NCT #: NCT01671956

# Statistical Analysis Plan

# Immune Pharmaceuticals, Inc.

# A Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Multi-Center Study Designed to Evaluate the Safety, Efficacy, Pharmacokinetic and Pharmacodynamic Profile of Bertilimumab in Patients with Active Moderate to Severe Ulcerative Colitis

Final

**15 January 2019**

## Signature Page

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|---|---|
| **Study Name** | **A Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Multi-Center Study Designed to Evaluate the Safety, Efficacy, Pharmacokinetic and Pharmacodynamic Profile of Bertilimumab in Patients with Active Moderate to Severe Ulcerative Colitis** |
| **Sponsor** | **Immune Pharmaceuticals, Inc.** |
| **SAP Date** | **15 January 2019** |

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The undersigned hereby declare that they have examined the Statistical Analysis Plan document and agree to its form and content.

Represente[redacted]

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Date:

Name:

Title:

# Version History

| Version Number | Date | Revision |
|---|---|---|
| 0.1 | 8 July 2018 | Draft |
| 0.2 | 6 September 2018 | Draft |
| 0.3 | 6 January 2019 | Draft |
| 0.4 | 10 January 2019 | Draft |
| 0.5 | 13 January 2019 | Draft |
| 1.0 | 15 January 2019 | Final |

# Table of Contents

# List of Abbreviations

| | |
|---|---|
| AE | Adverse Event |
| CRF | Case Report Form |
| CS | Clinically Significant |
| FAS | Full Analysis Set |
| IV | Intravenous Infusion |
| LOCB | Last Observation Carried Backward |
| LOCF | Last Observation Carried Forward |
| MI | Multiple Imputation |
| mITT | Modified Intent to Treat |
| NCS | Non-Clinically Significant |
| PD | Pharmacodynamics |
| PK | Pharmacokinetics |
| PO | Per Os |
| PP | Per Protocol |
| PPD | Purified Protein Derivative |
| SAE | Serious Adverse Event |
| SAP | Statistical Analysis Plan |
| SOC | System Organ Class |
| TB | Tuberculosis |
| TEAE | Treatment-Emergent Adverse Event |
| TNF | Tumor Necrosis Factor |
| UC | Ulcerative Colitis |
| UCEIS | Ulcerative Colitis Endoscopic Index of Severity |

# 1 Introduction

## 1.1 General

Ulcerative colitis (UC) is a chronic and relapsing inflammatory disease characterized by diffuse mucosal inflammation limited to the colon and rectum without evidence of any specific causative pathogens.

Bertilimumab is the first monoclonal antibody to specifically neutralize human eotaxin-1 to enter clinical trials. Bertilimumab has been shown to interrupt the eotaxin-stimulated migration of cells and may therefore be useful in the treatment of human diseases such as UC, where eosinophil accumulation is an important feature.

This is the first study investigating clinical outcome of treatment with bertilimumab in UC patients. The purpose of this study is to evaluate the safety and efficacy of bertilimumab compared to placebo in adult patients with active moderate to severe UC. In addition, the pharmacokinetics (PK) and pharmacodynamics (PD) of bertilimumab will be assessed throughout the study.

## 1.2 Study Design Configuration

This is a randomized, double blind, placebo-controlled, parallel group multi-center study in adult patients (18 to 70 years old) with active moderate to severe UC. Eligible subjects will be randomly assigned in a 2:1 ratio to one of two treatment groups, bertilimumab 10 mg/kg or matching placebo, stratified by previous anti-TNF treatment. Approximately the same proportion of subjects who received previous anti-TNF treatment will be included in each arm. Additionally, to reduce bias, the Mayo score and UCEIS will be evaluated by a central reader blind to subject identifier.

The study will consist of three periods:

- A screening period of up to four weeks- Visit 1 (Days -28 to -1)
- A 4-week double-blind treatment period (three IV infusions at two-week intervals) at Visit 2 (Day 0), Visit 3 (Day 14) and Visit 4 (Day 28).

  Before each bertilimumab 10 mg/kg or matching placebo treatment, subjects will receive a pretreatment regimen for infusion reaction prophylaxis. The regimen is as follows:

  - Dexamethasone 10 mg PO 24-18 hours prior to administration of study drug.

- Acetaminophen 1000 mg PO 1 hour prior to administration of study drug.
- Either loratadine 10 mg PO or cetirizine 10 mg PO one hour prior to the administration of study drug.

  If dexamethasone was not administered previously, then 10 mg dexamethasone IV may be administered 1-3 hours prior to study drug administration.

Following completion of pre-dose assessments and administration of pretreatment regimen according to the appropriate timelines above, study drug will be administered by IV infusion over 30 minutes.

- A safety and efficacy follow-up period of approximately 9 weeks- Visit 5 (Day 35), Visit 6 (Day 42), Visit 7 (Day 56) and Visit 8 (Day 90).

# 2 Centers

This is a multicenter trial. Approximately 10-12 sites in Israel will participate in this study. Additional sites in Europe may be added in the event of slow recruitment.

# 3 Study Objectives

## 3.1 Primary Objective

To evaluate, in patients with active moderate to severe UC, the safety and clinical efficacy of bertilimumab administered as 3 IV infusions over 4 weeks.

## 3.2 Secondary Objectives

To evaluate the pharmacokinetics (PK) and pharmacodynamics (PD) of bertilimumab in patients with active moderate to severe UC.

# 4 Treatment Groups

Bertilimumab (10 mg/kg) or placebo will be administered by intravenous infusion over 30 minutes. A pretreatment prophylactic regimen will be administered prior to dosing on each treatment dosing day (Days 0, 14 and 28) to reduce the likelihood of an infusion reaction.

# 5 Study Schedule

**Table 1 Schedule of Study Events**

| **Study Procedures** | **Screening Period** | **Treatment Period[1]** | | | **Early Discontinuation[2]** | **Follow-up Period[3]** | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Visit** | **1** | **2** | **3** | **4** | **-** | **5** | **6** | **7** | **8** |
| **Study Day** | **-28 to -1** | **0** | **14** | **28** | **-** | **35** | **42** | **56** | **90** |
| Inclusion/exclusion criteria | X | X | | | | | | | |
| Informed consent | X | | | | | | | | |
| Demographic & medical history | X | | | | | | | | |
| Physical examination | X | X* | X* | X* | X | X | X | X | X |
| Vital signs | X | X[4] | X[5] | X[5] | X | X | X | X | X |
| ECG | X | X[5] | X[6] | X[6] | X | X | X | X | X |
| Screen for active/latent tuberculosis and fecal sample for *C. difficile* toxin | X | | | | | | | | |
| Randomization | X | | | | | | | | |
| Mayo Score | X | | | | X | | | X | |
| Partial Mayo Score | X[11] | X* | X* | X* | X | X | X | X | X |
| Bertilimumab or Placebo infusion- (after administration of pretreatment regimen)[6] | | X | X | X | | | | | |
| Flexible sigmoidoscopy with biopsies[7] | X | | | | X | | | X | |
| Ulcerative Colitis Endoscopic Index of Severity | X | | | | X | | | X | |
| Adverse events | | X | X | X | X | X | X | X | X |
| Concomitant medications | X | X | X | X | X | X | X | X | X |
| Infusion reaction assessment[8] | | X | X | X | | | | | |
| Urine β-hCG | | X* | X* | X* | | | | | |
| Hematology and biochemistry | X[9] | X* | X* | X* | X | X | X | X | X |
| Serology | X | | | | | | | | |
| PK (bertilimumab) blood sampling | | X[10] | X[10] | X[10] | X | X | X | X | X |
| Anti-bertilimumab antibodies | | X* | X* | X* | X | X | X | X | X |
| Eotaxin-1, eosinophil count, eosinophil cationic protein (ECP)-s-CRP | | X* | X* | X* | X | X | X | X | X |
| Calprotectin in fecal sample | X | X* | X* | X* | X | X | X | X | X |
| Eotaxin-1 & eosinophil count in tissue samples | X | | | | X | | | X | |

* Denotes assessment will be done pre-dose.

[1] Visits during the treatment period have a ±2 day window.
[2] At this visit the activities relating to the study period at which time the patient discontinued will be performed.
[3] Visits during the follow-up period have a ±3 day window.
[4] Vital signs will be measured pre-dose and 15 min (during), 30 minutes (+15 minutes), 2 hr (± 20 minutes), and 4 hr (± 20 minutes) following initiation of study drug administration.
[5] ECG will be performed pre-dose, and at 30 (+ 15) minutes following initiation of study drug administration.
[6] The pretreatment dosing regimen is as follows: Dexamethasone 10 mg PO 24-18 hours prior to administration of bertilimumab. Acetaminophen 1000 mg PO 1 hour prior to administration of bertilimumab Loratadine 10 mg PO or cetirizine 10 mg PO one hour prior to the administration of bertilimumab. In the event that dexamethasone was not administered previously, then 10 mg dexamethasone IV may be administered one to three hours prior to bertilimumab administration.
[7] At least 3 tissue samples are required from area of active inflammation at Screening. On Day 56 (or early discontinuation visit), at least 3 tissue samples are required from the same region where Screening biopsies were obtained. Additional biopsy samples may be collected at the Investigator's discretion for histological assessment.
[8] Infusion reactions will be monitored for up to 4 hours following study drug administration and graded, as applicable, as appears in Appendix D
[9] Biochemistry will include serum β-hCG at screening.
[10] Blood samples for bertilimumab (PK analysis) will be collected pre-dose, 30 (+15) minutes (immediately post-dose) and 4 hours (± 20 minutes) following initiation of study drug infusion.
[11] Partial Mayo Score at Screening will be calculated from the Total Mayo Score.

# 6 Analysis Populations

## 6.1 Safety Analysis Population

The Safety Analysis Set will include all subjects who were exposed to any of the study treatments (bertilimumab or placebo; i.e. that drug administration data has been collected) and/or prophylactic treatment where applicable (i.e. prophylactic pre-medication form is completed or prophylactic pre-treatment medication was used, as per the concomitant medication form).

It should be noted that the requirement of prophylactic medications was added as part of the protocol version 8 amendment and, therefore, this information is not available for all subjects in the study.

## 6.2 Efficacy Analysis Populations

### 6.2.1 Modified Intent to Treat (mITT)

The modified intent to treat (mITT) analysis set will include all randomized subjects who received at least one dose of study treatment (placebo or bertilimumab) (i.e. "Date of Drug Administration" is not missing), and had a full Mayo score (i.e. all 4 sub-scores completed) at screening and at least one post-baseline full Mayo score (see Section 8). Subjects with major entry violations as determined by blind review will be excluded from this population.

**Handling of missing data:**

Missing primary efficacy data in mITT will be imputed as follows:

Full Mayo Score at Visit 7:

- Subjects with missing Mayo Score at visit 7 will be imputed with the post-screening Full Mayo Score (obtained from early discontinuation or unscheduled visit) according to the date which is most close to visit 7's date of that subject. In other words, visit 7 score will be imputed by last observation carried forward (LOCF) or last observation carried backward (LOCB) depending on the date of the score. Note: Imputation will be done only if the score date is no more than ± 4 weeks from Visit 7 date.
- In the case there is non-trivial amount of missing data sensitivity analyses will be explored.

UCEIS (a secondary endpoint that will be analyzed in mITT as well)

- Subjects with missing UCEIS Score at visit 7 will be imputed with the post-screening UCEIS Score (obtained from early discontinuation or unscheduled visit) according to the date which is most close to visit 7's date of that subject. In other words, visit 7 score will be imputed by last observation carried forward (LOCF) or last observation carried backward (LOCB) depending on the date of the score. Note: Imputation will be done only if the score date is no more than ± 4 weeks from Visit 7 date.
- In the case there is non-trivial amount of missing data sensitivity analyses will be explored.

### 6.2.2 Per Protocol Population (PP)

The per protocol (PP) analysis set will be a subset of mITT subjects who had no major protocol violations likely to affect outcome as determined by blind review and who received at least 2 of 3 study treatments (placebo or bertilimumab) (i.e. "Date of Drug Administration" is not missing) and who had a full Mayo score at screening and at visit 7. A list of major protocol deviations likely to affect outcome will be provided by the Sponsor prior to database lock.

**Handling of missing data:**

Missing data will not be imputed, i.e. only observed data will be used.

# 7 Definition of Endpoints

## 7.1 Safety Endpoints

Following are the study's safety endpoints:

- Treatment-emergent adverse events (TEAEs), including serious adverse events (SAEs)
- Infusion reactions
- Physical examination
- Vital signs (blood pressure, heart rate, temperature and respiratory rate)
- ECG
- Concomitant medications

- Laboratory evaluation (hematology, biochemistry, anti-bertilimumab antibodies).

## 7.2 Primary Efficacy Endpoints

Clinical response at Day 56 (Visit 7), defined as:

| | |
|---|---|
| "Success" (‘1’) | A decrease from the pre-treatment screening total Mayo score of at least 3 points and at least 30%<br><br>AND<br><br>Either a decrease from the pre-treatment screening sub-score for rectal bleeding of at least 1 point, or Rectal Bleeding Sub-score of 0 or 1. |
| "Failure" (‘0’) | Otherwise |

## 7.3 Secondary Efficacy Endpoints

- Change in Mayo Score from screening to Day 56 (Visit 7), calculated as
    - *Change in Mayo Score = Mayo Score at Screening – Mayo Score at Day 56*
- Change in UCEIS score from screening to Day 56 (Visit 7), calculated as
    - *Change in UCEIS score = UCEIS score at Screening – UCEIS score at Day 56*
- Clinical remission at Day 56 will be defined as
    - Success “1”, if total Mayo score of 2 points or lower, with no relevant individual sub-score exceeding 1 point.
    - Failure “0”, otherwise.
- Mucosal healing at Day 56 will be defined as
    - Success “1”, if absolute sub-score for endoscopy of 0 or 1.
    - Failure “0”, otherwise.
- Change in partial Mayo score from Day 0 to all scheduled measurement timepoints (efficacy follow up) calculated as
    - *Change in partial Mayo score = Partial Mayo score at Screening – partial Mayo score at Visit t*

## 7.4 Pharmacokinetics (PK) Endpoints

Blood samples will be collected on dosing days (pre-dose and at 30 minutes (+ 15 minutes) and 4 hours (±20 minutes) following the initiation of study drug infusion) and at the follow-up visits. The following PK parameters will be calculated: $C_{max}$, $T_{max}$, $C_{avg}$, $C_{min}$, and $t_{1/2}$. Additional standard and exploratory PK parameters will be calculated if deemed necessary.

## 7.5 Pharmacodynamic (PD) Endpoints

- Fecal calprotectin change from Day 0 (baseline) to all scheduled measurement timepoints.
- Change in eosinophil count, serum eotaxin-1, hs-CRP and ECP from Day 0 to all scheduled measurement timepoints.
- Change in eotaxin-1 concentration and max and mean eosinophil count in biopsy tissue from Screening to Day 56.

# 8 Data Derivation and Transformation

Data not originally part of CRF will be derived as follows:

- Subjects age [years] = [Date of Informed Consent – Date of Birth] / 365.25
- Study Duration [days]= Date of Last Visit – Date of First Visit + 1.
- BMI = Weight (kg) / Height $(m)^2$
- Coding of Adverse Events will be done using MedDRA version 21.0.
- Coding of Concomitant Medication will be done using WHODrug Dictionary 2018.
- Mayo score will be calculated as sum of 4 sub-scores: Stool Frequency Sub-score, Rectal Bleeding Sub-score, Endoscopic Finding Sub-score and Physician's Global Assessment Sub-score, each of which ranges from 0 (normal) to 3 (severe disease). The sub-scores are summed to give a total score that ranges from 0–12.
- Partial Mayo Score will be calculated as sum of the 3 following sub-scores: Stool Frequency Sub-score, Rectal Bleeding Sub-score and Physician's Global

Assessment Sub-score. The sub-scores are summed to give a total score that ranges from 0–9.

- UCEIS score will be calculated as sum of 3 sub-scores: Vascular pattern (which range from 0 to 2), Bleeding (range from 0 to 3) and Erosions and Ulcers (range from 0 to 3). The sub-scores are summed to give a total score that ranges from 0–8.
- Baseline values will be taken as the last available pre-treatment measures.

# 9 Statistical Analysis

All descriptive statistics will be provided by treatment group and overall, as relevant.

Numerical variables will be tabulated using mean, standard deviation, minimum, median, maximum and number of observations. Categorical variables will be tabulated using number of observations and percentages.

## 9.1 Subject Disposition

The following will be provided:

- Number and percent of subjects in each of the analysis populations (Safety, mITT, PP) by center and overall
- Listing of subjects excluded from each of the analysis populations along with reason for exclusion.
- Consort flow diagram (showing splits by previous anti-TNF treatment and treatment group)
- Number and percent of subjects who are eligible for randomization by site/ medical monitor.
- By-subject listing of the reason for not eligible for randomization
- Number and percent of subjects who meet all eligibility criteria at screening
- Number and percent of subjects who meet the inclusion/exclusion criteria at visit 2.

**Study termination**:

- Frequency of subjects who completed the trial

- For those subjects who did not complete the trial, frequency of the primary reason for premature discontinuation
- Listing of all dropouts along with reason for termination and supportive information if available, treatment and time of termination

**Protocol Deviations**

- Listing of protocol deviations including subject ID, date of deviation, visit/CRF term and protocol deviation.

## 9.2 Baseline Characteristics

Baseline characteristics will be analyzed using the safety analysis population.

Descriptive statistics will be provided for the following:

- Demographic characteristics (Age, Gender, Race, Ethnicity, Height, Weight at screening and BMI).
- Number and percent of patients who have any relevant medical history
- By-subject listing of medical history including subject ID, center, Diagnosis/Symptoms, start date, stop date, whether ongoing.

**Previous Anti-TNF Treatment**

- Number and percent of subjects who received previous anti-TNF treatment
- By-subject listing of previous anti-TNF treatment including subject ID, center, trade name, dose, frequency, unit, route, start date, end date, anti-TNF treatment status, indication.

## 9.3 Safety

All safety analyses will be performed on the safety analysis population.

The following will be provided:

**Adverse Events (AEs):**

All treatment-emergent adverse events (including serious) will be tabulated using incidence tables with number and percentage of subjects by:

- System Organ Class (SOC) and Preferred Term
- Maximal Severity, System Organ Class (SOC) and Preferred Term

- Maximal Relation to study drug, System Organ Class (SOC) and Preferred Term

In the above frequency tables, the number and percentage of subjects who experienced AEs coded with the same preferred term will be tabulated by treatment group in descending order according to the incidence of AEs in the treatment group.

- By subject listing of all Adverse Events including subject ID, center, adverse event description, start date and time, intensity, whether treatment-emergent, relationship to study drug, action taken with study drug, corrective measurement, whether serious, seriousness specification, outcome, date and time of outcome

- Serious Adverse Events (SAEs):
  Same as the previous bullet (Adverse Events), limited to Serious Adverse Events only.

**Vital Signs (Body Measurements):**

- Descriptive statistics of weight, blood pressure (Systolic/ Diastolic), pulse rate, temperature and respiratory rate by visit, time point and treatment group.
- For each treatment visit (visits 2, 3 and 4) descriptive statistics of change from pre-dose of the given visit to each time point (15 minutes, 30 minutes, 2 hours and 4 hours post infusion), by treatment group.
- For each treatment visit (visits 2, 3, 4 at 4 hours post infusion time point) and follow up visits (visits 5, 6, 7 and 8) descriptive statistics of change from Screening will be provided by visit and by treatment group.
- Vital signs will also be presented graphically over time by treatment group.

**Laboratory Sample Collection**

- Descriptive statistics of laboratory results, including frequency of normality for tests over time and summary of shift in results post-treatment (e.g. shift tables or listings, as relevant)

Tuberculosis Screen

The following tables will be presented by visit and treatment group.

- Frequency distribution of Patient´s current TB status.

  For “Inactive”- frequency distribution of status (No evidence of active TB, Latent)

- Frequency distribution of Clinical examination (PPD)
- Frequency distribution of radiographic
- Frequency distribution of laboratory

  For Tuberculosis screening- frequency distribution of test result (positive, negative)

  For "Other"- frequency distribution of test result (positive, negative) by test.

**Physical Examination by body system:**

- Frequency distribution of evaluation (Normal /Non-Clinically Significant (NCS) Abnormal / Clinically Significant (CS) Abnormal) by body system, visit, and treatment group.
- Shift table of Normal / NCS Abnormal / CS Abnormal transitions from baseline to all subsequent visits. (Note, that "Other" category will not be presented in Shift tables).
- Listings of clinically significant abnormal physical examination results, including subject ID, Site, Visit, Body System and diagnosis.

**ECG**

- Descriptive statistics of ECG parameters (heart rate, RR, PR, QRS, QT, QTc) by visit, time point and treatment group.
- Frequency distribution of overall evaluation of ECG (Normal /Non-Clinically Significant (NCS) Abnormal / Clinically Significant (CS) Abnormal/not done) by visit, time point and treatment group.
- For each treatment visit (visits 2, 3 and 4)
  - Descriptive statistics of change from pre-dose to 30 minutes post-dose will be provided
  - Shift table of normal/abnormal NCS/abnormal CS transitions from pre-dose to 30 minutes post-dose
- For each treatment visit (2, 3 and 4)
  - Descriptive statistics of change from screening to pre-dose will be provided.

  - Shift table of normal/abnormal NCS/abnormal CS transitions from screening to pre-dose time point

- For each follow up visit (5, 6, 7)
  - Descriptive statistics of change from screening to visit will be provided.
  - Shift table of normal/abnormal NCS/abnormal CS transitions from screening to visit

- By-subject listings of abnormal ECG results, including subject ID, site, visit, time point, heart rate, RR, PR, QRS, QT, QTc intervals, abnormality description and whether clinically significant.

**General Infusion Reaction (CRF Injection Site Reaction Assessment)**

- Frequency distribution of Skin Tolerability by visit, time point and treatment group.

**Concomitant medications**

- By-subject listing of past and concomitant medication including subject ID, site, trade name, dose, units, frequency, route, start date and time, end date and time, whether ongoing, indication.

# 9.4 Efficacy

## 9.4.1 Primary Efficacy Analysis

Primary efficacy analysis will be conducted on mITT population. Because this is an exploratory study, alpha will be set at 0.1 for comparisons between groups.

- For each of the treatment groups, the incidence of success/ failure will be calculated along with a 90% exact binomial confidence interval.
- Additionally, descriptive statistics of total Mayo Score Clinical Response (Stool Frequency, Rectal Bleeding, Endoscopic Finding, Physician's Global Assessment and total score) will be presented by visit and treatment group including two-sided 95% Exact Binomial confidence intervals.

## 9.4.2 Secondary Efficacy Analysis

Secondary efficacy analysis will be conducted on mITT and PP populations.

- Primary analysis will be repeated using a 95% exact binomial confidence interval.
- Primary analysis will be repeated on PP population and with both 90% and 95% exact binomial confidence intervals.
- Frequency distribution of patient who had UCEIS assessments by visit and treatment group.
- Descriptive statistics of UCEIS score (Vascular pattern, Bleeding, Erosions & Ulcers and total score) by visit, treatment group.
- Descriptive statistics of change in UCEIS score (Vascular pattern, Bleeding, Erosions & Ulcers and total score) from screening to Day 56 (visit 7) by treatment group.
- Frequency distribution of dichotomous clinical remission at Day 56 (Visit 7) as defined in section 7.3.
- Frequency distribution of dichotomous mucosal healing at Day 56 (Visit 7) as defined in section 7.3.
- Descriptive statistics of partial Mayo score (Stool Frequency, Rectal Bleeding, Physician's Global Assessment and total of these sub-scores) by visit and treatment group.
- Descriptive statistics of change in partial Mayo score by visit and treatment group.

### 9.4.3 Pharmacokinetics (PK)

- Descriptive statistics of PK parameters as described in section 7.4 by visit, time point and treatment group.

### 9.4.4 Pharmacodynamics (PD)

- Descriptive statistics of PD parameters as described in section 7.5 by visit, time point and treatment group.

### 9.4.5 Covariate Analysis

The primary and secondary analysis will be conducted on the mITT population, and examine the following covariates:

- Age

- Gender
- Prior TNF treatment
- Screening total Mayo score
- Screening UCEIS total score
- Screening tissue Eotaxin-1 levels
- Screening tissue Eosinophil count
- Baseline fecal calprotectin levels (visit 2)
- Baseline Hs-CRP (visit 2)
- Combined Site

For each of the listed above covariates descriptive statistics of primary endpoint/s by covariate levels will be presented. Continuous covariates will be divided into quartiles for this presentation.

# 10 Data Listings

Data listings will be provided for all data available from the CRF.

# 11 Computer Software

All statistical analyses will be carried out using SAS® Version 9.4 or higher under Windows® 2016 Terminal.