Statistical Analysis Plan

NCT Number: NCT04985682

Title: Phase 4, Multicenter, Prospective, Interventional, Post-Marketing Study in Hemophilia A Patients in India Receiving ADVATE as On-Demand or Prophylaxis Under Standard Clinical Practice

Study Number: TAK-761-4009

Document Version and Date: Version 1.0 (09-May-2023)

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STATISTICAL ANALYSIS PLAN

Study Number: *TAK-761-4009*

Study Title: *Phase 4, Multicenter, Prospective, Interventional, Post-Marketing Study in Hemophilia A Patients in India Receiving ADVATE as On-demand or Prophylaxis Under Standard Clinical Practice*

Phase: *Phase 4 (post-marketing)*

Version: *1.0*

Date: *09-May-2023*

Prepared by: [redacted]

Based on:

Protocol Version: *5.1*

Protocol Date: *31-Jul-2019*

JSS Sign off			
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REVISION HISTORY

Version	Approval Date	Primary Rationale for Revision
[Not Applicable]	[Not Applicable]	[Not Applicable]

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ABBREVIATIONS

Abbreviation	Definition
Ab	Ab antibody
AE	AE adverse event
AHF	AHF antihemophilic factor
ALT	ALT alanine aminotransferase (synonymous with SGPT)
aPTT	aPTT activated partial thromboplastin time
AST	AST aspartate aminotransferase (synonymous with SGOT)
AUC	AUC area under the curve
AUC0-∞	AUC0-∞ area under the curve from time 0 to infinity
AUC0-tlast	AUC0-tlast area under the curve from time 0 to the time of last concentration measured
AUMC	AUMC area under the moment curve
BI	BI bolus infusion
BUN	BUN blood urea nitrogen
CFR	CFR Code of Federal Regulations
CHO	CHO Chinese hamster ovary
CI	CI confidence interval
C_{max}	Cmax maximum concentration
CRF	CRF case report form
CRO	CRO contract research organization
DMC	DMC data monitoring committee
EC	EC ethics committee
ECG	ECG electrocardiogram
eCRF	eCRF electronic case report form
ED	ED exposure day
EDC	electronic data capture/collection
EFAS	effectiveness full analysis set
ELISA	enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EU	European Union
EUDRA	European Union Drug Regulatory Authorities
EUDRACT	European Union clinical trials database
FVIII	factor VIII
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLM	generalized linear model

h	hour(s)
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IgG	Immunoglobulin G
INR	international normalized ratio
IP	investigational product
IR	incremental recovery
IRB	institutional review board
ISTH	International Society for Thrombosis and Haemostasis
IU	international unit(s)
IV	intravenous(ly)
MedDRA	Medical Dictionary for Regulatory Activities
mmHg	millimeter(s) of mercury
NA	not applicable
PCR	polymerase chain reaction
PFM	plasma/albumin free method
PK	pharmacokinetic(s)
PTP	previously treated patient
PUP	previously untreated patient
rAHF	antihemophilic factor (recombinant)
rAHF-PFM	Antihemophilic Factor (Recombinant) - Plasma/Albumin Free Method
rFVIII	recombinant FVIII
SAE	serious adverse event
SAP	statistical analysis plan
SAS	safety analysis set
SAS	statistical analysis system
SC	subcutaneous(ly)
SmPC	Summary of Product Characteristics
SOC	system organ class
SoC	standard of care
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse reaction
SWFI	sterile water for injections
$t_{1/2}$	half-life
TBD	to be determined
T_{max}	time to maximum concentration
US	United States
VWD	von Willebrand´s disease
VWF	von Willebrand factor

WHO	World Health Organization

1.0 OBJECTIVES, ENDPOINTS AND ESTIMANDS

1.1 Objectives

Objective	Endpoint(s)
Primary	
• To assess the safety of ADVATE based on SAEs (including FVIII inhibitors)	• Incidence of SAEs (including FVIII inhibitor formation) that are at least possibly related to ADVATE
Secondary	
• To assess the safety of ADVATE based on AEs and changes in laboratory parameters	• Incidence of non-serious AEs that are at least possibly related to ADVATE • Clinically significant changes in clinical laboratory parameters (hematology and clinical chemistry)
• To assess the efficacy of prophylactic treatment with ADVATE	• Annualized bleeding rate (ABR) with prophylactic use of ADVATE • Total number of infusions and the average number of infusions per week per month during prophylactic treatment • Total and average body mass adjusted consumption of ADVATE per week per month during prophylactic treatment
• To assess the efficacy of on-demand treatment with ADVATE in the control of bleeding episodes.	• Overall hemostatic efficacy rating for treatment of bleeding episodes • Number of ADVATE infusions required to achieve bleed resolution • Body mass adjusted consumption of ADVATE per bleeding episode

1.2 Estimand(s)

Not Applicable

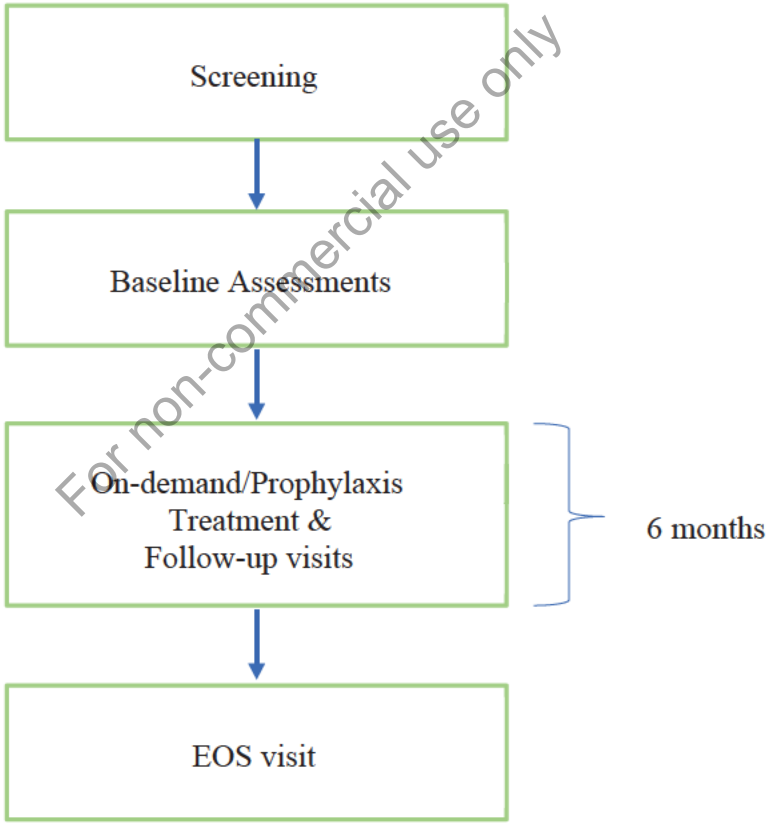
2.0 STUDY DESIGN

This is a Phase 4, open-label, multicenter, uncontrolled, prospective, interventional, single-group, post-marketing study in previously treated hemophilia A patients (PTPs) in India receiving ADVATE under standard clinical practice.

Overall 50 subjects legally authorised having age < 18 years and subjects belonging to any age group with hemophilia A will be included in this study. All enrolled subjects who have met the inclusion and exclusion criteria will be treated with ADVATE according to a regimen determined by the treating physician and in accordance with the national product label. The individual subject´s maximum duration of participation is expected to be approximately 7-8 months. The period of observation for each subject will be 6 months; another 10 to 15 days are anticipated for the study completion visit ("End-of-Treatment Visit"). The starting point of the observation will be an infusion of ADVATE at baseline (dose: 50±5 IU/kg) to determine incremental recovery (IR).

For the ADVATE infusion to determine IR, a dose of 50±5 IU/kg of ADVATE shall be given, as in previous ADVATE clinical studies.

Figure 1. Study Design and Visit Schedule



Schedule of Activities

Table 1. Schedule of Study Procedures and Assessments

Procedures/ Assessments	**Screening Visit**	**Baseline Visit**	**Visit 1**	**Visit 2**	**Unscheduled Visit(s)[a]**	**End of Treatment Visit**	**Study Termination Visit[b]**
Time point	**Up to 45 days prior to Day 0**	**Day 0**	**1 month ± 1 week**	**3 month ± 1 week**		**6 month ± 1 week**	
Informed Consent[c]	X						
Eligibility Criteria	X	X[d]					
Medical History	X						
Hemophilia A Disease History, Bleeding History and FVIII Treatment History	X						
Medications History (other than Hemophilia A)	X						
Physical Exam	X	X	X	X	X	X	X
Vital Signs	X	X	X	X	X	X	X
Concomitant Medications and Non-drug Therapies	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X
Laboratory assessments	See Table 2						
Bleeding Episodes and Treatment[e]	X	X	X	X	X	X	X
Review of Subject Diary		X	X	X	X	X	X
IP Use		X	X	X	X	X	X
IP Dispense[f]		X	X	X	X		

[a] Unscheduled visits could be performed for any reason (bleed management, safety event, etc.) as per Investigators' discretion.
[b] Study Termination Visit will be performed only if subject is discontinuing the study or withdrawing from the study without completing the End of Treatment Visit.
[c] Occurs prior to any study-specific procedure.
[d] Same eligibility criteria to be used as at Screening.
[e] To collect information on the type of bleeding episodes (site, severity, duration) and the treatment used for the bleeding episodes (drug, dose, frequency, duration).
[f] ADVATE should be dispensed to provide sufficient treatment until at least the next scheduled visit, or as appropriate.

Table 2. Schedule of Clinical Laboratory Assessments

Procedures/ Assessments	**Screening Visit**	**Baseline Visit**	**Visit 1**	**Visit 2**	**Unscheduled Visit(s)[a]**	**End of Treatment Visit**	**Study Termination Visit[b]**
Time point	**Up to 45 days prior to Day 0**	**Day 0**	**1 month ± 1 week**	**3 month ± 1 week**		**6 month ± 1 week**	
Hematology[c]	X				X (optional)	X	X
Clinical chemistry[d]	X				X (optional)	X	X
Viral serology[e]	X					X	X
FVIII Antigen	X						
FVIII Activity	X				X (optional)		
Incremental Recovery (IR)[f]		X		X (optional)		X	X
FVIII Inhibitor[g]	X	X	X	X	X	X	X

[a] Unscheduled visits could be performed for any reason (bleed management, safety event, etc.) as per Investigators' discretion
[b] Study Termination Visit will be performed only if subject is discontinuing the study or withdrawing from the study without completing the End of Treatment Visit.

[c] Hematology assessments include: hemoglobin, hematocrit, red blood cell count, and white blood cell count with differential (ie, basophils, eosinophils, lymphocytes, monocytes, neutrophils), mean corpuscular volume (MCV), mean corpuscular hemoglobin concentration (MCHC), and platelet count.

[d] Clinical chemistry assessments include: sodium, potassium, chloride, bicarbonate, total protein, albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, alkaline phosphatase, blood urea nitrogen (BUN), creatinine, and glucose.

[e] Viral serology includes: HIV-1Ab, HIV-2 Ab, HBcAb, HBsAb, HBsAg, and HCVAb. Any HIV or HCV positive sample will be tested by PCR for viral titer, HIV positive subjects will have CD4 counts monitored every 3 months during the course of the study.

[f] For assessment of IR: samples will be taken within 0.5 h before the start of the infusion, and at 15-30 minutes after the infusion. Prior to the pre-infusion blood draw for IR determination, subjects should have a washout period from previous plasma-derived and/or recombinant FVIII concentrate(s) treatment. The washout period will depend on the type of product the subject receives, ie, at least 48 hours for products with standard half-life and 84-96 hours for extended half-life products.

[g] If an inhibitory titer ≥ 0.6 BU by Nijmegen, the test will be confirmed in the central laboratory within 2 weeks of study site notification.

3.0 STATISTICAL HYPOTHESES AND DECISION RULES

95% CI will be calculated using negative binomial distribution but no statistical hypotheses and decision rules required in this study.

4.0 SAMPLE-SIZE DETERMINATION

According to the WFH Report on the Annual Global Survey 2017 (World Federation of Hemophilia, 2018) there were a total of 15,920 cases of hemophilia A in India in 2017. Due to the low prevalence of hemophilia A and the difficulty in switching patients from their current therapy, the planned sample size is 50 subjects. The sample size is not based on the statistical consideration.

5.0 ANALYSIS SETS

5.1 Effectiveness Full Analysis Set (EFAS)

The EFAS will be comprised of all subjects for whom all inclusion and none of the exclusion criteria are met. This dataset will be used for the efficacy analyses.

5.2 Safety Analysis Set (SAS)

All subjects having received ADVATE at any time during the study will be included in the SAS.

6.0 STATISTICAL ANALYSIS

6.1 General Considerations

In general, the variables will be summarized by using standard descriptive statistics. Continuous variables will be summarized with the number (n) of non-missing observations, mean, standard deviation, median, quartiles and interquartile range, minimum, and maximum, unless otherwise specified. For categorical data, descriptive statistics will be presented with the number and percentage of subjects in the various categories of the endpoint. Individual data listings will also be provided.

6.1.1 Handling of Treatment Misallocations

This is a single arm study. All subjects will take ADVATE.

6.2 Disposition of Subjects

The summary for study disposition will include number of subjects screened, number of screen failures, number and percentage of enrolled subjects who have met all inclusion and exclusion criteria and will be treated as ADVATE, reason of screen failure, the number and percentage of subjects who are in each analysis set, who complete the study, and who withdraw early from the study. The primary reasons for early withdrawals will also be tabulated.

6.3 Demographic and Other Baseline Characteristics

6.3.1 Demographics

Demographic and baseline characteristics will be summarized descriptively for the effectiveness full analysis set. The demographic variables include age, gender, weight, height, and BMI. Variables that are measured on a continuous scale, such as age of the subject at time of enrolment, number of non-missing observations (n), mean, median, SD, quartiles and interquartile range, minimum, and maximum will be tabulated. Variables that are measured on a categorical scale will be summarized using frequencies and percentages.

6.3.2 Medical History

Medical History will be reported and will be medically coded using Medical Dictionary for Regulatory Activities (MEDRA) dictionary version 25.0 or higher. Summary tables for medical history will be provided in the study and will be summarized by reporting subject count and percentage of subjects by System Organ Class and Preferred Term on Effectiveness Full Analysis Set and Safety Analysis Set.

6.3.3 Hemophilia History

Hemophilia History will be summarized by number and percentage of subjects diagnosed with Hemophilia A prior to the enrolment. Summary statistics for Deficient Factor Level and counts and percentage for Disease Severity will be provided for those subjects diagnosed with Hemophilia A prior to the enrolment.

6.3.4 Previous Hemophilia Treatments and Bleeding History

Previous Hemophilia Treatments and Bleeding History will be summarized by number and percentage of subjects having any previous treatment for Hemophilia A. Summary statistics for Treatment Regimen, Number of Bleeds during the regimen period will be provided.

6.4 Prior Medications and Concomitant Medications and Non-drug Therapies

All medications(Prior, concomitant and Non-drug therapies) will be coded using the WHO-DRUG Dictionary (WHO-DD) Version 1 Sep 2021 or later. Summary tables and listing for medications will be provided and will be summarized by reporting subject count and percentage of subjects by Therapeutic Class and Generic name.

6.4.1 Prior Medications

Prior medications include all treatment received within 6 months before the date of first dose of investigational product.

6.4.2 Concomitant Medications

Concomitant medications include any medication other than for Hemophilia A started 3 months prior to the ICF signing and still ongoing after the first dose of investigational product until completion/termination of the study.

6.4.3 Non-drug Therapies

Non-drug Therapies include all non-drug therapy taken by the subject, 3 months prior to the ICF signing and still ongoing after the first dose of investigational product until completion/termination of the study.

6.5 Efficacy Analysis

6.5.1 Primary Endpoint(s) Analysis

Not applicable. There is no primary efficacy endpoint.

6.5.2 Secondary Endpoint(s) Analysis

- Annualized bleeding rate (ABR) with prophylactic use of ADVATE

The annualized bleeding rate (ABR) during the prophylactic treatment will be assumed to have a negative binomial distribution, and the mean ABR (95% CI) will be estimated using a generalized linear model (GLM) with logarithmic link function.

Annualized bleeding rate (ABR) is the dependent variable and the log time of the observed prophylactic treatment period is used as an offset variable.

The observed prophylactic treatment period(OTP) in days is to be determined as:
(Study completion visit or withdrawal date - Treatment start date + 1)

$$\text{OTP(years)} = \frac{\text{OTP(days)}}{365.2425}$$

The following SAS code is to be used to perform the analysis:

proc genmod data = <dataset_name>;
class < Injury bleeds > < Spontaneous bleeds > < Joint bleeds>;
model < ABR > = < Injury bleeds > < Spontaneous bleeds > < Joint bleeds> < age >
/ dist = negbin
offset = <log_ OTP > link = log;
run;

where < dataset_name > refers to the input dataset, <ABR> the annualized bleeding rate and <log_ OTP > the logarithm of the OTP in years. Point estimates and confidence intervals obtained from the generalized linear model are to be anti-logged prior to presentation.

ABR was defined as number of bleeding episodes during the study period / total number of study period days × 365.25.

The total ABR and ABR by bleed cause/ site, i.e. joint, soft tissue, muscle, body cavity, intracranial, spontaneous, injury will be summarized descriptively as well.

- Total number of infusions and the average number of infusions per week per month during prophylactic treatment

Summary statistics for the total number of infusions, as well as the average number of prophylactic infusions per week and per month of prophylaxis treatment excluding infusions to treat bleeds will be provided.

Total number of infusions:
Total number of infusions in this study are determined as the count of the number of infusions, regardless of date and time, the subject had.
Average number of infusions :
The average number of infusions per time period (weeks, months) should be determined as the total number of infusions during the full observation period, divided by the duration for the particular time period (weeks, months).
Duration (weeks)= (Date of last dose - Date of first dose +1)/7
Duration (months)= (Date of last dose - Date of first dose +1)/12

- Total and average body mass adjusted consumption of ADVATE per week per month during prophylactic treatment

Summary statistics for the total body mass adjusted consumption and the average consumption of ADVATE per week and per month during prophylactic treatment will be provided.
Body mass adjusted consumption (IU/kg) is to be derived as the total units infused (IU) divided by the last available body weight (kg) prior to the infusion.

- Overall hemostatic efficacy rating for treatment of bleeding episodes

Summary for overall hemostatic efficacy rating for treatment of bleeding episodes will be provided. This table will be also presented by bleeding site, cause and severity.

- Number of ADVATE infusions required to achieve bleed resolution

Summary statistics for number of ADVATE infusions required to achieve bleed resolution will be provided. This table will be also presented by bleeding site, cause and severity.

- Body mass adjusted consumption of ADVATE per bleeding episode

Summary statistics for body mass adjusted consumption of ADVATE per bleeding episode will be provided. This table will be also presented by bleeding site, cause and severity.

6.6 Safety Analysis

6.6.1 Primary Endpoint(s) Analysis

- Incidence of SAEs (including FVIII inhibitor formation) that are at least possibly related to ADVATE

Frequency counts and percentages for possibly or probably related SAEs (including FVIII inhibitor formation) as well as for subjects with possibly or probably related SAEs (including FVIII inhibitor formation) that occurred during or after first ADVATE infusion will be summarized. The incidence of FVIII inhibitor development will also be summarized by high-titer (>5 BU) and low-titer (0.6-5 BU). 95% CI will also be calculated by using clopper Pearson method.
A listing of all SAEs will be presented by subject identifier, age, sex, preferred term and reported term of the SAE, severity, causality (Casual relationship between study drug and event?) and (Casual relationship between device and event?), outcome, Seriousness Criteria onset date, stop date and medication or non-drug therapy to treat the SAE.

6.6.2 Secondary Endpoint(s) Analysis

- Incidence of non-serious AEs that are at least possibly related to ADVATE

All AEs will be cross-tabulated for relatedness, seriousness, and severity. AEs will be categorized according to the MedDRA version 25.0 or higher and summarized by system organ class and preferred term. A listing of all AEs will be presented by subject identifier, age, sex, preferred term and reported term of the AE, duration, severity, seriousness, action taken, outcome, causality assessment by investigator, onset date, stop date and medication or non-drug therapy to treat the AE. 95% CI will also be calculated by using clopper Pearson method.

- Clinically significant changes in clinical laboratory parameters (hematology and clinical chemistry)

Blood samples collected for the following laboratory tests for safety assessment will be summarized for actual and change from screening with the standard descriptive statistics for continuous data. Also, range indicator (high, low) and clinical significance (yes, no) will be presented by frequency and percentage. Shift tables will be presented for the results of clinical laboratory data.

- Hematology assessments include: hemoglobin, hematocrit, red blood cell count, and white blood cell count with differential (ie, basophils, eosinophils, lymphocytes, monocytes, neutrophils), mean corpuscular volume (MCV), mean corpuscular hemoglobin concentration (MCHC), and platelet count.
- Clinical chemistry assessments include: sodium, potassium, chloride, bicarbonate, total protein, albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, alkaline phosphatase, blood urea nitrogen (BUN), creatinine, and glucose.

6.6.3 Other Safety Analysis

Physical Examination and Vital Signs

Physical examination includes assessment of the following body parameters: head and neck, eyes and ears, nose and throat, chest, lungs, heart, abdomen, extremities and joints, lymph nodes, skin, and neurological.
Vital signs include body temperature (°F), respiratory rate (breaths/ min)), pulse rate (beats/ min), and systolic and diastolic blood pressure (mm/Hg)

Both physical examination and vital sign will be summarized descriptively in the tabular format at each visit. Individual data listings of each vital sign parameter (observed data) will be presented for each subject. Change from baseline for vital sign parameters and shift table from baseline for physical examinations will be presented at each visit.

Viral Serology

Viral Serology results (HIV-1Ab, HIV-2 Ab, HBcAb, HBsAb, HBsAg, and HCVAb) at screening will be summarized descriptively.

FVIII antigen and activity

FVIII antigen and activity will be summarized with the standard descriptive statistics for continuous data Also, range indicator (high, low) and clinical significance (yes, no) will be presented by frequency and percentage.

Incremental Recovery

Incremental Recovery will be summarized with the standard descriptive statistics for continuous data. Also, range indicator (high, low) and clinical significance (yes, no) will be presented by frequency and percentage.

6.6.4 Extent of Exposure and Compliance

Study Drug Exposure

Duration of study drug exposure is defined as the time the subjects will be on study drug during the study and will be calculated as follows: number of days between the last dose date and the first dose date + 1 i.e. date of last dose -date of first dose +1.

Duration of treatment exposure will be summarized by Descriptive Statistics.

Exposure summaries will be based on the Safety Analysis Set.

Study Drug Compliance

Study drug compliance will be calculated as:

$$\frac{\text{Number of doses actually taken by the subject during the study}}{\text{Total Number of doses prescribed/planned}} * 100$$

Percentage of study drug compliance will be summarized by Descriptive Statistics. Summaries will be based on the Effectiveness Full Analysis Set.

6.7 Interim Analyses

No interim analysis is planned for this study.

6.8 Data Monitoring Committee/Internal Review Committee/ [Other Data Review Committees]

No data monitoring committee (DMC) is planned for this study.

7.0 REFERENCES

• ICH E3: Structure and content of Clinical Study Reports, November 1995 (Step 5), CPMP.

• ICH E9: Statistical Principles for Clinical Trials, February 1998 (Step 5), CPMP.

• TAK-761-4009 Takeda ADVATE Protocol v5.1 dated 31JUL2019

• TAK-761-4009 Takeda ADVATE CRF v1.0 dated 08SEP2021

• 261302 BAX 855 SAP v3.0 dated 18APR2018 :

https://clinicaltrials.gov/ProvidedDocs/93/NCT01945593/SAP_004.pdf

8.0 CHANGES TO PROTOCOL PLANNED ANALYSES

Not Applicable

9.0 APPENDIX

9.1 Changes From the Previous Version of the SAP

Not Applicable

9.2 Data Handling Conventions

9.2.1 General Data Reporting Conventions

Reporting of Numeric Values

All raw data will be presented to the original number of decimal places. The mean, median and quartiles will be presented with 1 decimal place more than raw data. The standard deviation (SD), Standard Error of Mean and Confidence Interval (CI) of mean will be presented with 1 decimal place more than mean. The range (minimum and maximum) will be presented as per the raw data Percentages will be presented in xx.x% format. All categories of variables will be presented even if there is no data.

Precision of p-values will be 4 decimal places. p-values less than 0.0001 will be presented as <0.0001 and if equal to 1 then ≥ 0.9999.

Output (Tables, Listings and Graphs) Considerations

The default Tables, Listings and Graphs (TLG) layout will be as follows.

Orientation	All pages should preferably be landscape.
Paper Size	Legal size
Margins	Top: 1.25 in Bottom: 1 in Left: 1 in Right: 1 in
Font	Font style (preferably Times New Roman) of the Text
Headers	**Titles of Table/Listing will be center** **Left** Sponsor: Study Name: Protocol No:
Footers	**Left** Analyst Initials: Program Name: Program Run date: time: **Right** Datasets Used: Page XXX of YYY

The margin may be reduced as necessary to allow additional rows to be presented, but not at the expense of clarity. In addition, the orientation may be changed to portrait if appropriate. The date format for all presentations will be 'DDMMMYYYY'.

9.2.2 Definition of Baseline

Baseline values are defined as the last observed value before the first dose of study medication.

9.3 Change from Baseline

Value of change from baseline at any post baseline visit will be defined as the difference of the non-missing baseline value to the non-missing post baseline value i.e.

Change from baseline (Δ) = post-baseline value at visit X - baseline value, where both values are non-missing.

Percent change from baseline will be calculated as:

(Assessment value at post-baseline visit X – baseline value) / baseline value * 100.

9.4 Analysis Software

All the statistical analyses including summary Tables, Listings, and Figures (TLFs) will be generated using a customized reporting SAS® Version 9.4 (SAS Institute Inc., Cary, NC) or higher.