Statistical Analysis Plan

NCT Number: NCT04804540

Title: A Multicenter, Single-arm, Open-label, Phase 4 Study to Evaluate the Safety and Efficacy of Vedolizumab in Indian Patients With Ulcerative Colitis and Crohn's Disease

Study Number: Vedolizumab-4020

Document Version and Date: Version 1.0, 23 September 2022

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STATISTICAL ANALYSIS PLAN

Study Number: Vedolizumab-4020

Study Title: A Multicenter, Single arm, Open- label, Phase 4 study to Evaluate Safety and Efficacy of Vedolizumab in Indian Patients with Ulcerative Colitis and Crohn's Disease.

Phase: Phase 4

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REVISION HISTORY

Version	Approval Date	Primary Rationale for Revision
1.0	23-Sept-2022	Baseline Version
		[To make SAP consistent with Amendment 1 of the protocol]

TABLE OF CONTENTS

ABBREVIATIONS

%	Percentage
ADR	Adverse Drug Reaction
AE	Adverse Event
AESI	Adverse Event of Special Interest
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass Index
CD	Crohn's disease
CI	Confidence Interval
CM	Centimeter
DCGI	Drug Controller General of India
EAIR	Exposure-Adjusted Incidence Rates
ECG	Electrocardiogram
eCRF	Electronic Case Report form
HBI	Harvey-Bradshaw Index
IBD	Inflammatory Bowel Disease
IV	Intravenous
Kg	Kilogram
MedDRA	Medical Dictionary for Regulatory Activities
N	Number/count
PK	Pharmacokinetic
PPAS	Per-Protocol Analysis Set
PRO	Patient-Reported Outcomes
PT	Preferred Term
Q1	First Quartile
Q3	Third Quartile
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Safety Analysis Set
SCCAI	Simple Clinical Colitis Activity Index
SD	Standard Deviation
SIBDQ	Short Inflammatory Bowel Disease Questionnaire
SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Event
UC	Ulcerative Colitis
WHODD	World Health Organization Drug Dictionary

1.0 OBJECTIVES, ENDPOINTS AND ESTIMANDS

1.1 Objectives

1.1.1 Primary Objective

- To assess the safety of vedolizumab IV in patients with UC or CD in India

1.1.2 Secondary Objective(s)

- To assess the efficacy of vedolizumab IV in patients with UC or CD in India

1.1.3 Additional Objective(s)

Not Applicable

1.2 Endpoints

1.2.1 Primary Endpoint(s)

The primary endpoint includes:

- Incidence of AEs, SAEs, AEs of special interest (AESIs), ADRs, and unexpected ADRs

1.2.2 Secondary Endpoint(s)

1.2.2.1 Key Secondary Endpoints(s)

• Proportion of patients with clinical response at Weeks 14, 30, and 46 in UC and CD groups
• Proportion of patients with clinical remission at Weeks 14, 30, and 46 in UC and CD groups
• Proportion of patients with vedolizumab discontinuation in UC and CD groups
• Proportion of patients with mucosal healing/endoscopic response at Week 46 in UC and CD groups
• Change in the patient-reported Quality of Life (Short Inflammatory Bowel Disease Questionnaire [SIBDQ]) from baseline to Weeks 14, 30, and 46

1.2.2.2 Other Secondary Endpoint(s)

Not applicable

1.2.3 Exploratory Endpoint(s)

Not Applicable.

1.2.4 Safety Endpoints

Since safety endpoints are used in the analysis of primary endpoints, the analysis of these variable are described in section 1.2.1.

1.2.5 Other Endpoints

Not Applicable.

1.3 Estimand(s)

Not applicable

2.0 STUDY DESIGN

This is an open-label, single-arm, prospective, Phase 4 study to be conducted at multiple sites in India to evaluate the safety and efficacy of vedolizumab 300 mg IV infusion in patients with moderately to severely active UC or CD.

Approximately 150 patients with moderately to severely active UC or CD who have demonstrated inadequate response to, loss of response to, or intolerance to either conventional therapy or tumor necrosis factor-alpha (TNFα) antagonist will be enrolled in this study. At least 30% of the total recruited patients will be enrolled in each UC or CD group.

The total duration of the study for each patients will be up to 74 weeks, consisting of a 4-week screening period (Days -28 to -1), a 46-week treatment period, and 16-week (ie, 5 vedolizumab half-lives) safety follow-up period after the last dose of study drug. Additionally, patients will be required to participate in a long-term follow-up safety survey through telephonic visit at 6 months after the last dose of study drug i.e. 8 weeks after the 16-week follow-up visit.

Patients who meet all the inclusion criteria and none of the exclusion criteria will be administered vedolizumab 300 mg IV at the site. Patients will visit the site for dosing at Weeks 0 (Day 1), 2, 6, 10 (CD- Patients who have not shown a response can receive a dose at 10 week), 14, 22, 30, 38, and 46.

Patients will be evaluated for safety and efficacy from initiation of vedolizumab until 46 weeks (the treatment period), or until discontinuation of vedolizumab, whichever occurs earlier. All patients will be observed further for safety assessments for 16 weeks after the study treatment period or discontinuation of vedolizumab for post-treatment AE monitoring.

In addition, patients will participate in the long-term follow-up safety survey through telephonic visit at 6 months after the last dose i.e. 8 weeks after the 16-week follow-up visit, during which information will be collected on events such as infections resulting in hospitalizations, cancer, UC or CD related surgeries, and development of progressive multifocal leukoencephalopathy (PML).

3.0 SAMPLE-SIZE DETERMINATION

The study will recruit 150 patients. This sample size was recommended by the DCGI on approval of vedolizumab as a new drug. At least 30% of the total recruited patients will be enrolled in each UC or CD group.

This sample size will enable a serious infection rate of 6 per 100 person-years to be measured with a precision of ±3.8 with 95% CI based on a normal approximation of the annualized proportion of patients to be infected. This anticipated serious infection rate is based on observed rates in a post hoc pooled analysis of data from Indian sites participating in the vedolizumab global Phase 3 C13006 and C13007 clinical studies and open label extension (Study C13008) of these studies.

4.0 ANALYSIS SETS

4.1 Safety Analysis Set

The Safety Analysis Set (SAS) will include all enrolled who receive at least 1 dose of study drug.

4.2 Per-Protocol Analysis Set

The per-protocol analysis set (PPAS) is a subset of the SAS (safety analysis set) and consists of all patients who do not violate the terms of the protocol in a way that would impact the study outcome significantly. All significant protocol deviations will be reviewed manually to decide which subjects will be excluded prior to database lock. The hierarchy of reasons for exclusion is as follows: inclusion and exclusion criteria violations, study medication dosing errors, receiving forbidden concomitant medications.

4.3 Pharmacokinetic Analysis Set

Not Applicable.

5.0 STATISTICAL ANALYSIS

5.1 General Considerations

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

Where applicable, variables will be summarized descriptively by study visit. For the categorical variables, the counts and proportions of each possible value will be tabulated by treatment group. The denominator for the proportion will be based on the number of subjects who provided non-missing responses to the categorical variable. For continuous variables, the number of subjects with non-missing values, mean, median, SD, minimum, and maximum values will be tabulated.

A windowing convention will be used to determine the analysis value for a given study visit for observed data analyses.

Mean, Median, Q1 and Q3 will have one more decimal place than the raw data and SD will have 2 decimal places more than the raw data. The decimal place for minimum and maximum values will be same as the raw data.

If relevant, the normality of distribution of continuous variables will be examined using the Shapiro-Wilk test/ Kolmogorov–Smirnov test in order to determine whether or not to use parametric methods for the analysis of the sample data. All statistical tests will be two-sided and will be performed at a 0.05 significance level. The interpretation of all results will be performed in a descriptive and explorative manner and no adjustment for multiple testing will be applied. All P-values will be rounded to four decimal places; P-values less than 0.0001 will be presented as '< 0.0001'.

95% confidence intervals will be provided when appropriate

Analysis of the data will be performed by the Biostatistics and Statistical Programming team at SIRO Clinpharm Pvt Ltd. All statistical analyses will be performed using SAS® Enterprise Guide® 7.1.

5.1.1 Analysis Approach for Continuous Variables

All continuous variables in this trial will use the analysis method below unless stated otherwise in the section specific to an endpoint.

All continuous variables will be summarized using descriptive statistics such as

- Number of subjects (n), number of subjects with missing values (Missing),
- Mean,
- Standard Deviation (SD),

- Median,
- First Quartile (Q1), Third Quartile (Q3),
- Minimum, Maximum,
- 95% confidence interval for the mean

The number of observations (n) will be presented with no decimal place, arithmetic mean and median will be presented up to two decimal places from the original value, SD up to three decimal places from the original value, minimum and maximum value as an original value. For changes from baseline in continuous endpoints, paired t-test will be used if normality assumption holds based on the Shapiro–Wilk test, or the Wilcoxon signed rank test will be used otherwise.

5.1.2 Analysis Approach for Binary Variables

All binary variables in this trial will use the analysis method below unless stated otherwise in the section specific to an endpoint.

The categorical variables will be summarized using the frequency count (n) and percentage (%) for each possible value. The frequencies will be presented up to no decimal places and percentage up to 1 decimal place.

5.1.3 Analysis Approach for Time-to-Event Variables

Not applicable

5.2 Disposition of Subjects

The following data on subject disposition will be summarized across treatment groups:

- Number of subjects screened (i.e. who provided informed consent)
- Number of screen failures
- Number of subjects in Safety Population
- Number of subjects in UC Safety Population

- Number of subjects in CD Safety Population
- Number of subjects in PPAS Population
- Number of subjects in UC PPAS Population
- Number of subjects in CD PPAS Population
- Number of subjects who completed the study
- Number of subjects who completed the study in CD group.
- Number of subjects who completed the study in UC group
- Number of subjects discontinued/withdrawn
- Primary Reasons for discontinuation/withdrawal

5.3 Demographic and Other Baseline Characteristics

5.3.1 Demographics

The following patient demographics will be summarized for safety population:

- Age (years)

Age (years) = ((Date of informed consent – Date of Birth) + 1)/365.25

- Gender
- Height (cm)
- Weight (kg)
- BMI

BMI= weight/$height^2$

Subjects' data listings will be provided.

5.3.2 Medical History and Concurrent Medical Conditions

Medical history and Concurrent Medical Conditions will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 24.0. The frequency count (n) and percentage (%) of patients will be tabulated according to the coded terms of system organ class (SOC) and preferred term (PT) for the safety population.

5.3.3 Baseline Characteristics

The following patient baseline characteristics will be summarized for safety population

Smoking and Alcohol Consumption History:

- Smoking status
- Alcohol consumption status

Tuberculosis History

- Outcome

5.4 Medication History and Concomitant Medications

5.4.1 Prior Medications

Medications, started up to 30 days prior to screening, per protocol (except biologics for which all past data will be recorded) other than study drug, started and stopped prior to the administration of first study drug administration are defined as prior medications.

Prior medications will be coded using World Health Organization Drug Dictionary (WHODD) Mar 2021 or higher version which employs the Anatomical Therapeutic Chemical (ATC) Classification system.

For all prior medications, counts (n) & percentages (%) of patients will be presented by ATC main group and preferred drug name/verbatim terms and will be sorted in descending order of frequency in total for safety population. Patients with more than one medication of the same verbatim term will be counted only once.

Patient data listings will be provided for safety population.

5.4.2 Concomitant Medications

Medications other than study medications,

- Started prior but ongoing at the time of first study drug administration

OR

- Started on or after the day of first study drug administration will be defined as concomitant medications.

Concomitant medications will be coded using World Health Organization Drug Dictionary (WHODD) Mar 2021 or higher version which employs the Anatomical Therapeutic Chemical (ATC) Classification system.

For all concomitant medications, counts (n) & percentages (%) of patients will be presented by ATC main group and preferred drug name/verbatim terms and will be sorted in descending order of frequency in total for safety population. Patients with more than one medication of the same verbatim term will be counted only once.

Patient data listings will be provided for safety population.

5.5 Efficacy Analysis

All the data and analysis would be provided for UC and CD groups and for overall study population.

5.5.1 Primary Endpoint(s) Analysis

Incidence of AEs, SAEs, AEs of special interest (AESIs), ADRs, and unexpected ADRs

If a patient has more than one AE, patients will be counted only once in system organ class and once for each PT. If a patient has more than one episode of an AE, the patient will be counted only once within a specific preferred term. If the same TEAE (Treatment Emergent Adverse Event) occurs on multiple occasions, the highest severity and relationship will be assumed.

Number (n) and percentage (%) of patients with adverse events will be provided by system organ class and preferred term:

- Incidence of AEs
- Serious AEs
- AEs of special interest (AESIs)

- AEs leading to discontinuation
- ADRs, and unexpected ADRs

No statistical inference between the treatment groups will be performed on AEs. Patient data listings will be provided for all AEs and TEAEs with information on causality, severity, frequency, seriousness, relationship to investigational product, outcome and action taken with the patient and study treatment.

Exposure-adjusted incidence rates

EAIR of AEs is defined as the number of subjects exposed to the drug and experiencing a certain event divided by the total exposure time of all subjects who are at risk for the event. Specifically, for subjects with no event, the exposure time is the time from the first drug intake to the last follow-up assessment; for subjects with at least one event, the exposure time is the time from the first drug exposure to first event.

- Incidence rates for events that occur while on vedolizumab therapy,
- Incidence rate for events that occur after discontinuation of vedolizumab.

It will be summarized by number of events (n), Incidence rate and its 95% CI using Poisson rate confidence Interval by using safety analysis set for all safety endpoints. The person time at risk of event (T) will be derived by adding the number of patients in the group and multiplying that number times the years that patients currently in the vedolizumab therapy/ after discontinuation of vedolizumab.

The Poisson (e.g. incidence) rate estimate $\hat{\lambda}$=Number of events (n)/person time at risk of event (T).

The 95-percent Poisson confidence interval is calculated as: $\hat{\lambda} \pm 1.96 * \hat{\lambda}/\sqrt{n}$.

Adverse Drug Reactions (ADRs) & unexpected ADRs / Events

Expected Adverse events – An expected AE is any adverse reaction whose nature and intensity have been previously observed and documented for the study product (e.g. in the investigator brochure, product information).

Unexpected Adverse Event – An AE or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended.

AEs/ ADR will be summarized per subject using number and percentage by SOC and PT from Safety Analysis Set. If an AE/ ADR is reported for a subject more than once during treatment, the

worst severity and the worst relationship to trial treatment will be tabulated. Listings will also be provided for all the AEs/ ADRs. AEs/ ADRs will be coded using MedDRA version 24.0.

Pre Treatment Event –
A PTE is defined as any untoward medical occurrence in a clinical investigation patient who has signed informed consent to participate in a study but prior to administration of any study drug; it does not necessarily have to have a causal relationship with study procedure. It will be summarized per subject using number and percentage by SOC and PT from SAS

5.5.2 Secondary Endpoint(s) Analysis

1) Proportion of patients with clinical response (defined as SCCAI ≥3 points decrease from baseline of clinical response (UC patients) and HBI≥3 point decrease from baseline of clinical response (CD patients) [Time frame: Week 14, 30 and 46].

Note: Baseline is defined as the assessment prior to first dose of study.

The patients with clinical response (defined as SCCAI ≥3 points decrease from baseline of clinical response (UC patients) and HBI≥3 point decrease from baseline of clinical response (CD patients)) will be summarized by using Number(n) and percentage (%) of responders and will be reported up to the time frame of Week 14, 30 and 46 by UC and CD groups from SAS.

Further, patients with clinical response will be summarized by using Number(n) and percentage (%) by visit, by UC and CD groups and by subgroups (Biologic-naïve patients and Biologic-experienced patients) as defined in section 5.5.3

95% CI by exact method will be used for proportion of patients with clinical response.

Patient data listings will be provided for SAS population.

2) Proportion of patients with clinical remission (as SCCAI of ≤2 with no individual score >1 (UC patients) or a HBI ≤4 (CD patients) [Time frame: Week 14, 30, 46].

Note: Baseline is defined as the assessment prior to first dose of study.

The patients with clinical remission (defined as SCCAI ≤2 points increase from baseline of clinical response (UC patients) and HBI≤4 point increase from baseline of clinical response (CD patients)) will be summarized by using Number (n) and percentage (%) of responders and will be reported up to the time frame of Week 14, 30 and 46 by UC and CD groups from SAS.

Further, patients with clinical remission will be summarized by using Number(n) and percentage (%) by visit, by UC and CD groups and by subgroups (Biologic-naïve patients and Biologic-experienced patients) as defined in section 5.5.3
95% CI by exact method will be used for proportion of patients with clinical remission.

Patient data listings will be provided for SAS population.

3) Proportion of patient with vedolizumab discontinuation in UC and CD groups
Vedolizumab discontinuation is defined as ceasing vedolizumab, or a treatment gap ≥90 days between consecutive doses.
The patients with vedolizumab discontinuation will be summarized by using number (n) and percentage (%) by UC and CD groups from SAS.
Further, patients with vedolizumab discontinuation will be summarized by using number(n) and percentage (%) by visit, by UC and CD groups and by subgroups (Biologic-naïve patients and Biologic-experienced patients) as defined in section 5.5.3
95% CI by exact method will be used for proportion of patients with vedolizumab discontinuation.

Patient data listings will be provided for SAS population.

4) Proportion of patients with mucosal healing/endoscopic response at Week 46 in UC and CD groups
Mucosal healing: Mucosal healing is defined as a Mayo endoscopic sub score of ≤1 point for UC or SES-CD 0-2 or SES-CD ≤4 and at least a 2 point reduction from baseline with no sub-score >1 for CD will be summarized by using number (n) and percentage (%) by visit, by UC and CD group and by subgroup (Biologic-naïve patients and Biologic-experienced patients).

Endoscopic response: Endoscopic response is defined as decrease in Mayo endoscopic sub score of ≥1 point in UC and >50% decrease in SES-CD in CD will be summarized by using number (n)

and percentage (%) by visit, by UC and CD group and by subgroup (Biologic-naïve patients and Biologic-experienced patients).
95% CI by exact method will be used for proportion of patients with mucosal healing/endoscopic response.

Patient data listings will be provided for SAS population.

5) Change in the patient-reported Quality of Life (Short Inflammatory Bowel Disease Questionnaire [SIBDQ]) from baseline to Weeks 14, 30, and 46
The patients-reported Quality of Life score of Actual, change from Baseline and Percentage change from Baseline will be summarized descriptively by using number of observations (n), mean, standard deviations (SD), median, first quartile (Q1), third quartile (Q3), minimum and maximum value by visit and by UC and CD groups. The change from baseline to Weeks 14, 30, and 46 respectively, paired t-test will be used if normality assumption holds based on the Shapiro–Wilk test, or the Wilcoxon signed rank test will be used otherwise.

Patient data listings will be provided for SAS population.

We will provide additional analysis by Biologic-naïve patients and Biologic-experienced patients group for primary and secondary endpoints. BNP and BEP group will be summarized by using number of observations (n), mean, standard deviations (SD), median, first quartile (Q1), third quartile (Q3), minimum and maximum value for SAS Population.
The change from baseline to Weeks 14, 30, and 46 respectively, paired t-test will be used if normality assumption holds based on the Shapiro–Wilk test, or the Wilcoxon signed rank test will be used otherwise.

5.5.3 Subgroup Analyses

Depending on number of subjects, subgroup analysis will be performed for primary and secondary endpoints on subjects as follows:

Subgroups to be explored include

- Biologic-naïve patients
- Biologic-experienced patients

Subjects who have received biologics for IBD treatment in past will be considered "Biologic-experienced". Subjects who have never received biologics for IBD treatment in past will be considered "Biologic-naïve" based on prior medication history from CRF.

5.6 Safety Analysis

All safety analyses will be performed for the safety population.

Safety will be analyzed based on:

- Adverse Events
- Vital signs
- ECG
- Laboratory variables
- Physical examination
- Urine analysis

Vital signs:

Vital signs (Body temperature, Diastolic Blood Pressure, Pulse rate, Systolic Blood Pressure and Respiratory rate) will be assessed daily till discharge.

Actual and change from baseline to each visit will be summarized using descriptive statistics (n, mean, SD, median, minimum, maximum) from safety population

Vital signs assessments will also be summarized categorically by response across treatment groups at each time point for safety population.

Patient data listings will be provided.

ECG:

ECG will be performed at screening and end of treatment visits.

Overall ECG will be summarized categorically by response across treatment at each time point for safety population.

Patient data listings will be provided

Laboratory Variables:

All laboratory parameters will be summarized descriptively and categorically by response from safety population.

Actual and change from baseline to each visit will be summarized using descriptive statistics (n, mean, SD, median, minimum, maximum) by treatment group for safety population

Patient data listings will be provided.

Physical Examination:

Physical examination and other examination assessments will be summarized descriptively and categorically by response at each time point for safety population.

Patient data listings will be provided.

5.6.1 Adverse Events

If a patient has more than one AE, patients will be counted only once in system organ class (SOC) and once for each PT. If a patient has more than one episode of an AE, the patient will be counted only once within a specific preferred term. If the same TEAE (Treatment Emergent Adverse Event) occurs on multiple occasions, the highest severity and relationship will be assumed.

Number (n) and percentage (%) of patients with adverse events will be provided across treatment groups by system organ class and preferred term:

- All AEs
- All TEAEs
- All Serious TEAEs
- All TEAEs by severity
- All TEAEs by outcome

- All TEAEs by Relationship

No statistical inference between the treatment groups will be performed on AEs. Patient data listings will be provided for all AEs and TEAEs with information on causality, severity, frequency, seriousness, relationship to investigational product, outcome and action taken with the patient and study treatment.

5.6.2 Adverse Events of Special Interest

If an AESI, which occurs during the treatment period or the follow-up period, is considered to be clinically significant based on the criteria below, it should be recorded in the Special Interest AE eCRF or SAE Form.

Adverse Events of Special Interest will be summarized per subject using number and percentage by SOC and PT from Safety Analysis Set in

1) Serious Infections
2) Malignancies
3) Infusion Related Reaction
4) Hypersensitivity
5) Hepatic Injury

5.6.3 Extent of Exposure and Compliance

Descriptive statistical summaries will be provided for the following variables:

- Overall treatment duration

Overall treatment duration is defined as the time from first study drug intake (dayfirst) until last study drug intake (day last), calculated as:

Overall treatment duration = day last – day first +1

- Number of doses received.

5.7 Interim Analyses

The interim analysis will be performed after all subjects completes week 14 weeks assessment. All statistical testing at Week 14 will be two-sided and will be performed using a significance (alpha) level of 0.05. All endpoint assessment including safety and efficacy analysis will be done till week 14 visit data. A separate Interim analysis plan will be prepared for elaborative discussion about the analysis plan and mocks for interim assessment.

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

Not applicable

6.0 REFERENCES

1) Vedolizumab-4020_Protocol Amendment_V3.0_30MAR2021
2) Vedolizumab-4020_eCRF_V1_02-Sep-2021
3) ICH E9: Statistical Principles for Clinical Trial.

7.0 CHANGES TO PROTOCOL PLANNED ANALYSES

This SAP contains no changes to the planned analyses described in the Protocol

8.0 APPENDIX

8.1 Changes from the Previous Version of the SAP

Not applicable

8.2 Data Handling Conventions

Missing data will not be imputed. Only data recorded in the CRF will be analyzed.
All missing data or partial dates will be presented in the subject data listing, as they are recorded on the Case Report Form (CRF). Except as noted, missing data will not be Estimated or carried forward in any statistical analysis.

8.2.1 General Data Reporting Conventions

Not applicable

8.2.2 Definition of Baseline

Non-missing values collected at immediately prior to the first dose of study drug administration will be considered as baseline values.

8.2.3 Definition of Visit Windows

The range of days in which a subject can occur according to the study protocol, typically around a date determined by the number of days since the initial visit. A study with every four-week visit schedule may have a visit window +/- 3 days. A study with every eight week visit schedule may have a visit window +/- 7 days. A safety follow up 16 weeks post dose visit schedule may have a visit window +/- 7 days.

8.3 Analysis Software

All statistical analyses will be performed using SAS® Enterprise Guide® 7.1.