# Statistical Analysis Plan

## Study M16-763

## A Phase 2, Multicenter, Double-Blind, Parallel Group Long Term Extension Study in Rheumatoid Arthritis Subjects Who Have Completed a Preceding Phase 2 Randomized Controlled Trial with ABBV-105 Given Alone or in Combination with Upadacitinib (ABBV-599)

## Date: 10 Feb 2020

## Version 2.0

## Table of Contents

## List of Tables



## List of Figures

## List of Appendices

# 1.0 Introduction

This Statistical Analysis Plan (SAP) describes the statistical analyses for ABBV-599 Study M16-763.

Study M16-763 evaluates the long-term safety, tolerability, and efficacy of ABBV-105 and ABBV-599 in RA subjects who have completed Study M16-063.

The SAP will not be updated in case of administrative changes or amendments to the protocol unless the changes impact the analysis.

Unless noted otherwise, all analyses will be performed using SAS Version 9.4 (SAS Institute Inc., Cary, NC 27513) under the UNIX operating system.

# 2.0 Study Design and Objectives

## 2.1 Objectives and Hypotheses

The primary objective of this study is to evaluate the long-term safety, tolerability, and efficacy of ABBV-105 and ABBV-599 in RA subjects who have completed Study M16-063.

**Clinical Hypothesis**

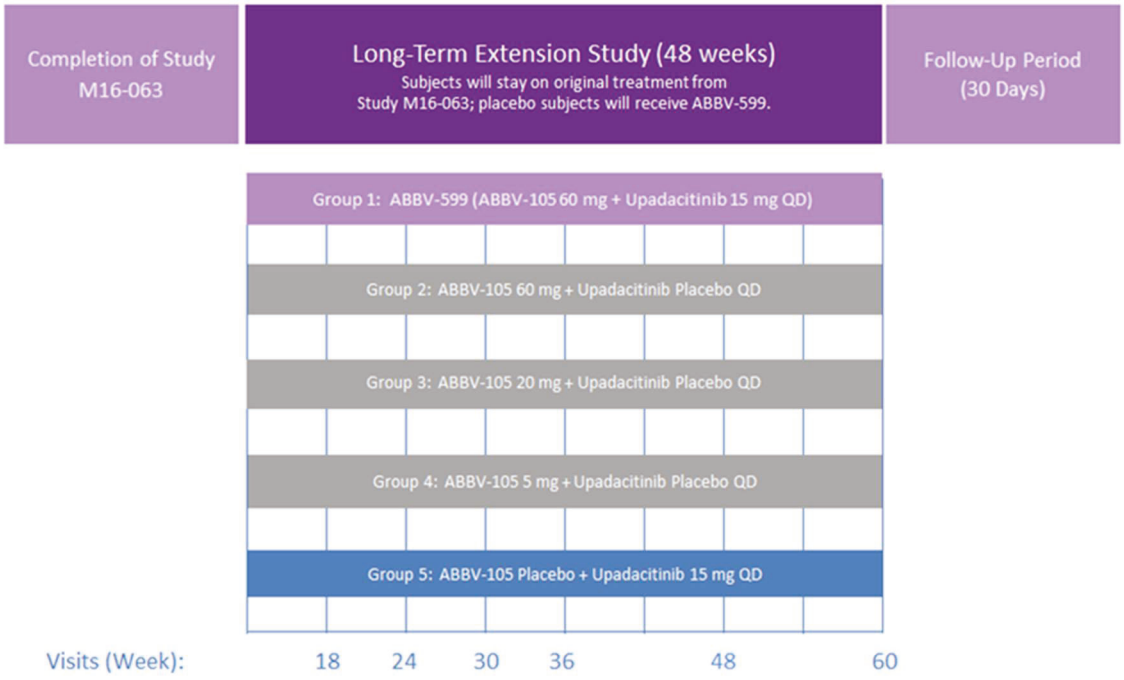
The safety and efficacy of ABBV-105 and ABBV-599 will be maintained over an extended period of treatment.

## 2.2 Study Design Overview

This is a Phase 2, double-blind, multicenter, long-term extension (LTE) study to assess the safety, tolerability, and efficacy of ABBV-105 and ABBV-599 in RA subjects who have completed Study M16-063.

The schematic of the study is shown in Figure 1.

**Figure 1. Study Schematic**




QD = once daily

## 2.3 Treatment Assignment and Blinding

Subjects who meet eligibility criteria as specified in Section 5.1 of the protocol and enter the study on ABBV-105, ABBV-599, or upadacitinib from Study M16-063 will continue on their previously-assigned treatment through the end of the LTE study. Subjects who meet eligibility criteria and enter the study on placebo for both ABBV-105 and upadacitinib from Study M16-063 will receive ABBV-599. Study drug treatment assignments include the following:

- Group 1: ABBV-599 (ABBV-105 60 mg and upadacitinib 15 mg) administered once a day (QD),
- Group 2: ABBV-105 60 mg and upadacitinib placebo QD,

- Group 3: ABBV-105 20 mg and upadacitinib placebo QD
- Group 4: ABBV-105 5 mg and upadacitinib placebo QD, and
- Group 5: Upadacitinib 15 mg and ABBV-105 placebo QD.

This study plans to enroll subjects who completed Study M16-063 at approximately 39 sites in Canada and the European Union. The number, allocation, and location of sites may vary depending on operational aspects of the study. Study sites and subjects will remain blinded for the duration of the study.

The duration of the LTE study will be approximately 52 weeks. This includes a 48-week double-blind treatment period with study visits conducted at Weeks 18, 24, 30, 36, 48, and 60 from the baseline visit of Study M16-063. In addition, subjects will also have a telephone follow-up call 30 days after their last visit to determine the status of any ongoing AEs/SAEs or the occurrence of any new AEs/SAEs.

### 2.4 Sample Size Determination

This is the LTE study for Study M16-063. All eligible subjects who completed Study M16-063 will be enrolled in this study if the subject signs and dates the informed consent. Based on discontinuation criteria mandating efficacy, it is estimated that 20 - 60% of subjects (i.e., between 40 and 120 subjects) will ultimately complete the LTE.

## 3.0 Endpoints

### 3.1 Primary Efficacy Endpoint

There is no primary efficacy endpoint since this is the extension to the feeder Study M16-063.

### 3.2 Secondary Efficacy Endpoints

1. Change in disease activity score (DAS)28 (C-reactive protein [CRP]) from baseline of Study M16-063;
2. DAS Low Disease Activity (LDA), defined as DAS28 CRP $\leq$ 3.2;

3. DAS Clinical Remission (CR), defined as DAS28 CRP < 2.6;
4. Change in clinical disease activity index (CDAI) from baseline of Study M16-063;
5. LDA based on CDAI criteria, defined as CDAI ≤ 10;
6. CR based on CDAI criteria, defined as CR ≤ 2.8;
7. American College of Rheumatology (ACR) 20/50/70 response. A subject will be considered an ACR 20/50/70 responder if:
    - The swollen joint count (SJC) and tender joint count (TJC) have decreased from baseline of Study M16-063 by 20/50/70% or more.
    - At least 3 of the 5 remaining ACR core set measures show reduction of 20/50/70% or more from baseline of Study M16-063.
        - Patient's Assessment of Pain [using visual analog scale, VAS],
        - Patient Global Assessment of Disease Activity [PtGA],
        - Physician Global Assessment of Disease Activity [PhGA],
        - Health Assessment Questionnaire Disability Index [HAQ-DI]
        - High-sensitivity C-reactive protein [hsCRP])
8. Change in individual components of ACR from baseline of Study M16-063, to include:
    - SJC,
    - TJC,
    - Patient's Assessment of Pain (using VAS),
    - PtGA,
    - PhGA,
    - HAQ-DI, and
    - hsCRP.
9. Change in Morning Stiffness Severity (11 point scale) from baseline of Study M16-063.

10. Change in Morning Stiffness Duration (Hours and Minutes) from baseline of Study M16-063

### 3.3 Other Efficacy Endpoints

The secondary efficacy endpoints are listed in Section 3.2, respectively. There are no additional efficacy endpoints.

### 3.4 Safety Endpoints

Safety evaluations include adverse event (AE) monitoring, physical examinations, vital sign measurements, electrocardiogram (ECG), and clinical laboratory testing (hematology, chemistry, and urinalysis) as a measure of safety and tolerability for the entire study duration.

An internal independent data monitoring committee (IDMC) will review unblinded safety data on a cohort level throughout the course of the study. A separate IDMC charter will be prepared outside of the protocol and will describe the roles and responsibilities of the IDMC members, frequency of data reviews, relevant safety data to be assessed, and expectations for blinded communications.

An independent Cardiovascular Adjudication Committee (CAC) will adjudicate blinded cardiac and cerebrovascular events. A CAC charter will be prepared separately from the protocol that will define objective, scope, frequency, and triggers of data reviews.

### 3.5 Additional Endpoint(s)

No additional endpoints will be analyzed in the SAP. Pharmacokinetic endpoints and biomarker endpoints will be analyzed separately.

## 4.0 Analysis Populations

The following population sets will be used for the analyses.

The Full Analysis Set (FAS) includes all subjects who enrolled in Study M16-763 and received at least 1 dose of assigned study drug. The FAS will be used for efficacy and baseline analyses. Subjects will be grouped according to treatments as randomized for Study M16-063.

The Safety Analysis Set consists of all subjects who enrolled in Study M16-763 and received at least 1 dose of assigned study drug. Subjects will be grouped according to treatments actually received in Study M16-763. The Safety Analysis Set will be used for safety analyses.

# 5.0 Subject Disposition

The number of subjects will be tabulated by country, investigator site and overall for all enrolled subjects.

The total number of subjects who were enrolled and treated will be summarized.

A summary of subject accountability will be provided where the number of subjects in each of the following categories will be summarized for each treatment group:

- Subjects enrolled in the study;
- Subjects who took at least one dose of study drug;
- Subjects who completed protocol-specified treatment;
- Subjects who prematurely discontinued study drug (all reasons and primary reason);
- Subjects in each analysis population.

In addition, the reasons for premature discontinuation (primary reason and all reasons) from the trial and/or from the medication collected from CRF by the following categories will be summarized with frequencies and percentages. Subjects with multiple reasons for premature discontinuation will be counted once in the calculation of the number and percentage of total discontinuations ("Premature Discontinuation").

- Adverse events,
- Lost to follow-up,
- Withdrew consent by subject,
- Lack of efficacy,
- Other.

## 6.0 Study Drug Duration and Compliance

A summary of study drug duration (days) will be provided by each treatment arm for the Safety Analysis Set.

The duration of exposure to study drug will be summarized by groups as specified below.

- Group 1: ABBV-599 Always
- Group 2: ABBV-105 60 mg
- Group 3: ABBV-105 20 mg
- Group 4: ABBV-105 5 mg
- Group 5: Upadacitinib
- Group 6: ABBV-599 After Placebo
- Group 7: Placebo (Not present in Study M16-763)

The duration of exposure to study drug will be summarized for each group as specified above, with the number of subjects, mean, standard deviation, median, minimum and maximum values. In addition, the number and percentage of subjects exposed to study drug will be summarized for Study M16-063/763 combined and for Study M16-763 treatment period only respectively. For Study M16-063/763 combined, the following duration intervals will be used:

- $\geq$ 1 day
- $\geq$ 15 days
- $\geq$ 29 days

- ≥ 57 days
- ≥ 85 days
- ≥ 127 days
- ≥ 169 days
- ≥ 211 days
- ≥ 252 days
- ≥ 336 days
- ≥ 420 days

The exposure to study drug in days for Study M16-063/763 combined period is calculated as:

Exposure = (date of last study medication in Study M16-763 – date of first study medication in Study M16-063 + 1)

For Study M16-763 only, the following duration intervals will be used:

- ≥ 1 day
- ≥ 42 days
- ≥ 85 days
- ≥ 127 days
- ≥ 168 days
- ≥ 252 days
- ≥ 336 days

The exposure to study drug in days for Study M16-763 period only is calculated as:

Exposure = (date of last study medication in Study M16-763 – date of first study medication in Study M16-763 + 1)

**Compliance**

Study drug compliance will be summarized for each treatment group for the FAS population. The compliance is defined as the number of tablets/capsules taken (i.e., the difference between the number of tablets/capsules dispensed and the number of tablets/capsules returned) divided by the number of tablets/capsules that should have been taken during the treatment period. Compliance with each study drug will be calculated for each subject and summarized with the mean, median, standard deviation, minimum, and maximum.

# 7.0 Demographics, Baseline Characteristics, Medical History, and Prior/Concomitant Medications

Demographics, baseline or disease characteristics, medical history, and prior and concomitant medications will be summarized for the FAS overall and by treatment group. Categorical variables will be summarized with the number and percentage of subjects; percentages will be calculated based on the number of non-missing observations. Continuous variables will be summarized with descriptive statistics (number of non-missing observations, mean and standard deviation, median, minimum and maximum).

## 7.1 Demographics and Baseline Characteristics

The following demographic and baseline characteristics, as measured at baseline of the Study M16-063 study, will be summarized.

**Demographic Characteristics**

- Age (years)
- Age category [18 – < 40 years old, 40 – < 65 years old, ≥ 65 years old]
- Sex [male/female]
- Race [White, Black or African American, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Asian, Other]

- Ethnicity [Hispanic/Latino, Non-Hispanic/Latino]
- Geographic region (North America, South/Central America, Western Europe, Eastern Europe, Asia, Other)
- Weight (kg)
- Weight Categories (< 60 kg, ≥ 60 kg)
- Height (cm)
- Body Mass Index (BMI) ($kg/m^2$)
- Body Mass Index (BMI) Category ($kg/m^2$) (BMI < 25 vs BMI ≥ 25)

**RA Medical History and Characteristics**

- Duration of RA Symptoms in years
- Duration of RA Diagnosis in years
- Duration of RA Diagnosis Categories (< 5 year or ≥ 5 year)
- Prior exposure to bDMARDs (failed 1 or 2 biologics with the same mechanism of action; failed ≥ 3 biologics with the same mechanism of action and/or ≥ 2 biologics with multiple mechanisms of action)
- Number of prior bDMARD received (1, 2, 3, ≥ 4)
- Concomitant csDMARDs at baseline (MTX alone, MTX and other csDMARDs, csDMARDs other than MTX)

**ACR and/or DAS Components at Baseline**

- Tender joint count (TJC68) defined as the number of tender joints out of 68 assessed joints
- Swollen joint count (SJC66) defined as the number of swollen joints out of 66 assessed joints
- Tender joint count (TJC28) defined as the number of tender joints out of 28 assessed joints used for DAS28 calculation
- Swollen joint count (SJC28) defined as the number of swollen joints out of 28 assessed joints used for DAS28 calculation

- Physician's global assessment of disease activity (mm on a 100-mm horizontal visual analogue scale [VAS])
- Patient's assessment of pain within last week (mm on a 100-mm horizontal (VAS))
- Patient's global assessment of disease activity within last 24 hours (mm on a 100-mm horizontal VAS)
- Health Assessment Questionnaire Disability Index of the (HAQ – DI) (range: 0 to 3)
- High sensitivity C-reactive protein (hsCRP) (mg/L)
- Erythrocyte sedimentation rate (ESR) (mm/hr)

**Other Baseline RA Disease Characteristics**

- Morning stiffness (severity and duration)
- Anti-cyclic citrullinated peptide (Anti-CCP) (units)
- Anti-CCP status: Positive or Negative
- Rheumatoid Factor (RF) (units)
- Rheumatoid Factor (RF) status: Positive or Negative
- Percentage of subjects on oral steroid at baseline
- Oral steroid dose (prednisone equivalent) at baseline
- DAS28 [ESR]
- DAS28 [CRP]
- CDAI
- DAS28 [ESR] Categories:
  a. DAS28 [ESR] > 5.1 (High Disease Activity)
  b. DAS28 [ESR] ≤ 5.1
- DAS28 [CRP] Categories:
  a. DAS28 [CRP] > 5.1 (High Disease Activity)
  b. DAS28 [CRP] ≤ 5.1
- CDAI categories:

a. CDAI > 22 (High Disease Activity)
b. CDAI ≤ 22

**Clinical Tests at Screening**

- Chest x-ray
- Tuberculin PPD skin test, QuantiFERON TB Gold test
- Serum pregnancy test

**Immunization History**

- BCG immunization
- Herpes Zoster immunization
- Hepatitis B immunization

**Tobacco/Nicotine and Alcohol Use**

- Tobacco/Nicotine Use (current, former, never, or unknown)
- Alcohol Use (current, former, never, or unknown)

## 7.2 Medical History

Medical history data will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The actual version of the MedDRA coding dictionary will be noted in the statistical tables and clinical study report. Medical history data will be summarized and presented for the FAS population using body systems and conditions/diagnoses as captured on the CRF. The body systems will be presented in alphabetical order and the conditions/diagnoses will be presented in alphabetical order within each body system. The number and percentage of subjects with a condition/diagnosis will be summarized for each treatment group as well as overall. Subjects reporting more than one condition/diagnosis within a body system will be counted only once for that body system. No statistical comparison will be performed for medical history reporting.

### 7.3 Prior and Concomitant Medications

Prior and concomitant medications will be summarized by each treatment group as well as overall for the FAS. Prior medications are those medications taken prior to the first dose of study drug. This includes medications with a start date before the first study drug administration date, regardless of the end date of these medications. Medications taken on the day of the first dose of study drug are not counted as prior medications. Concomitant medications are those medications, other than study drug, taken after the first dose of study drug and within 1 day of the last dose of study drug. This includes medications with a start date between first study drug administration and last study drug administration + 1 day, as well as, medications with a start date prior to first dose of study drug and which are ongoing after first dose of study drug. Medications taken on the day of the first dose of study drug are counted as concomitant medications.

The number and percentage of subjects who received a prior medication and the number and percentage of subjects who received a concomitant medication will be tabulated separately by the generic name assigned by the most current version of the World Health Organization (WHO) Drug Dictionary.

## 8.0 Efficacy Analyses

### 8.1 General Considerations

Analysis of efficacy endpoints will be conducted on the FAS.

For all efficacy endpoints, the descriptive statistics will be provided by treatment group. The statistics include number of observations, mean, standard deviation, minimum, median, and maximum for continuous variables; and number and percentage of subjects for categorical variables.

The analysis treatment groups will be described as follows indicating from Study M16-063 to extension Study M16-763:

- Group 1: ABBV-599 to ABBV-599

- Group 2: ABBV-105 60 to ABBV-105 60 mg
- Group 3: ABBV-105 20 to ABBV-105 20 mg
- Group 4: ABBV-105 5 to ABBV-105 5 mg, and
- Group 5: Upadacitinib to Upadacitinib
- Group 6: Placebo to ABBV-599
- Group 7: All ABBV-599 (Group 1 and 6)

"Baseline" refers to the last non-missing observation before the first administration of study drug in Study M16-063 or randomization in Study M16-063 if no study drug is given.

## 8.2 Handling of Missing Data

The analysis will be based on As Observed data, and no imputation will be conducted.

## 8.3 Primary Efficacy Endpoint and Analyses

There are no primary efficacy endpoints or analyses for this study.

## 8.4 Secondary Efficacy Analyses

Descriptive statistics will be provided for each treatment group for all visits. These include the number of observations, mean with 95% confidence interval, standard deviation, median, minimum and maximum for continuous endpoints; and frequencies and percentages with 95% confidence interval using Wilson score[1] for binary endpoints.

No missing data imputation will be applied. All efficacy analyses will be based on As Observed (AO) analysis, and thus a subject who does not have an evaluation at the primary analysis time point will not be included.

## 8.5 Additional Efficacy Analyses

No additional efficacy analyses are planned.

### 8.6 Efficacy Subgroup Analyses

No subgroup analyses will be performed.

## 9.0 Safety Analyses

### 9.1 General Considerations

Safety analyses will include reporting of adverse events, laboratory, and vital signs measurements. Safety analyses will be carried out using the Safety Analysis Set.

The following summary statistics will be presented for subjects who have both baseline and post-baseline values for laboratory parameters and vital signs: the mean value at Baseline and at each respective protocol specified visit, and the mean, standard deviation and median for changes from Baseline. Categorical data will be summarized using frequencies and percentages. The number of non-missing values will be given. Missing safety data will not be imputed.

### 9.2 Adverse Events

Adverse events (AEs) will be summarized and presented using primary MedDRA System Organ Classes (SOCs) and preferred terms (PTs) according to the version of the MedDRA coding dictionary used for the study at the time of database lock. The actual version of the MedDRA coding dictionary used will be noted in the AE tables and in the clinical study report. Specific adverse events will be counted once for each subject for calculating percentages, unless stated otherwise. In addition, if the same adverse event occurs multiple times within a subject, the highest severity and level of relationship to investigational product will be reported.

TEAEs will be summarized using subject data from Study M16-763 and a combination of data from Studies M16-063 and M16-763 that includes any subject receiving a dose in Study M16-763, respectively. Only the datasets from Studies M16-063 and M16-763 that includes any subject receiving a dose in Study M16-763 will be used for per 100 patient years of exposure analyses (for the Study M16-763 study).

### 9.2.1 Treatment-Emergent Adverse Events

To summarize data from Study M16-763 only, a treatment-emergent Adverse Event (TEAE) is defined as an adverse event with an onset date that is on or after the first dose of study drug from Study M16-763, and no more than 30 days after the last dose of study drug from Study M16-763.

To summarize a combination of data from Studies M16-063 and M16-763, a treatment-emergent Adverse Event (TEAE) is defined as an adverse event with an onset date that is on or after the first dose of study drug from Study M16-063, and no more than 30 days after the last dose of study drug from Study M16-763.

Events where the onset date is the same as Study M16-063 study drug start date are assumed to be treatment-emergent. If an incomplete onset date was collected for an adverse event, the event will be assumed to be treatment-emergent unless there is other evidence that confirms that the event was not treatment-emergent (e.g., the event end date was prior to the study drug start date).

The number and percentage of subjects experiencing TEAEs will be summarized.

### 9.2.2 Adverse Event Overview

The number and percentage of subjects experiencing TEAEs will be summarized by treatment group as specified in Section 6.0 and overall.

An overview of AEs will be presented consisting of the number and percentage of subjects experiencing at least one event for each of the following AE categories:

- All TEAEs
- Treatment-emergent serious adverse events (SAEs)
- Treatment-emergent severe adverse events
- TEAEs reasonably possibly related to study drug
- TEAEs of special interest (AESIs)
- TEAEs leading to discontinuation of study drug

- TEAE leading to death
- All deaths

Additional AEs may be considered for tabulation/summary based on recommendations from Clinical and Safety as deemed appropriate.

For AESIs, the point estimate and 95% CI (using normal approximation) will be provided for the treatment difference in AE percentages.

### 9.2.3 Treatment-Emergent Adverse Events by SOC and/or PT

The number and percentage of subjects experiencing adverse events will be tabulated by SOC and MedDRA PT by "as treated" treatment groups and overall. The SOCs will be presented in alphabetical order, and the PTs will be presented in alphabetical order within each SOC.

The following summaries of adverse events will be generated:

- All TEAEs
- Treatment-emergent serious adverse events (SAEs)
- Treatment-emergent severe adverse events
- TEAEs reasonably possibly related to study drug
- TEAEs leading to discontinuation of study drug
- TEAE leading to death
- Frequent AEs (reported in 2% of subjects or more in any treatment group)

Subjects reporting more than one adverse event for a given MedDRA preferred term will be counted only once for that term (most severe incident for the severity tables and most related incident for the relationship tables). Subjects reporting more than one type of adverse event within a SOC will be counted only once for that SOC. Subjects reporting more than one type of adverse event will be counted only once in the overall total. In addition, if the same adverse event occurs multiple times within a subject, the highest

severity and level of relationship to investigational product will be reported. In addition, TEAEs will be summarized by PT and sorted by decreasing frequency for the total active group.

### 9.2.4 Treatment-Emergent Adverse Events per Patient-Years of Exposure

TEAEs occurring during Study M16-063 and Study M16-763 will be summarized by event rate per 100 subject years, defined as

100 * (Number of TEAEs)/(Total Patient Years)

where total patient years is defined as the sum of the study drug exposure of all subjects normalized by 365.25 and rounded to 1 decimal place.

### 9.2.5 SAEs (Including Deaths) and Adverse Events Leading to Study Drug Discontinuation

All serious adverse events (SAEs), deaths, and adverse events leading to discontinuation of study drug will be listed. The number and percentage of subjects experiencing SAEs (including deaths) and adverse events leading to discontinuation of study drug will be tabulated by SOC and PT or each treatment group.

### 9.2.6 Adverse Events of Special Interest

The Adverse Events of Special Interest (AESI) categories will be summarized and presented by "as treated" treatment group and overall using SOC and MedDRA PT. The AESI categories will be identified by the following search criteria per Standard MedDRA Queries (SMQs)/Company MedDRA Queries (CMQs) in Appendix B.

### 9.2.7 Adverse Events by Maximum Severity

TEAEs will also be summarized by maximum severity by "as treated" treatment group and overall. If a subject has an AE with an unknown severity, then the subject will be counted in the severity category of unknown, even if the subject has another occurrence of

the same event with a severity present. The only exception is that if the subject has another occurrence of the same AE with the most extreme severity – severe. In this case, the subject will be counted under the severe category.

### 9.2.8 Adverse Events by Maximum Relationship

TEAEs will also be summarized by maximum relationship to treatment, as assessed by the investigator, by "as treated" treatment group and overall. If a subject has a TEAE with an unknown relationship, then the subject will be counted in the relationship category of "unknown," even if the subject has another occurrence of the same event with a relationship present. The only exception is if the subject has another occurrence of the same TEAE with a relationship assessment of "reasonable possibility." In this case, the subject will be counted under the "reasonable possibility" category.

### 9.2.9 Adverse Events by "Reasonably Possibly Related" Relationship

TEAEs and reasonably possibly related AEs occurring for more than 2% of the subjects in any of the treatment groups will also be summarized by MedDRA SOC and PT. If a subject has an AE with an unknown relationship, then the subject will be counted in as 'related.'

### 9.2.10 Frequent (> 5%) Adverse Events and Reasonably Possibly Related Adverse Events by Preferred Term in Decreasing Frequency

TEAEs and reasonably possibly related AEs occurring for more than 5% of the subjects in any of the treatment arms will be summarized by MedDRA PT in decreasing frequency separately.

### 9.2.11 Listing of Adverse Events

The following additional summaries of AEs will be prepared.

- Listing of Subjects with Treatment-Emergent AESIs

- Listing of Subjects with Pretreatment SAEs
- Listing of Subjects with Treatment-Emergent SAEs
- Listing of Treatment-Emergent AEs that led to discontinuation of study drug
- Listing of all deaths.

## 9.3 Analysis of Laboratory Data

Data collected from central and local laboratories, including additional laboratory testing due to an SAE, will be used in all analyses, except for Baseline, where SAE-related laboratory assessments on or before the first dose of study drug will be excluded. Baseline is defined as the last available measurement before Study M16-063 study drug administration. The clinical laboratory tests defined in the protocol operations manual (e.g., hematology and clinical chemistry) will be summarized.

Mean change from baseline to each applicable post-baseline visit will be summarized for selected laboratory variables, with the number of observations, baseline mean, and visit mean, at each visit in Study M16-063 and Study M16-763 for each treatment group. An ANOVA model with only treatment as a factor, not controlling for baseline, will be used to test statistical significance for the mean change from baseline among different arms.

The baseline and post-baseline laboratory observations will be categorized as Grade 1, Grade 2, Grade 3, and Grade 4 according to OMERACT criteria (Rheumatology Common Toxicity Criteria v.2.0). For creatine phosphokinase and creatinine, NCI CTC criteria will be used.

For each laboratory variable, shift tables will be generated that cross tabulate the subjects as deemed appropriate by "as treated" treatment group:

- Category of the baseline value versus category of the final value.
- Category of the baseline value versus maximum category.
- Category of the baseline value versus minimum category.

Note that the minimum/maximum category is used, rather than the category of the minimum/maximum value. The two may be different due to variation in the reference range.

No statistical tests will be performed for this analysis.

Laboratory abnormalities will be evaluated based on Potentially Clinically Significant (PCS) criteria (Appendix C). For each laboratory PCS criterion, the number and percentage of subjects who have a laboratory value meeting the criteria will be summarized. Listings will be provided to summarize subject-level laboratory data for subjects meeting PCS criteria.

According to FDA's Guidance for Industry "Drug-Induced Liver Injury: Premarketing clinical evaluation" (July 2009), when aminotransferase (AT) abnormalities indicating hepatocellular injury are accompanied by evidence of impaired hepatic function (bilirubin elevation > 2 × ULN), in the absence of evidence of biliary obstruction (i.e., significant elevation of ALP) or some other explanation of the injury (e.g., viral hepatitis, alcohol hepatitis), the combined finding (i.e., Hy's Law cases) represents a signal of a potential for the drug to cause severe DILI.

For the purpose of assessing for potential Hy's law cases, the frequencies and percentages of subjects with post baseline liver-specific function test values that meet the following criteria of potential clinical interest will be summarized by "as treated" treatment group:

- ALT ≥ 3 × ULN
- ALT ≥ 5 × ULN
- ALT ≥ 10 × ULN
- ALT ≥ 20 × ULN
- AST ≥ 3 × ULN
- AST ≥ 5 × ULN
- AST ≥ 10 × ULN
- AST ≥ 20 × ULN

- Total Bilirubin Level (TBL) ≥ 2 × ULN
- Alkaline phosphatase ≥ 1.5 × ULN
- ALT and/or AST ≥ 3 × ULN and concurrent TBL ≥ 1.5 × ULN
- ALT and/or AST ≥ 3 × ULN and concurrent TBL ≥ 2 × ULN

## 9.4 Analysis of Vital Signs

Vital sign variables include sitting systolic blood pressure, sitting diastolic blood pressure, pulse, body temperature, and weight. The criteria for potentially clinically significant vital sign findings are presented in Appendix C.

Mean changes from Baseline to post-baseline visits will be summarized with the baseline mean, the visit mean, change from baseline mean, standard deviation, and median. An ANOVA model with only treatment as a factor, not controlling for baseline, will be used to test statistical significance for the mean change from baseline.

The number and percentage of subjects meeting the criteria for potentially clinically significant vital sign values will be summarized.

Vital sign variables will be evaluated based on potentially clinically significant (PCS) criteria (Appendix C). For each vital sign PCS criterion, the number and percentage of subjects who have a vital sign value meeting the criteria will be summarized. Listings will be provided to summarize subject-level vital sign data for subjects meeting PCS criteria.

## 9.5 Safety Subgroup Analyses

No planned safety subgroup analyses.

## 9.6 Other Safety Analyses

ECG is collected at Weeks 18, 24, 30, 36, 48, and 60. ECG findings will be summarized by treatment group for each parameter and visit.

# 10.0 Other Analyses

No other analyses are planned.

# 11.0 Interim Analysis

An interim analysis to review long-term safety and efficacy will be conducted after Study M16-063 Week 12 database lock and analysis. The descriptive statistics will be presented for key efficacy and safety endpoints with all available data at the interim analysis. Key efficacy endpoints include DAS28(CRP), CDAI, ACR20/50/70, Patient's Assessment of Pain [using visual analog scale, VAS], and HAQ-DI. Key safety endpoints include overview of TEAE, TEAEs reasonably possibly related to study drug, SAEs, TEAE leading to death, AESIs, mean change from baseline for hematology and chemistry, PCS for hematology and chemistry and liver-related elevations.

Unblinded interim analyses for safety will be conducted by a DMC to review safety. The sponsor, study sites and subjects will remain blinded for the duration of the study until the database lock of Study M16-063.

An internal data monitoring committee (DMC) will review unblinded safety data from the ongoing study. The primary responsibility of the DMC will be to protect the safety of the subjects participating in this study. A separate DMC charter has been prepared outside of the protocol and describes the roles and responsibilities of the DMC members, frequency of data reviews, relevant safety data to be assessed, and expectations for blinded communications.

# 12.0 Overall Type-I Error Control

No hypothesis tests will be conducted for the efficacy analysis.

# 13.0 Version History

**Table 1. SAP Version History Summary**

| Version | Date | Summary |
|---|---|---|
| 1.0 | 30 Jan 2019 | Original version |
| 2.0 | 07 Feb 2020 | The changes made between the second and the first version are:<br>• Change of formatting to adhere to a new SAP template<br>• Small editorial changes for readability and to maintain consistency with the protocol<br>• An update to include interim analysis.<br>• Updated the criteria for Liver-Related Elevations to align with Immunology RA project conventions |

# 14.0 References

1. Julious SA. Two-sided confidence intervals for the single proportion: comparison of seven methods by Robert G. Newcombe. Stat Med. 2005;24(21):3383-4.

## Appendix A. Protocol Deviations

The number and percentage of subjects who reported at least one of the following protocol deviation categories will be provided.

- Subject entered into the study even though s/he did not satisfy entry criteria.
- Subject developed withdrawal criteria during the study and was not withdrawn.
- Subject received wrong treatment or incorrect dose of study.
- Subject took prohibited concomitant medication.

## Appendix B. Definition of Adverse Events of Special Interest

Adverse Events of Special Interest (AESI) will be identified using the following search criteria:

| AESI | Type of MedDRA Query | Broad or Narrow Search | SMQ/CMQ Search Criteria |
|---|---|---|---|
| Serious Infections | CMQ | | "Infections" – Subset for SAEs |
| Opportunistic Infection | CMQ | | "Opportunistic Infection" |
| Possible Malignancy | SMQ | Narrow | "Malignancies" |
| Malignancy | SMQ | | "Malignant tumours" |
| Non-Melanoma Skin Cancer (NMSC) | SMQ | Broad | Skin Malignant tumours (Broad SMQ) removing Melanoma CMQ |
| Malignancy excluding NMSC | | | "Malignant tumours" SMQ removing NMSC output |
| Lymphoma | SMQ | | "Malignant Lymphomas" |
| Hepatic Disorder (Hepatic Events and Increased Hepatic Transaminases) | SMQ | Narrow | "Drug Related Hepatic Disorders" |
| Gastrointestinal Perforations | SMQ | Narrow | "Gastrointestinal Perforation" |
| Anemia | CMQ | | "Non-Hemolytic and Non-Aplastic Anemias" |
| Neutropenia | CMQ | | "Hematological Toxicity – Neutropenia" |
| Lymphopenia | CMQ | | "Hematological Toxicity – Lymphopenia (Veliparib Product Specific)" |
| Herpes Zoster | CMQ | | "Herpes Zoster" |
| Creatine Phosphokinase (CPK) Elevation | PT | | Search only for the PT of "Blood creatine phosphokinase increased" |
| Renal Dysfunction | SMQ | Narrow | "Acute Renal, Failure" |
| Tuberculosis | CMQ | | "Tuberculosis" |
| Adjudicated Cardiovascular Events | Output from CAC | | |

## Appendix C. Potentially Clinically Significant Criteria for Safety Endpoints

The criteria for Potentially Clinically Important (PCS) laboratory findings are determined by OMERACT criteria in Table C-1, and the PCS criteria for vital sign findings are described in Table C-2.

## Table C-1. OMERACT Criteria

| **Rheumatology Common Toxicity Criteria v.2.0**<br>**Based on Woodworth TG, et al. Standardizing assessment of adverse effects in rheumatology clinical trials II. Status of OMERACT Drug Safety Working Group May 2006: OMERACT 8. Standardizing Assessment and Reporting of Adverse Effects in Rheumatology Clinical Trials: Enabling Description of Comparative Safety Profiles for Antirheumatic Therapies** | | | | |
|---|---|---|---|---|
| | **1 – Mild**<br>Asymptomatic, or transient<br>Short duration (< 1 week)<br>No change in life style<br>No medication or OTC | **2 – Moderate**<br>Symptomatic<br>Duration (1 – 2 weeks)<br>Alter lifestyle occasionally<br>Meds relieve. (may be prescription),<br>Study drug continued | **3 – Severe**<br>Prolonged symptoms, reversible, major functional impairment<br>Prescription meds/partial relief<br>May be hospitalized < 24 hr<br>Temporary study drug discontinuation, or/and dose reduced | **4 – Includes Life Threatening**<br>At risk of death<br>Substantial disability, especially if permanent.<br>Multiple meds<br>Hospitalised > 24 hr<br>Study drug discontinued |
| **A. Allergic/Immunologic** | | | | |
| A1. Allergic reaction/hypersensitivity (includes drug fever) | Transient rash: drug fever < 38°C: transient, asymptomatic bronchospasm | Generalised urticaria responsive to meds; or drug fever > 38°C, or reversible bronchospasm | Symptomatic bronchospasm requiring meds; symptomatic urticaria persisting with meds, allergy related oedema/angioedema | Anaphylaxis, laryngeal/pharyngeal oedema, requiring resuscitation |
| A2. Autoimmune reaction | Seriologic or other evidence of autoimmune reaction, but patient asymptomatic: all organ function normal and no treatment is required (e.g., vitiligo) | Evidence of autoimmune reaction involving a non-essential organ or functions, requiring treatment other than immunosuppressive drugs (e.g., hypothyroidism) | Reversible autoimmune reaction involving function of a major organ or toxicity requiring short term immunosuppressive treatment (e.g., transient colitis or anaemia) | Causes major organ dysfunction, or progressive, not reversible, or requires long-term administration of high dose immunosuppressive therapy |

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| A3. Rhinitis (includes sneezing, nasal stuffiness, post-nasal discharge) | Transient, non-prescription meds relieve | Prescription med. required, slow | Corticosteroids or other prescription med. with persistent disabling symptoms such as impaired exercise tolerance | NA |
| A4. Serum sickness | Transient, non-prescription meds relieve | Symptomatic, slow response to meds (e.g., oral corticosteroids) | Prolonged; symptoms only partially relieved by meds; parenteral corticosteroids required | Major organ dysfunction, requires long-term high-dose immunosuppressive therapy |
| A5. Vasculitis | Localised, not requiring treatment; or rapid response to meds; cutaneous | Symptomatic, slow response to meds (e.g., oral corticosteroids) | Generalised, parenteral corticosteroids required or/and short duration hospitalisation | Prolonged, hospitalisation, ischemic changes, amputation |
| **B. Cardiac** | | | | |
| B1. Arrhythmia | Transient, asymptomatic | Transient, but symptomatic or recurrent, responds to meds | Recurrent/persistent; maintenance prescription | Unstable, hospitalisation required, parenteral meds |
| B2. Cardiac function decreased | Asymptomatic decline in resting ejection fraction by > 10%, but < 20% of baseline value | Asymptomatic decline of resting ejection fraction ≥ 20% of baseline value | CHF responsive to treatment | Severe or refractory CHF |

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|---|---|---|---|---|
| B3. Edema | Asymptomatic (e.g., 1 + feet/calves), self-limited, no therapy required | Symptomatic (e.g., 2 + feet/calves), requires therapy | Symptoms limiting function (e.g., 3 + feet/calves, 2 + thighs), partial relief with treatment prolonged | Anasarca; no response to treatment |
| B4. Hypertension (new onset or worsening) | Asymptomatic, transient increase by > 20 mmHg (diastolic) or to > 150/100 if previously normal, no therapy required | Recurrent or persistent increase > 150/100 or by > 10 mmHg (diastolic), requiring and responding readily to treatment | Symptomatic increase > 150/100, > 20 mmHg, persistent, requiring multi agency therapy, difficult to control | Hypertensive crisis |
| B5. Hypotension (without underlying diagnosis) | Transient, intermittent, asymptomatic, orthostatic decrease in blood pressure > 20 mmHg | Symptomatic, without interference with function, recurrent or persistent > 20 mmHg decrease, responds to treatment | Syncope or symptomatic, interferes with function, requiring therapy and sustained medical attention, dose adjustment or drug discontinuation | Shock |
| B6. Myocardial ischaemia | Transient chest pain/ECG changes; rapid relief with nitro | Recurring chest pain, transient ECG ST-T changes; treatment relieves | Angina with infarction, no or minimal functional compromise, reduce dose or discontinue study drug | Acute myocardial infarction, arrthymia or/and CHF |
| B7. Pericarditis/ pericardial effusion | Rub heard, asymptomatic | Detectable effusion by echocardiogram, symptomatic NSAID required | Detectable on chest x-ray, dyspnoea; or pericardiocentesis; requires corticosteroids | Pulsus alternates with low cardiac output; requires surgery |

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| B8. Phlebitis/thrombosis/Embolism (excludes injection sites) | Asymptomatic, superficial, transient, local, or no treatment required | Symptomatic, recurrent, deep vein thrombosis, no anticoagulant therapy required | Deep vein thrombosis requiring anticoagulant therapy | Pulmonary embolism |
| **C. General (constitutional)** | | | | |
| C1. Fatigue/malaise (asthenia) | Increase over baseline; most usual daily functions maintained, short term | Limits daily function intermittently over time | Interferes with basic ADL, persistent | Unable to care for self, bed or wheelchair bound > 50% of day debilitating, hospitalisation |
| C2. Fever (pyrexia) (note: fever due to drug allergy should be coded as allergy) | Transient, few symptoms 37.7 – 38.5°C | Symptomatic, recurrent 38.6 – 39.9°C. Relieved by meds | ≥ 40°C; ≤ 24 h, persistent symptoms; partial response to meds | ≥ 40°C, debilitating, > 24 h, hospitalisation; no relief with meds |
| C3. Headache | Transient or intermittent, no meds or relieved with OTC | Persistent, recurring, non-narcotic analgesics relieve | Prolonged with limited response to narcotic medicine | Intractable, debilitating, requires parenteral meds |
| C4. Insomnia | Difficulty sleeping, short term, no interfering with function | Difficulty sleeping interfering with function, use of prescription med | Prolonged symptoms, with limited response to narcotic meds | Debilitating, hospitalisation; no relief with meds |
| C5. Rigors, chills | Asymptomatic, transient, no meds, or non-narcotic meds relieve | Symptomatic, narcotic meds relieve | Prolonged symptoms, with limited response to narcotic meds | Debilitating, hospitalisation; no relief with meds |
| C6. Sweating (diaphoresis) | Episodic, transient | Frequent, short term | Frequent, drenching, disabling | Dehydration, requiring IV fluids/hospitalization > 24 hrs |

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| C7. Weight gain | 5% – 9.9% | 10% – 19.9% | 20% – 30% | NA |
| C8. Weight loss | 5% – 9.9% | 10% – 19.9% | 20% – 30% | NA |
| **D. Dermatologic** | | | | |
| D1. Alopecia | Subjective, transient | Objective, fully reversible | Patchy, wig used, partly reversible | Complete, or irreversible even if patchy |
| D2. Bullous eruption | Localised, asymptomatic | Localised, symptomatic, requiring treatment | Generalised, responsive to treatment; reversible | Prolonged, generalised, or requiring hospitalisation for treatment |
| D3. Dry skin | Asymptomatic, controlled with emollients | Symptoms eventually (1 – 2 wks) controlled with emollients | Generalised, interfering with ADL > 2 wks, persistent pruritis, partially responsive to treatment | Disabling for extended period, unresponsive to ancillary therapy and requiring study drug discontinuation for relief |
| D4. Injection site reaction | Local erythema, pain, pruritis, < few days | Erythema, pain, oedema, may include superficial phlebitis, 1 – 2 wks | Prolonged induration, superficial ulceration; includes thrombosis | Major ulceration necrosis requiring surgery |
| D5. Petechiae (without vasculitis) | Few, transient asymptomatic | Dependent areas, persistent up to 2 wks | Generalised, responsive to treatment; reversible | Prolonged, irreversible, disabling |

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| D6. Photosensitivity | Transient erythema | Painful erythema and oedema requiring topical treatment | Blistering or desquamation, requires systematic corticosteroids | Generalised exfoliation or hospitalisation |
| D7. Pruritis | Localised, asymptomatic, transient, local treatment | Intense, or generalised, relieved by systematic medication | Intense or generalised; poorly controlled despite treatment | Disabling, irreversible |
| D8. Rash (not bullous) | Erythema, scattered macular/popular eruption; pruritis transient; TOC or no meds | Diffuse macular/popular eruption or erythema with pruritus; dry desquamation; treatment required | Generalised, moist desquamation, requires systemic corticosteroids; responsive to treatment; reversible | Exfoliative or ulcerating; or requires hospitalisation; or parenteral corticosteroids |
| D9. Induration/fibrosis/Thickening (not sclerodermal) | Localized, high density on palpation, reversible, no effect on ADL and not disfiguring | Local areas < 50% body surface, not disfiguring, transient interference with ADL, reversible | Generalized, disfiguring, interferes with ADL, reversible | Disabling, irreversible, systemic symptoms |
| **E. Ear/Nose/Throat** | | | | |
| E1. Hearing loss | Transient, intermittent, no interference with function | Symptomatic, treatment required, reversible | Interferes with function; incomplete response to treatment | Irreversible deafness |
| E2. Sense of smell | Slightly altered | Markedly altered | Complete loss, reversible | Complete loss, without recovery |
| E3. Stomatitis | Asymptomatic | Painful, multiple, can eat | Interferes with nutrition, slowly reversible | Requires enteral support; residual dysfunction |

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| E4. Taste disturbance (dysgeusia) | Transiently altered; metallic | Persistently altered; limited effect on eating | Disabling, effect on nutrition | NA |
| E5. Tinnitus | Intermittent, transient, no interference with function | Requires treatment, reversible | Disabling, or associated with hearing loss | Irreversible deafness |
| E6. Voice changes (includes hoarseness, loss of voice, laryngitis) | Intermittent hoarseness, able to vocalise | Persistent hoarseness, able to vocalise | Whispered speech, slow return of ability to vocalise | Unable to vocalize for extended |
| E7. Xerostomia (dry mouth) | Transient dryness | Relief with meds | Interferes with nutrition, slowly reversible | Extended duration interference with nutrition, requires parenteral nutrition |
| **F. Eye/Ophthalmologic** | | | | |
| F1. Cataract | Asymptomatic, no change in vision, non-progressive | Symptomatic, partial visual loss, progressive | Symptoms impairing function, vision loss requiring treatment, including surgery | NA |
| F2. Conjunctivitis | Asymptomatic, transient, rapid response to treatment | Symptomatic, responds to treatment, changes not interfering with function | Symptoms prolonged, partial response to treatment, interferes with function | NA |
| F3. Lacrimation increased (tearing, watery eyes) | Symptoms not requiring treatment, transient | Symptomatic, treatment required, reversible | Unresponsive to treatment with major effect on function | NA |
| F4. Retinopathy | Asymptomatic, non-progressive, no treatment | Reversible change in vision; readily responsive to treatment | Disabling change in vision ophthalmological findings reversible, sight improves over time | Loss of sight |

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| F5. Vision changes (e.g., blurred, photophobia, night blindness, vitreous floaters) | Asymptomatic, transient, no treatment required | Symptomatic, vision changes not interfering with function, reversible | Symptomatic, vision changes interfering with function | Loss of sight |
| F6. Xerophtalmia (dry eyes) | Mild scratchiness | Symptomatic without interfering with function, requires artificial tears | Interferes with vision/function, corneal ulceration | Loss of sight |
| **G. Gastrointestinal** | | | | |
| G1. Anorexia | Adequate food intake, minimal weight loss | Symptoms requiring oral nutritional supplementation | Prolonged, requiring iv support | Requires hospitalization for nutritional support |
| G2. Constipation | Asymptomatic, transient, responds to stool softener, OTC laxatives | Symptomatic, requiring prescription laxatives, reversible | Obstipation requiring medical intervention | Bowel obstruction. Surgery required |
| G3. Diarrhea | Transient, increase of 2 – 3 stools/day over pre-treatment (no blood or mucus), OTC agents relieve | Symptomatic, increase 4 – 6 stools/day, nocturnal stools, cramping, requires treatment with prescription meds | Increase > 6 stools/day, associated with disabling symptoms, e.g., incontinence, severe cramping, partial response to treatment | Prolonged, dehydration, unresponsive to treatment, requires hospitalization |
| G4. Dyspepsia (heartburn) | Transient, intermittent, responds to OTC antacids, H-2 blockers | Prolonged, recurrent, requires prescription meds, relieved by meds | Persistent despite treatment, interferes with function, associated with GI bleeding | NA |

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| G5. GI bleed (gastritis, gastric or duodenal ulcer diagnosed-define aetiology) | Asymptomatic, endoscopic finding, haemocult + stools, no transfusion, responds rapidly to treatment | Symptomatic, transfusion ≤ 2 units needed; responds to treatment | Haematemesis, transfusion 3 – 4 units, prolonged interference with function | Recurrent, transfusion > 4 units, perforation, requiring surgery, hospitalisation |
| G6. Haematochezia (rectal bleeding) | Haemorrhodial, asymptomatic, no transfusion | Symptomatic, transfusion ≤ 2 units, reversible | Recurrent, transfusion > 3 – 4 units | > 4 units, hypotension, requiring hospitalization |
| G7. Hepatitis | Laboratory abnormalities, asymptomatic, reversible | Symptomatic laboratory abnormalities, not interfering with function, slowly reversible | Laboratory abnormalities persistent > 2 wks, symptoms interfere with function | Progressive, hepato-renal, anasarca, pre-coma or coma |
| G8. Nausea, or nausea/vomiting (use diagnostic term) | Transient, intermittent, minimal interference with intake, rapid response to meds | Persistent, recurrent, requires prescription meds, intake maintained | Prolonged, interferes with daily function and nutritional intake, periodic iv fluids | Hypotensive, hospitalization, parenteral nutrition, unresponsive to out-patient management |
| G9. Pancreatitis | Anylase elevation, intermittent nausea/vomiting, transient, responds rapidly to treatment | Amylase elevation with abdominal pain, nausea, occasional vomiting, responsive to treatment | Severe, persistent abdominal pain with pancreatitic enzyme elevation, incomplete or slow response to treatment | Complicated by shock, haemorrhage (acute circulatory failure) |

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| G10. Proctitis | Perianal pruritus, haemorrhoids (new onset), transient, or intermittent, relieved by OTC meds | Tenesmus or ulcerations, anal fissure, responsive to treatment, minimal interference with function | Unresponsive to treatment, marked interference with function | Mucosal necrosis with haemorrhage, infection, surgery required |
| **H. Musculoskeletal** | | | | |
| H1. Avascular necrosis | Asymptomatic MRI changes, non-progressive | MRI changes and symptoms responsive to rest and analgesia | MRI changes, symptoms requiring surgical intervention | Wheelchair bound; surgical repair not possible |
| H2. Arthralgia | Intermittent transient symptoms, no meds or relieved by OTC meds | Persistent or recurrent symptoms, resolve with meds, little effect on function | Severe symptoms despite meds impairs function | Debilitating, hospitalisation required for treatment |
| H3. Leg cramps | Transient, intermittent, does not interfere with function | Recurrent symptoms, minimally interferes with function or sleep, responds to meds | Persistent, prolonged interference with function or sleep, partial or no response to meds | NA |
| H4. Myalgia | Occasional; does not interfere with function | Frequent, requires meds (non-narcotic); minor effects on function | Major change in function/lifestyle, narcotic pain meds | Debilitating, profound weakness, requires wheelchair, unresponsive to meds |

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|---|---|---|---|---|
| **I. Neuropsychiatric** | | | | |
| I1. Anxiety or Depression (mood alteration) | Symptomatic, does not interfere with function; no meds | Frequent symptoms, responds to meds; interferes with ADL at times | Persistent, prolonged symptoms, partial or no response to meds, limits daily function | Suicidal ideation or danger to self |
| I2. Cerebrovascular ischaemia | NA | Single transient ischaemic event, responsive to treatment | Recurrent transient ischaemic events | Cerebrovascular vascular accident with permanent disability |
| I3. Cognitive disturbance | Subjective symptoms, transient, intermittent, not interfering with function | Objective symptoms, persisting, interferes with daily function occasionally | Persistent, or worsening objective symptoms; interferes with routine daily routine | Debilitating/disabling and permanent; toxic psychosis |
| I4. Depressed consciousness (somnolence) | Observed, transient, intermittent, not interfering with function | Somnolence or sedation, interfering with function | Persistent, progressive, obundation, stupor | Coma |
| I5. Inability to concentrate | Subjective symptoms, does not interfere with function | Objective findings, interferes with function | Persistent, prolonged objective findings or organic cause | NA |
| I6. Insomnia (in absence of pain) | Occasional difficulty sleeping, transient intermittent, not interfering with function | Recurrent difficulty sleeping; requires meds for relief; occasional interference with function | Persistent or worsening difficulty sleeping; severely interferes with routine daily function | NA |
| I7. Libido decreased | Decrease in interest | Loss of interest; influences relationship | Persistent, prolonged interfering with relationship | NA |

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|---|---|---|---|---|
| I8. Peripheral motor neuropathy | Subjective or transient loss of deep tendon reflexes; function maintained | Objective weakness, persistent, no significant impairment of daily function | Objective weakness with substantial impairment of function | Paralysis |
| I9. Peripheral sensory neuropathy (sensory disturbance) | Subjective symptoms without objective findings, transient, not interfering with function | Objective sensory loss, persistent, not interfering with function | Prolonged sensory loss or paraethesias interfering with function | NA |
| I10. Seizure | NA | Recurrence of old seizures, controlled with adjustment of medication | Recurrence/exacerbation with partial response to medication | Recurrence not controlled, requiring hospitalization; new seizures |
| I11. Vertigo (dizziness) | Subjective symptoms, transient, intermittent, no treatment | Objective findings, recurrent, meds relieve, occasionally interfering with function | Persistent, prolonged, interfering with daily function; partial response to medication | Debilitating without response to medication, hospitalization |
| **J. Pulmonary** | | | | |
| J1. Asthma | Occasional wheeze, no interference with activities | Wheezing, requires oral meds, occasional interference with function | Debilitating, requires nasal $O_2$ | Requires ventilator assistance |
| J2. Cough | Transient, intermittent, occasional OTC meds relieve | Persistent, requires narcotic or other prescription meds for relief | Recurrent, persistent coughing spasms without consistent relief by meds, interferes with function | Interferes with oxygenation; debilitating |

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| J3. Dyspnea | Subjective, transient, no interference with function | Symptomatic, intermittent or recurring, interferes with exertional activities | Symptomatic during daily routine activities, interferes with function, treatment with intermittent nasal $O_2$ relieves | Symptomatic at rest, debilitating, requires constant nasal $O_2$ |
| J4. Pleuritic pain (pleurisy) | Transient, intermittent symptoms, no treatment or OTC meds relieve | Persistent symptoms, requires prescription meds for relief | Prolonged symptoms, interferes with function, requires frequent narcotic pain relief | Debilitation, requiring hospitalisation |
| J5. Pneumonitis (pulmonary infiltrates) | Asymptomatic radiographic changes, transient, no treatment required | Symptomatic, persistent, requiring corticosteroids | Symptomatic, requiring treatment including $O_2$ | Debilitating, not reversible; or requiring assisted ventilation |
| J6. Pulmonary function decreased (FVC or carbon monoxide diffusion capacity – DLCO) | 76% – 90% of pre-treatment value | 51% – 75% of pre-treatment value | 26% – 50% of pre-treatment value | ≤ 25% of pre-treatment value |
| **Laboratory Data** | | | | |
| **K. Haematology** | | | | |
| K1. Hgb (g/dl) decrease from pre-treatment | 1.0 – 1.4 | 1.5 – 2.0 | 2.1 – 2.9, or Hgb < 8.0, > 7.0 | ≥ 3.0; or Hgb < 7.0 |
| K2. Leukopenia (total WBC) × 1000 | 3.0 – 3.9 | 2.0 – 2.9 | 1.0 – 1.9 | < 1.0 |

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| K3. Neutropenia (× 1000) | 1.5 – 1.9 | 1.0 – 1.4 | 0.5 – 0.9 | < 0.5 |
| K4. Lymphopenia (× 1000) | 1.5 – 1.9 | 1.0 – 1.4 | 0.5 – 0.9 | < 0.5 |
| K5. Platelets (× 1000) | 75 – LLN | 50 – 74.9 | 20 – 49.9; platelet transfusion required | < 20; recurrent platelet transfusions |
| **L. Chemistry** | | | | |
| L1. Hypercalcaemia (mg/dl) | 1.1 × ULN – 11.5 | 11.6 – 12.5 | 12.6 – 13.5; or symptoms present | > 13.5; or associated coma |
| L2. Hyperglycemia (mg/dl) Fasting | 140 – 160 | 161 – 250 | 251 – 500 | > 500, or associated with ketoacidosis |
| L3. Hyperkalaemia (mmol/l)*** | 5.5 – 5.9 | 6.0 – 6.4 | 6.5 – 7.0 or any ECG change | > 7.0 or any arrhythmia |
| L5. Hypocalcaemia (mg/dl) | 0.9 × LLN – 7.8 | 7.7 – 7.0 | 6.9 – 6.5; or associated with symptoms | < 6.5 or occurrence of tetany |
| L6. Hypoglycemia (mg/dl) | 55 – 64 (no symptoms) | 40 – 54 (or symptoms present) | 30 – 39 (symptoms impair function) | < 30 or coma |
| L7. Hyponatraemia (mmol/l)*** | - | 125 – 129 | 120 – 124 | < 120 |
| L8. Hypokalaemia (mg/dl)*** | - | 3.0 – 3.4 | 2.5 – 2.9 | < 2.5 |

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|---|---|---|---|---|
| L9. CPK (also if polymyositis-disease **** | 1.2 – 1.9 × ULN | 2.0 – 4.0 × ULN | 4.0 × ULN with weakness but without life-threatening signs or symptoms | > 4.0 × ULN with signs or symptoms of rhabdomyolysis or life-threatening |
| L10. Serum uric acid | 1.2 – 1.6 × ULN | 1.7 – 2.9 × ULN | 3.0 – 5.0 × ULN or gout | NA |
| L11. Creatinine (mg/dl)**** | 1.1 – 1.3 × ULN | 1.4* – 1.8 × ULN | 1.9 – 3.0 × ULN | > 3.0 × ULN |
| L12. SGOT (AST) | 1.2 – 1.5 × ULN | 1.6 – 3.0 × ULN | 3.1 – 8.0 × ULN | > 8.0 × ULN |
| L13. SGPT (ALT) | 1.2 – 1.5 × ULN | 1.6 – 3.0 × ULN | 3.0 – 8.0 × ULN | > 8.0 × ULN |
| L14. Alkaline phosphatase | 1.1 – 1.5** × ULN | 1.6 – 3.0 × ULN | 3.0 – 5.0 × ULN | > 5.0 × ULN |
| L15. T. bilirubin | 1.1 – 1.4 × ULN | 1.5 – 1.9 × ULN | 2.0 – 3.0 × ULN | > 3.0 × ULN |
| L16. LDH | 1.3 – 2.4 × ULN | 2.5 – 5.0 × ULN | 5.1 – 10 × ULN | > 10 × ULN |
| M. Urinalysis | | | | |
| M1. Haematuria | Micro only | Gross, no clots | Clots, transfusion < 2 units | Transfusion required |
| M2. Proteinuria (per 24 h) | 300 – 500 mg (tr/1+) | 501 – 1999 mg (2+) | 2 – 5.0 g (3+) nephrotic syndrome | 5.0 g (4+) anasarca |
| M3. WBC in urine | NA | NA | Indicating acute interstitial nephritis | Associated with acute renal failure |
| M4. Uric acid crystals | Present without symptoms | NA | With stones or symptoms of stones (e.g., renal colic) | Causing renal outflow obstruction and hospitalization |

* In L11, 1.5 – 1.8 × ULN is changed to 1.4 – 1.8 × ULN.

** In L14, 1.1 – 2.0 × ULN is changed to 1.1 – 1.5 × ULN.

*** In L3, L7 and L8, mg/dl is changed to mmol/l.

**** For CPK and Creatinine NCI CTC grading will be used. For CPK therefore the following gradings apply: Grade 1: > ULN – 2.5 × ULN; Grade 2: > 2.5 – 5.0 × ULN; Grade 3: > 5.0 – 10.0 × ULN; Grade 4: > 10.0 × ULN; For Creatinine the following gradings apply: Grade 1: > 1 – 1.5 × Baseline; > ULN – 1.5 × ULN; Grade 2: > 1.5 – 3.0 × Baseline; > 1.5 – 3.0 × ULN; Grade 3: > 3.0 baseline; > 3.0 – 6.0 × ULN; Grade 4: > 6.0 × ULN

## Table C-2. Criteria for Potentially Clinically Significant Vital Sign Values

| Vital Sign | Category | Criteria for Potential Clinically Significant Vital Signs |
|---|---|---|
| Systolic blood pressure | Low | Value ≤ 90 mmHg and/or decrease ≥ 20 mmHg from Baseline |
| | High | Value ≥ 160 mmHg and/or increase ≥ 20 mmHg from Baseline |
| Diastolic blood pressure | Low | Value ≤ 50 mmHg and/or decrease ≥ 10 mmHg from Baseline |
| | High | Value ≥ 100 mmHg and/or increase ≥ 10 mmHg from Baseline |
| Pulse | Low | Value ≤ 50 bpm and/or decrease ≥ 15 bpm from Baseline |
| | High | Value ≥ 120 bpm and/or increase ≥ 15 bpm from Baseline |
| Weight | High | > 7% increase from baseline |
| | Low | > 7% decrease from baseline |