-}24h}$, will be analysed using a restricted maximum likelihood (REML)-based repeated measures approach. This model will include treatment, visit and treatment by visit interaction as fixed effects, and baseline as well as baseline by visit interaction as covariates. An unstructured covariance structure will be used to model the within patient errors. The SAS procedure MIXED will be used for the restricted maximum likelihood estimation and Kenward-Roger approximation for denominator degrees of freedom. Adjusted mean values as well as treatment contrasts will be presented together with 95% confidence intervals. The primary treatment comparisons will be the contrasts between treatments after 12 weeks of treatment.

```
PROC MIXED DATA=alldat cl method=reml order=formatted;
CLASS usubjid ptrsort tptno;
MODEL ept = ptrsort*tptno eptbase*tptno
/ ddfm=kr solution;
REPEATED tptno / subject=usubjid type=un r rcorr;
LSMEANS tptno*ptrsort / pdiff=all om cl alpha=0.05 slice=tptno;
RUN;
```

Here tptno is the planned analysis day number for each visit. The endpoint is ept, baseline value of the endpoint is eptbase, treatment is ptrsort and patient number is usubjid.

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.

If the number of patients in PPS is less than 90% of the number of patients in FAS, then the primary analyses for the primary efficacy endpoints will be repeated using PPS and the results will be presented as supportive analyses

#### 7.4.1 Adjusted Multiple Imputation sensitivity analysis for missing data

The MMRM primary analysis implicitly accounts for missing observations under the MAR (missing at random) assumption. The robustness of the primary analysis to the MNAR (missing not at random) assumption will be assessed by performing an adjusted multiple imputation sensitivity analysis.

The aim of the multiple imputation approach is to assess the robustness of the primary analysis with respect to departures from MAR by applying specific shift parameters to missing data in the T+O 5/5 arm, corresponding to substantially worse outcomes for these patients.

As a first step non-monotone missing data will be imputed m = 100 times using MCMC (Markov Chain Monte Carlo) under an assumption of MAR to generate m data sets with monotone missingness. This large number of imputations is chosen to minimize the standard error of the estimates. The seed number will be set to 123763.

The monotone missing data in the 100 generated datasets will then be imputed once per each of the 100 imputations using sequential regression including baseline $FEV_1$ and Week 6 $FEV_1$ $AUC_{0\text{-}24h}$ as covariates in the model, with a shift parameters S applied to the treatment arm T+O 5/5 at the first missing visit and no shift applied to the F+S 250/50 treatment arm. Subsequent visits will have no additional shift but due to the sequential method, the impact of the initial shift will propagate to all future visits.

Point estimates for treatment differences and respective p-values will be reported for all S.
Selection of S
a. -250 ml (large shift, conservative analysis)
b. -125 ml,
c. negative treatment difference from the primary analysis

### *7.5 SECONDARY ENDPOINTS*

#### 7.5.1 Key secondary endpoint

This section is not applicable as no key secondary endpoint has been specified in the protocol.

#### 7.5.2 (Other) Secondary endpoints

The MMRM model described for the primary analysis will be performed for the continuous secondary endpoints. Adjusted mean values as well as treatment contrasts will be presented together with the 95% confidence intervals. All calculated p-values should be considered descriptive for the analysis of the secondary endpoints.

## *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 specified in Section 5.4.

## *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 (3, 4).

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 will be assigned to the randomised 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). 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 summarised 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).

### *7.9 LABORATORY DATA*

The absolute eosinophil count recorded at Visit 1 and 2 will be analysed descriptively.

### *7.10 VITAL SIGNS*

Only descriptive statistics are planned for this section of the report.

### *7.11 ECG*

Not applicable since ECG data will not be collected in the database.

### *7.12 OTHERS*

Not applicable since there were no additional endpoints.

# 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-80-606*: “Handling of Non-Compliances in Clinical Development, Medicine and QRPE”, 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 summarisation 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 | 31-Aug-2017 | | None | This is the initial TSAP with necessary information for trial conduct |
| Final | 14-May-2018 | | 7 | This is the final TSAP |