Trial Statistical Analysis Plan

c14108328-02

BI Trial No.:	1237.36
Title:	An exploratory, randomised, double-blind, double-dummy, active-controlled, two period cross-over study to investigate the effect of 6 weeks treatment of orally inhaled tiotropium + olodaterol fixed dose combination (FDC) delivered by the Respimat® Inhaler with fluticasone propionate + salmeterol FDC delivered by the Accuhaler® Inhaler, on left ventricular function and arterial stiffness in patients with Chronic Obstructive Pulmonary Disease (COPD)
Investigational Product(s):	Tiotropium + olodaterol fixed dose combination inhalation solution - Respimat®
Responsible trial statistician(s):	Telephone: Fax:
Date of statistical analysis plan:	13 MAR 2018 SIGNED
Version:	Final

1. TABLE OF CONTENTS

LIST OF TABLES

2. LIST OF ABBREVIATIONS

Include a list of all abbreviations used in the TSAP

Term	Definition / description
AE	Adverse Event
AESI	Adverse Event of Special Interest
AI	Augmentation Index
AMP	Auxiliary Medicinal Product
ATS	American Thoracic Society
AUC	Area under the Curve
BAC	Benzalkonium chloride
BI	Boehringer Ingelheim
bid	bis in die (twice daily dosing)
BMI	Body Mass Index
BRPM	Blinded report planning meeting
BSA	body surface area
CABG	Coronary Artery Bypass Graft
CI	Confidence Interval
CML	Local Clinical Monitor
CMR	Cardiac Magnetic Resonance
COPD	Chronic Obstructive Pulmonary Disease
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Contract Research Organisation
CT	Computer tomography
CTC	Common Terminology Criteria
CTMF	Clinical trial master file
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
CV	Cardiovascular
DEDP	drug exposure during pregnancy
DM&SM	Boehringer Ingelheim Data Management and Statistics Manual
DMG	Dictionary Maintenance Group

Term	Definition / description
DPI	Dry Powder Inhaler
DRA	Drug Regulatory Affairs
ECG	Electrocardiography
eCRF	Electronic Case Report Form
ECSC	European Coal and Steel Community
ED	end diastolic
EDTA	Disodium edentate
EF	ejection fraction
EFL	Expiratory flow limitation
EMEA	European Agency for the Evaluation of Medicinal Products
EoO	End of Observation
EoT	End of Treatment
ERS	European Respiratory Society
ERV	Expiratory reserve volume
EU	European Union
EudraCT	European Clinical Trials Database
FAS	Full Analysis Set
FC	Flow Chart
FDC	Fixed Dose Combination
FEV1	Forced Expiratory Volume in 1st second
FRC	Functional Residual Capacity
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
GOLD	Global Initiative for Chronic Obstructive Lung Disease
HCG	human chorionic gonadotropin
HFA	hydrofluoroalkane
IB	Investigator's Brochure
IC	Inspiratory capacity
ICH	International Conference on Harmonisation
ICS	Inhaled corticosteroids
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product

Term	Definition / description
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISF	Investigator Site File
IVC	inspiratory vital capacity
LABA	Long-acting β2-agonist
LAMA	Long-acting muscarinic antagonists
LBBB	Left bundle branch block
LDH	Lactate Dehydrogenase
LOCF	Last observation carried forward
LPDD	Last Patient Drug Discontinuation
LV	Left Ventricle
LVEDVI	Left Ventricular End Diastolic Volume Index
LVH	Left ventricular hypertrophy
MACE	Major adverse cardiovascular event
MCID	Minimal clinically important difference
MD	Medical Degree
MDI	Metered Dose Inhaler
MedDRA	Medical Dictionary for Drug Regulatory Activities
MMI	Myocardial mass index
mMRC	Modified Medical Research Council Dyspnoea Scale
MMRM	Mixed-effects Model for Repeated Measures
MQRM	Medical Quality Review Meeting
MST	Medical Sub Team
NIMP	Non Investigational Medicinal Product
NYHA	New York Heart Association
O*C	Oracle Clinical
PD	Pharmacodynamics
PA	pulmonary artery
PDE-4	Phosphodiesterase Type 4
Pleth	Body Plethysmography
PFT	Pulmonary function testing
PK	Pharmacokinetics

Term	Definition / description
PPS	Per protocol set
PRN	pro re nata (as needed)
PSTAT	Project Statistician
PT	Preferred term
PV	Protocol violation
PWA	Pulse Wave Analysis
Q1	Lower quartile
Q3	Upper quartile
qd	quaque die (once a day)
REML	Restricted Maximum Likelihood
REP	Residual effect period, after the last dose of medication with measureable drug levels or pharmacodynamic effects still likely to be present
RV	right ventricular
RVol	Residual Volume
SA	Statistical analysis
SAE	Serious Adverse Event
SD	Standard deviation
SGOT	Serum glutamic-oxaloacetic transaminase
SGPT	Serum glutamic-pyruvic transaminase
SGRQ	St. George´s Respiratory Questionnaire
SOC	System organ class
SOP	Standard operating procedures
SmPC	Summary of Product Characteristics
SMQ	Standardised MedDRA query
STORM	storage conditions for trial medication
SUSAR	Suspected Unexpected Serious Adverse Reaction
SVI	Stroke volume index
TCM	Trial Clinical Monitor
TDI	Transitional dyspnoea index
TESS	Treatment emergent signs and symptoms
TLC	Total Lung Capacity
TMF	Trial Master File
TMW	Trial Medical Writer

Term	Definition / description
ToC	Table of contents
TSAP	Trial Statistical Analysis Plan
UK	United Kingdom
US	United States

3. INTRODUCTION

As per ICH E9, 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 will be used for all analyses.

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

All analyses described in the TSAP are outlined in the CTP.

5. ENDPOINT(S)

5.1 PRIMARY ENDPOINT

Primary endpoint of efficacy will be used as described in the CTP, Section 5.1.1 “Primary endpoint”.

5.2 SECONDARY ENDPOINT(S)

5.2.1 Key secondary endpoint(s)

No key secondary endpoints were specified in the CTP.

5.2.2 Secondary endpoints

Secondary endpoints of efficacy will be used as described in the CTP, Section 5.1.2 “Secondary Endpoints”.

- All adverse events (AEs), including any clinically relevant changes/abnormalities in physical examination, vital signs, laboratory values, and electrocardiogram (ECG)

6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENT(S)

The doses to be administered are described in Section 4 of the CTP.

This is a crossover trial consisting of a one to three-week run-in period followed by two six-week treatment periods and a three-week post-treatment period. The day after the follow-up visit will be considered the start of the post-study period in case there are any subsequent AE data we become aware of. In this study, there will be no washout between treatment periods.

In general, the first period will be considered last until 12 hours after the last intake of medication assigned for the first period, then the second period will start

For the main safety analysis, data occurring during the treatment periods and within 21 days of stop of study drug for that period will be assigned to the respective treatment for that period. Data occurring before the first drug intake date is assigned to "screening". If the next treatment period starts within 21 days of the end of the last period, data after the start of treatment for the next period will be assigned to the treatment for that period. In this trial, next treatment will be started after end of treatment of first period as soon as possible because there is no washout period planned. The last day of the first period is the day of the last intake of medication for the first period. AEs occurring at the last day of the first period will be assigned to the first period even if the medication of the evening dose already belongs to the second period. Data more than 21 days after drug stop date for a period but before the start of the next period will be assigned to washout. 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 summarised as an important protocol violation (PV).

- If a patient was treated with a treatment sequence different from the randomised treatment sequence throughout the on-treatment period, i.e., a patient was treated with incorrect study medication during every treatment period, this patient will be included in the treated set and will be analysed as treated for both efficacy and safety analyses, including patient disposition. Such a case will be reported as an important PV and this patient will be excluded from the per-protocol set (PPS).

- If a patient was treated with incorrect study medication throughout one treatment period only, but not both treatment periods, this patient will be included in the treated set and will be analysed as treated for safety analysis. For efficacy analysis, only efficacy data collected in the correct treatment period will be used and efficacy data collected in the other treatment period with the duplicate study medication will not be used. For patient disposition, such a patient will be analysed as randomised. Such a case will also be reported as an important PV but this patient will not be excluded from the PPS.

If a patient was treated with incorrect study medication during part of a treatment period, data of this patient will be discussed case by case at final Blinded report planning meeting (BRPM) or data base lock meeting (DBLM).

6.2 IMPORTANT PROTOCOL VIOLATIONS

A patient's deviation from the trial protocol is considered "relevant" 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/rights.

Table 6.2:1 gives the important protocol violations (IPVs) for the trial. The final decision with regards to important PVs and exclusion from the PPS will be made at the final blinded report planning meeting (BRPM) or data base lock meeting (DBLM).

In the case that a patient was randomised in both this trial and another trial or was randomised at two different sites in this trial, the patient will be indicated as having an important PV (IPV, see Table 6.2: 1-Exclusion Criterion 26). 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) (for 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 was randomised twice in this study, the patient's data of periods with the same treatment will be combined (i.e. the patient is only counted once). If the patient participated in two different trials in the same 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, baseline characteristics and important PVs, the patient will be analysed as treated. If the patient was randomised twice in this study and the treatments in periods 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 demographics, baseline data and important PVs.

Table 6.2: 1 Important protocol violations

Category / Code		Description	Requirements	Excluded from*
A		**Entrance criteria not met**		
	A1	Inclusion criteria not met	Inclusion Criteria 2-8 not met as specified in the protocol.	Exclude from PPS*: 2-8
	A2	Exclusion criteria not met	Exclusion Criteria 1-28 not met as specified in the protocol	Exclude from PPS*: 3-8, 10-14, 16-22, 26-28
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, or a patient signed the correct version of the ICF after Visit 0. If date of informed consent equals to date of Visit 1, such cases will be discussed at MQRM/BRPM/DBL meetings.	None
C		**Trial medication and randomisation**		
	C1	Incorrect trial medication taken	Not throughout the entire study treatment period; could be at a clinic visit or between clinic visits. External vendor will check before unblinding.	PPS (decision at BRPM)
	C2	Randomisation order not followed	Throughout the study	PPS
	C3	**Non- compliance with study medication**		
	C3.1	Serious non-compliance with study medication as reported in monitoring report or issue listing (formerly manual PV spreadsheet)	Decision at BRPM/MQRM.	PPS if at Visit 3 or 4 and at respective second and third CMR assessments
	C4	Medication code broken inappropriately	To be discussed and decided during MQRM/BRPM. Only inappropriate code breaks are IPVs (e.g. unblinding by Global Pharmacovigilance is not considered inappropriate code break).	PPS

Table 6.2: 1 (continued) Important protocol violations

Category / Code		Description	Example/Comment	Excluded from*
D		**Concomitant medication**		
	D1	Improper medication washout for CMR assessment (at baseline CMR or on-treatment CMRs for primary endpoint)	Washout not met for baseline CMR assessment and for on-treatment CMRs. Decision at BRPM*	PPS
	D2	Prohibited medication use during study	Check CT. Decision at BRPM.	PPS if in the week prior to Visit 2, 3, and 4
F		**Incorrect timing**		
	F3	Primary endpoint recorded outside time window	A. With respect to treatment duration: 1) CMR < 35 days of treatment in each period B. With respect to clinic visits: 1) CMR baseline assessment at or after Visit 2 date, and/or 2) second CMR assessment after Visit 3 date, and/or 3) third CMR assessment after Visit 4 date, and/or 4) second CMR assessment < 1 hour or > 8 hours post morning dose of study medication at Visit 3 and/or 5) third CMR assessment < 1 hour or > 8 hours post morning dose of study medication at Visit 4	PPS
Z		**Other**		
	Z1	Serious GCP non-compliance	Manual PVs reported by CML/CRA which are considered as important. Carefully reviewed, described and documented in DBL meeting minutes.	PPS
	Z2	Other PV affecting efficacy and possibly 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
	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

KEY: CT = Concomitant Therapy, BRPM = Blinded report planning meeting, CML = Local Clinical Monitor, CRA = Clinical Research Associate, ICF = informed consent form, MQRM = Medical Quality Review Meeting, PPS = Per protocol set, DBL = Data Base Lock, ADS = Analysis Data Set

*Final decision will be discussed and determined prior to database lock.

Note: Missing visits, evaluations, and tests are considered as missing data, but not protocol deviations.

6.3 PATIENT SETS ANALYSED

The following nested patient sets are defined:

- Randomised set (RS):

  This patient set includes all patients who signed informed consent form and were also randomised, regardless whether the patient was treated with study medication or not.

- Treated set (TS):

  This patient set is nested within RS and includes all patients who were dispensed study medication and were documented to have taken any dose of study medication. TS will be used for patient disposition, demographics and baseline disease characteristics, concomitant therapies, treatment compliance, treatment exposure and safety analyses (including AEs and vital signs).

- Full analysis set (FAS):

  This patient set is nested within TS and includes patients who had baseline measurement and at least one post-baseline measurement for the primary endpoint or secondary endpoints. Assignment to the FAS will be done after implementation of any data handling rules which set measurements to missing.

- Full analysis set excluding exacerbation (FAS-EE):

  This patient set is nested within FAS and the data from patients who have had an exacerbation during the treatments will be excluded from this data set. FAS-EE will be used for the efficacy analyses.

- Per protocol set (PPS):

  This patient set is nested within FAS-EE and includes only patients who had no important PVs which are specified to be excluded from the PPS (Table 6.3: 1).

  The final decision regarding which patients are excluded from PPS will be made at BRPM or data base lock meeting (DBLM) prior to data unblinding.

Table 6.3: 1 Patient sets analysed

		Patient Sets
Class of endpoint	TS	FAS-EE
Primary endpoint		primary analysis
Secondary endpoints		X
Safety endpoints	X	
Demographic/baseline endpoints/exposure	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

As noted in the protocol, in general, missing data at a given visit will be imputed by the available data from the patient at that visit and completely missing visits will be handled through the statistical model.

Completely missing visits will not be imputed and will stay as missing, and will be handled in the mixed model repeated measures model.

It could happen that a patient needed therapy for COPD symptoms at a clinic visit. This therapy was entered on the rescue medication electronic Case Report Form (eCRF). This may or may not be the rescue medication provided by Boehringer Ingelheim (BI). For purposes of the imputation rules this will be termed “rescue medication” regardless of whether or not it was BI-supplied rescue medication.

The following rules will be used for spirometry data which were collected at Visits 2, 3 and 4:

- Since there is only one spirometry measurement at each on-treatment clinic visit, rescue medication use on or before the spirometry measurement or rescue use with unknown time will both result in all spirometry measurements for the visit being set to missing.

- Randomly missing spirometry measurements at Visits 2, 3, and 4, e.g., due to a mechanical failure, will not be imputed.

The rules used for spirometry data will also be applied to Body Plethysmography. CMR data will not be imputed.

Missing or incomplete AE dates are imputed according to BI standards (see "Handling of missing and incomplete AE dates") (3).

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

Baselines for Primary Endpoint

The primary endpoint is change from baseline in LVEDVI in the 6th week of treatment with tiotropium+olodaterol FDC versus fluticasone propionate+salmeterol FDC.

- The baseline is defined as the (pre-dose) measurement of the LVEDVI performed in a week prior to Visit 2 (or prior to dosing on the Visit 2).

Baseline for endpoints not related to CMR is defined as the pre-dose measurement at Visit 2.

Time windows and calculated visits

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

Visit	Relative to period start		Relative to study start	
	Planned day	Actual day	Planned day	Actual day
2	1	1	1	1
3	43	Visit 3 date - Visit 2 date + 1	43	Visit 3 date - Visit 2 date + 1
4	43	Visit 4 date - Visit 3 date + 1	85	Visit 4 date - Visit 2 date + 1

7. PLANNED ANALYSIS

For End-Of-Text tables, the set of summary statistics is: N / Mean / Standard deviation (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.

7.2 CONCOMITANT DISEASES AND MEDICATION

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

Use of pulmonary medications during treatment period and testing will be summarised in the end-of-text tables in the Clinical Trial Report (CTR) and a subject data listing of all concomitant medications will be provided in Appendix 16.2.

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

Descriptive statistics and frequency tables (%) will be presented for history of trial indication.

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

7.3 TREATMENT COMPLIANCE

Only descriptive statistics are planned for this section of the report. Only descriptive statistics, i.e. the number (%) and percent of patients with compliance in the range of 80% - 120% will be provided. (cf. Section 5.4 for calculation of treatment compliance).

7.4 PRIMARY ENDPOINT(S)

In the primary analysis, the two-sided hypothesis as given in Section 7.2 in the CTP will be tested based on adjusted mean change from baseline in LVEDVI, as listed in Section 5.1.1 in the CTP, using a restricted maximum likelihood (REML)-based MMRM. This model will include treatment and period as fixed effects, patient as a random effect and baseline as covariate. Unstructured covariance structure will be used for within patient variation. If convergence is not achieved, the compound symmetry covariance structure will be used. The SAS procedure MIXED will be used involving the restricted maximum likelihood estimation and the Kenward-Roger approximation for denominator degrees of freedom. This approach is described in (2). Adjusted mean values as well as treatment contrasts will be presented together with the 95% confidence intervals (CI) and p-values. The primary analysis will be performed on FAS-EE.

7.5 SECONDARY ENDPOINT(S)

7.5.1 Key secondary endpoint(s)

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

7.5.2 (Other) Secondary endpoint(s)

The MMRM described for the primary endpoint will be performed for secondary continuous endpoints. Adjusted mean values as well as treatment contrasts will be presented together with the 95% CIs and nominal p-values. All p-values will be considered as descriptive.

7.7 EXTENT OF EXPOSURE

Extent of exposure is calculated as drug stop date minus drug start date plus one day and treatment interruptions are not taken into account in the calculation.

Extent of exposure will be summarised using descriptive statistics for the total treatment exposure in days as well as tabulation of number of patients with total exposure fall into the following categories:

- 1 day
- 2 – 21 days
- 22 – 42 days
- 43 – 63 days
- 64 - 84 days
- >=85 days.

Extent of exposure will also be summarised using descriptive statistics into the following categories:

- 1 – 39 days
- 40 – 46 days
- >=47 days.

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 (5), 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 (5), for subjects with adverse events of special interest (only if defined), for subjects with serious adverse events, for subjects with adverse events leading to discontinuation, for subjects with drug-related adverse events, and for subjects with related 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

The analyses of laboratory data will be descriptive in nature.

In general lab data will not be analyzed.

Clinically significant findings in other laboratory data will be reported as "baseline conditions" or "adverse events" and will be analysed accordingly.

7.8.3 Vital signs

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

7.8.4 ECG

Clinically significant findings in ECG data will be reported as “baseline conditions” or “adverse events” and will be analysed accordingly.

7.8.5 Others

None.

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	R10-4391: Kenward, M.G. The use of baseline covariates in crossover studies. Biostatistics 11(1),1-17 (2010)
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
6	*001-MCG-157: "Handling, Display and Analysis of Laboratory Data", 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
Initial	**23-MAR-17**		None	This is the initial TSAP with necessary information for trial conduct
Final	**13-MAR-18**		Overall	This is the final TSAP without any Modification.