Statistical Analysis Plan

NCT Number: NCT02924272

Title: An Open-Label, Rollover Protocol for Patients Previously Enrolled in Takeda-Sponsored Ixazomib Studies

Study Number: C16027

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STATISTICAL ANALYSIS PLAN

STUDY NUMBER: C16027

An Open-Label, Rollover Protocol for Patients Previously Enrolled in Takeda-Sponsored Ixazomib Studies

Ixazomib Rollover Study

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Based on:

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Date	Amendment Number	Amendment type	Reason
23 March 2017	Initial SAP	Not applicable	
04 February 2021	2.0		Initial SAP not signed off
01 February 2023	3.0	Substantial amendment	Updated to align with protocol v3.0. Protocol deviation categories added.
15 September 2023	4.0		Previous SAP not signed off

1.0 APPROVAL SIGNATURES

Electronic signatures can be found on the last page of this document.

2.0 TABLE OF CONTENTS

3.0 LIST OF ABBREVIATIONS

Abbreviation	Term
AE	adverse event
AL amyloidosis	systemic light-chain amyloidosis
ASCT	autologous stem cell transplant
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
BUN	blood urea nitrogen
CO2	carbon dioxide
eCRF	case report form (electronic or paper)
CRO	contract research organization
CSR	clinical study report
ECG	electrocardiogram
EOS	end of study
EOT	end of treatment
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	g-glutamyl transferase
ICH	International Conference on Harmonisation
IEC	independent ethics committee
IP	investigational product
IRB	institutional review board
IV	Intravenous
IVRS	interactive voice response system
IWRS	interactive web response system
LDH	lactate dehydrogenase
LenDex	lenalidomide plus dexamethasone
MedDRA	Medical Dictionary for Regulatory Activities
MLN2238	research name for ixazomib, the biologically active boronic acid form of the drug substance
MLN9708	research name for ixazomib citrate, the stable citrate ester of ixazomib
MM	multiple myeloma
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NOS/NEC	MedDRA terms for “Not otherwise specified” and “Not elsewhere classified”
NDMM	newly diagnosed multiple myeloma
PN	peripheral neuropathy
RRAL amyloidosis	relapsed and/or refractory systemic light-chain amyloidosis
RRMM	relapsed and/or refractory multiple myeloma
SAE	serious adverse event
SAP	statistical analysis plan
SmPC	Summary of Product Characteristics
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
US	United States
USPI	United States Prescribing Information
WHO	World Health Organization

4.0 OBJECTIVES

4.1 Primary Objectives

The primary objective is to provide continued access to ixazomib and/or other study drugs from an ixazomib parent study and to evaluate the long-term safety profile of ixazomib.

4.2 Study Design

This is an open-label, multicenter, rollover study to provide continued access to ixazomib and/or other study drugs from a designated ixazomib parent study (ie, Studies C16003, C16005, C16006, C16007, C16008, C16010 Global, C16011, C16013, C16014 Global and Korean Continuation, C16017, C16020, C16029, and C16047) when the patient has no other means to access study treatment. The study will also evaluate the long-term safety profile of ixazomib in those patients who continue to receive ixazomib. The patient population will consist of patients who have previously received and tolerated treatment in a Takeda-sponsored clinical study of ixazomib, and in the investigator's opinion and approved by the Takeda medical monitor, may benefit from continued therapy with 1 or more of the drugs from a parent protocol (eg, response to therapy or stable disease without evidence of disease progression).

Patients participating in a designated ixazomib parent study will enter the rollover study at the time-point when they have completed the end of treatment (EOT) visit in the parent study and when the rollover study is active at the investigative site. Patients should enter the study within a maximum of 8 weeks of their last dose of ixazomib in the parent study or as agreed upon with the Takeda clinician/designee. Following enrollment, patients may receive study drug(s) until they experience disease progression, clinical deterioration in the investigator's judgment, experience an unacceptable toxicity, withdraw consent, pursue an alternative therapy, meet other study-specified reasons for discontinuation of study drug, or until the patient is transitioned to ixazomib/other therapy through commercial channels.

The disease assessments are recommended to be performed per standard of care. At the end of study (EOS) visit, an overall investigator assessment of best response during this rollover study and the investigator assessment of date of progression will be captured in the electronic case report forms (eCRFs).

Local safety-related laboratory evaluations and vital sign measurements will be performed according to the parent study schedule; however, they will only be recorded in the eCRFs prior to the first dose of ixazomib in the rollover study, at the EOT, and as spontaneously reported by the investigator. Electrocardiogram assessments will only be performed as clinically indicated. During treatment, dosing modification decisions will be made per the parent study. Systemic treatment with strong cytochrome P-450 (CYP) 3A inducers is prohibited during the study. The procedures and medication prohibited in the patient's parent study are prohibited during this study.

5.0 ANALYSIS ENDPOINTS

5.1 Primary Endpoints

The primary endpoint is safety which will be assessed by the incidence of the following treatment-emergent adverse events (TEAEs):

- All serious adverse events (SAEs).
- All ≥Grade 3 AEs.
- ≥Grade 2 peripheral neuropathy.
- New primary malignancies.
- Any AE resulting in dose modification or discontinuation of any study drug.
- Any other AE that in the opinion of the investigator is a clinically significant event.

6.0 DETERMINATION OF SAMPLE SIZE

There is no statistical hypothesis and no power consideration in this study. The estimated number of patients to be enrolled is approximately 250. Enrollment is defined as when the patient receives the first dose of study drug in this rollover study.

7.0 METHODS OF ANALYSIS AND PRESENTATION

7.1 General Principles

In general, analyses will be primarily descriptive in nature. No formal statistical tests will be performed.

Summary tabulations will be presented to display the number of observations, mean, standard deviation, median, minimum, and maximum for continuous variables. Means and medians will be presented to 1 more decimal place than the recorded data. The standard deviations (SDs) will be presented to 2 more decimal places than the recorded data.

For categorical variables, the number and percentage per category for categorical data will be presented, unless specified otherwise. The denominator for the proportion will be based on the number of patients who provided non-missing responses to the categorical variable.

Patients will be analyzed by whether they received monotherapy of ixazomib or ixazomib in combination with other anticancer agent(s) according to the regimen the patient was receiving at the time of rollover from the parent study, or according to the required modification from a parent study. A windowing convention will be used to determine the analysis value for a given study visit for observed data analyses.

At the time of clinical study report (CSR) lock, all relevant data will be queried and cleaned; a database snapshot will be taken and used for the CSR.

All statistical analyses will be conducted using SAS® Version 9.4, or higher.

7.1.1 Study Definitions

Ixazomib in combination with lenalidomide and dexamethasone was approved by the US FDA in November 2015 for the treatment of patients with multiple myeloma who have received at least 1 prior therapy. The exploration of the drug is ongoing in other indications. This study will enable continued access to ixazomib for qualified patients who have participated in previous designated ixazomib clinical studies and have derived clinical benefit until ixazomib is available to the patient through commercial channels, or until patient treatment discontinuation, whichever is sooner up to approximately 5 years post study entry. Upon the review and agreement with the Takeda medical monitor, done every 24 months, continued access to ixazomib will be allowed for patients who in the investigator's opinion are deriving clinical benefit from ixazomib.

7.1.2 Definition of Study Days

Study Day 1 is defined as the date on which a patient is administered their first dose of medication in the rollover study. The Study Entry/Day 1 visit for this rollover study should be coincident with or as soon as possible after the EOT/EOS visit in the parent study. Other study days are defined relative to the Study Day 1 with Day 1 being Study Day 1 and Day -1 being the day prior to Study Day 1.

Baseline values are defined as the last observed value before the first dose of study drug in the roll-over study.

Unless otherwise specified, the reference for assessment during this study will be based on the value collected at the time closest to, but before, the start of study drug administration in the rollover study. The end of parent study assessment could serve as the baseline evaluation if occurring within 8 weeks from the start of rollover study.

These imputation rules will be applicable where baseline/screening dates are incomplete;

- If only the day-component is missing, the first day of the month will be used if the year and the month are the same as those for the first dose of study drug. Otherwise, the fifteenth will be used.
- If only the year is present, and it is the same as the year of the first dose of study drug, the fifteenth of January will be used unless it is later than the first dose, in which case the date of the first of January will be used.
- If only the year is present, and it is not the same as the year of the first dose of study drug, the fifteenth of June will be used.

7.1.3 Definition of Study Visit Windows

All data will be categorized based on the scheduled visit at which it was collected. These visit designators are predefined values that appear as part of the visit tab in the eCRF. Notwithstanding visit windows used in the course of treatments. During the treatment period, there will be a +/- 2-day window for study visits unless otherwise noted. Therefore, a scheduled visit will account appropriately for the windows applied without any effect on the visit schedule designation.

Where a patient is provided a 3-month supply of study medication and an on-site visit is not completed for the 2nd and 3rd dose cycles, the date of visit should be entered as at the date of the first dose of study drug.

7.1.4 Conventions for Missing Adverse Event Dates

All data will be categorized based on the scheduled visit at which it was collected. These visit designators are predefined values that appear as part of the visit tab in the eCRF.

If an AE start date is missing, the derived start date will be calculated as the first non-missing valid date from the following list (in order of precedence):

a. First study medication date in the C16027 study

b. Informed consent date (for SAEs only)

AEs or SAEs, with start date that are completely or partially missing will be imputed as follows:

1. If the start date has month and year but day is missing
   a. If the start month and year are same as that of first dose date, the first dose date will be used instead. If the onset month and year are different from that of the first dose date, then the first day of the month will be used.
   b. After imputation, the imputed dates will be compared against the stop date. If this imputed date is later than the stop date (possibly imputed), then the stop date will be used instead.
2. If the start date has year, but day and month are missing
   a. If the start year is same as that of first dose date, then the first dose date will be used instead.
   b. If start year is different than that of the first dose date, the 1st of January of the year will be imputed.
   c. After the imputation, the imputed dates will be compared against the dose stop date. If this imputed date is later than the stop date (possibly imputed), then the stop date will be used instead.
3. If the start date of an adverse event is completely missing, then it is imputed with the first dose date.
4. When imputing a start date ensure that the new imputed date is sensible, that is, the imputed date is prior to the end date of the AE.

For AEs or SAEs, a missing or incomplete end date will be imputed according to the following conventions:

1. If an end date is missing, the derived end date will be imputed as the last assessment date, assuming that the last assessment occurs after the AE start. If the last assessment occurs prior to the AE start date, the derived end date will be imputed as the AE start date.
2. If an end date is incomplete, the derived end date will be calculated following:

a. Missing day, but month and year present: the day will be imputed as the last date (for example February 2021 will be imputed as 28 February2021) of the month.

b. Missing day and month, but year present: the day and month will be imputed as the 31st December of the year.

c. If the imputed AE end date occurs after the database lock date, the imputed AE end date will be imputed as the database lock date

d. After the imputation, the imputed dates will be compared against the date of death, if available. If the imputed date is later than the date of death, the date of death will be used as the imputed date instead.

3 If the stop date of an adverse event is completely missing, then this event will be regarded as ongoing and will be included in the summary table.

7.1.5 Conventions for Missing Concomitant Medication/Procedure Dates

Concomitant therapies with start date that are completely or partially missing will be analyzed as follows:

If the start date has month and year but day is missing, the therapy will be included in the summary table if the month and year are:

a) On or after the month and year of the date of the first dose of study drug and

b) On or before the month and year of the date of the last dose of study drug plus 30 days.

If the start date has year, but day and month are missing, the therapy will be included in the summary table if the year is:

a. On or after the year of the date of the first dose of study drug and

b. On or before the year of the date of the last dose of study drug plus 30 days.

If the start date of concomitant therapies is completely missing and the stop date of concomitant therapies is prior to the date of the first dose of study drug, then this therapy will not be included.

If the start date of concomitant therapies is completely missing and the stop date of concomitant therapies is on or after the date of the first dose of study drug, then the therapy will be included in the summary table.

When imputing a start date ensure that the new imputed date is sensible, that is, the imputed date is prior to the end date of the concomitant medication.

If the stop date is missing, partial or "continuing:":

a. If the day is missing, the stop day will be the last day of the month reported

b. If the month is missing, the stop month will be the month during which the last assessment occurred

c. If the month and day are missing, the stop date will be imputed in this order; the month according to (b), and the day according to (a).

d. If the year or the entire date is missing or if the medication is "continuing", the date will be the date of the last assessment.

If the start date and stop date of concomitant therapies are completely missing, then the therapy will be included in the summary table.

7.2 Analysis Sets

Data will be presented by the entire Safety population. This will include all enrolled patients who receive at least 1 dose of ixazomib medication.

7.3 Disposition of Patients

Summary of patient disposition will be presented by monotherapy of ixazomib or ixazomib in combination, and will include the number and percentage of patients for the following:

- Number of Patients Enrolled by Site and Treatment dosage group
- Disposition of patients - this should include;
    - patients on-going on study,
    - patients discontinued from the study, and
    - primary reason to discontinue from the study. All percentages will be based on the number of patients in the Safety population.

Important Protocol Deviations – Identification of significant protocol deviations will be according to the Clinical Study Protocol Deviations Management Plan (version 3.0) for the study.

Summary of significant protocol deviations will be presented by monotherapy of ixazomib or ixazomib in combination, and will include the number and percentage of patients with a significant deviation in at least one of the following categories:

- Entered study but did not satisfy entry criteria (inclusion/exclusion)
- Informed consent
    - Failure to obtain initial written consent prior to study-related procedures being performed
    - Patient was not re-consented in a timely manner, or at all
    - Use of Incorrect Informed Consent Form
- No safety lab results collected prior to dosing
- Endpoint not assessed correctly/Safety reporting
- Used prohibited concomitant medication

- Treatment of patient before receipt of IRB/EC approval
- Study treatment compliance
    - Non adherence to scheduled IP dose administration times
    - Patient IP compliance- major overdose
- Other protocol deviations
    - Pregnancy event
    - Pt met criteria for discontinuation but remained on treatment

By-patient listings will present data on;

- Patient disposition including.
    - Study Information, including date first patient signed ICF, date of last patient's last visit/contact, date of last patient's last procedure for collection of data for primary endpoint, dose level, and cycle duration.
    - MedDRA Version,
    - WHODrug Version and
    - Any other information of clinical importance
- Protocol deviations

7.4 Demographic and Other Baseline Characteristics

Demographic and baseline characteristics will be summarized and presented by monotherapy of ixazomib or ixazomib in combination. For continuous variables, summary statistics (mean, median, standard deviation, minimum and maximum of non- missing values) will be generated. For categorical variables, counts and percentages of each possible value will be generated.

Demographic and baseline characteristics such as age, age group (<65, >=65 - <75, >=75), sex and weight, will be summarized by monotherapy of ixazomib or ixazomib in combination. Age will be calculated from date of birth to date of enrollment.

Listing of by patient demographic and baseline characteristics will also be provided.

7.5 Concomitant Medications and Procedures

Only concomitant medications and therapeutic procedures related to the treatment of AEs, that are to be reported in this study, will be recorded in the eCRF. Concomitant medications and will be summarized and reported separately by monotherapy of ixazomib or ixazomib in combination. This includes all medications and procedures meeting this criterion initiated on/after the date of first dose of ixazomib and within 30 days after the last dose date.

Concomitant medication will be assessed through the study period will be classified by generic terms according to the World Health Organization (WHO) drug dictionary.

The number and percentage of patients receiving concomitant medications or procedures will be tabulated separately by Anatomical Therapeutic Chemical (ATC) classification pharmacological subgroup and WHO drug generic term for monotherapy of ixazomib or ixazomib in combination for the safety population.

By-patient listing will also be presented for concomitant medications and/or procedures.

7.6 Study Drug Exposure and Compliance

A summary of drug exposure to ixazomib will be characterized by number of treated cycles, numbers and percentages of patients who had ≥1, ≥2 , …, and ≥ 18 treated cycles, total amount of dose taken, total number of dose taken, relative dose intensity (%) and drug compliance in the safety population. Aggregate summary of numbers and percentages of patients who had 1 to 6, 7 to 12, 13 to 18, and ≥ 19 treated cycles will also be presented in the same table. All summaries will be presented by monotherapy of ixazomib or ixazomib in combination.

Extent of exposure (days), which is calculated as (last dose date of study drug – first dose date of study drug + 1), will also be presented. The number of patients, and summary of duration of exposure (days) will be provided as mean, SD, median, minimum and maximum duration of exposure.

A treated cycle is defined as a cycle in which the patient received any amount of any study drug. A length of treatment cycle (days) is determined per the patient's parent study (e.g., 21- or 28-day cycles).

Drug exposure is presented by relative dose intensity (RDI) and calculated as follows:

Relative dose intensity (%) = 100 * (Total amount of dose taken) / (Total prescribed dose of treated cycles).

The number of patients with 100% relative dose intensity, 80% to < 100%, 50% to < 80%, and < 50% will be summarized by monotherapy of ixazomib or ixazomib in combination, and for all patients.

Percent compliance is calculated as 100% * (study drug taken in mg) / (study drug expected to be taken in mg). Only reduced prescribed or increased prescribed or dose hold or discontinued permanently will change the expected prescribed dose.

The actions on the study drug, ixazomib, such as dose reduction, held, missed, increased, delayed, or discontinued permanently will be summarized separately for monotherapy of ixazomib or ixazomib in combination, and for all patients. and by cycle aggregates such as for Cycles 1-6, 7-12, 13-20 and >20 if there is sufficient data for analysis.

Dosing data will also be presented in a by-patient listing.

7.7 Efficacy Analysis

No efficacy analyses are planned for this study as there is no statistical hypothesis testing. The overall investigator assessment of best response obtained during this rollover study and investigator assessment of date of progression will be listed.

7.8 Pharmacokinetic/Pharmacodynamic Analysis

Not applicable

7.9 Other Outcomes

Not applicable

7.10 Safety Analysis

Safety analysis will include assessments of:

- Adverse events
- All clinically relevant deterioration in clinical laboratory assessments
- Vital signs
- Other clinically relevant assessments

7.10.1 Adverse Events

All reported adverse events, including all clinically relevant deterioration in laboratory assessments or other clinical findings, will be coded using the current Medical Dictionary for Regulatory Activities (MedDRA) version at time of database lock. Severity of AEs will be determined according to NCI CTCAE, Version 5.0 or appropriate version. Treatment-emergent AE is defined as any AE that occurs after administration of the first dose of the study treatment through 30 days after the last dose of the study treatment. TEAEs will be tabulated according to the MedDRA by system organ class and preferred terms separately for monotherapy of ixazomib or ixazomib in combination. Adverse events of interest that are ongoing at the time of study entry will be recorded in the eCRF as baseline AEs.

The following TEAEs will be summarized using the safety analysis set:

- All SAEs.
- All ≥Grade 3 AEs.
- ≥Grade 2 peripheral neuropathy.
- New primary malignancies.
- Any AE resulting in dose modification or discontinuation of any study drug.

- Any other AE that in the opinion of the investigator is a clinically significant event. This includes any clinically relevant deterioration in laboratory assessments or other clinical finding. These events will be included as part of the overall AE table and not reported separately.

Patients with the same AE more than once will have that event counted only once within each body system and once within each preferred term.

An overall summary TEAE table will include numbers and percentages of patients who had at least one TEAE of the above-mentioned categories, respectively.

Most commonly reported (at least 10% of all patients) treatment-emergent AEs will be presented by preferred term only.

In this study, intensity for each AE, including any lab abnormality, will be determined using the NCI CTCAE, Version 5.0 or appropriate version.

A by-patient listing of all deaths regardless of whether on study or not will also be presented. In this listing, on-study deaths will be flagged. On-study death is defined as the death that occurs between the first dose of any study drug and 30 days of the last dose of any study drug.

7.10.2 Serious Adverse Events

Serious adverse events, including all TEAEs of the following characteristics;

- Results in **death**.
- Is **life-threatening**: Refers to an AE in which the patient was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe.
- Requires inpatient **hospitalization or prolongation of an existing hospitalization** (see Section 10.2 of Protocol).
- Results in **persistent or significant disability or incapacity**: Defined as a substantial disruption of a person's ability to conduct normal life functions.
- Is a **congenital anomaly/birth defect**.
- Is a **medically important event**. This refers to an AE that may not result in death, be immediately life threatening, or require hospitalization, but may be considered serious when, based on appropriate medical judgment, may jeopardize the patient, require medical or surgical intervention to prevent 1 of the outcomes listed above, or involves suspected transmission via a medicinal product of an infectious agent. Examples of such medical events include:
    - allergic bronchospasm requiring intensive treatment in an emergency room or at home,
    - blood dyscrasias or convulsions that do not result in inpatient hospitalization,

- development of drug dependency or drug abuse;
- any organism, virus, or infectious particle (eg, prion protein transmitting transmissible spongiform encephalopathy), pathogenic or nonpathogenic, is considered an infectious agent.

The number and percentage of patients experiencing at least one SAE will be summarized by MedDRA primary system organ class, and preferred term by monotherapy of ixazomib or ixazomib in combination.

In addition, a by-patient listing of all SAEs will be presented regardless of status or causality.

7.10.3 All Grade 3 or Higher Adverse Events

The number and percentage of patients experiencing at least one grade 3 or higher treatment-emergent adverse event will be summarized by MedDRA primary system organ class, and preferred term for monotherapy of ixazomib or ixazomib in combination.

In addition, a by-patient listing of all grade 3 or higher adverse events will be presented (the listing will contain all grade 3 or higher AEs regardless of treatment-emergent AE status).

7.10.4 All Grade 2 or Higher Peripheral Neuropathy Events

A peripheral neuropathy (PN) event is defined as the treatment-emergent adverse event in the high-level term of peripheral neuropathies NEC according to MedDRA.

A PN event is considered resolved if its final outcome is resolved with no subsequent PN event of the same preferred term occurring on the resolution date or the day before and after. A PN event is considered as improved if the event improves from the maximum grade.

The number of patients with grade 2 or higher PN events, resolution of any grade 2 or higher PN event, improvement of any grade 2 or higher PN event during the treatment period and entire study period may be summarized for monotherapy of ixazomib or ixazomib in combination if data permits.

7.10.5 New Primary Malignancies

The incidence proportions for new primary malignancies will be calculated for the safety population based on the new primary malignancy assessment. The incidence proportion is defined as the percentage of the patients reporting any new primary malignancy in the safety population with available information. A by-patient listing of new primary malignancies will be presented for monotherapy of ixazomib or ixazomib in combination.

7.10.6 Adverse Events Resulting in Dose Modification or Discontinuation of Study Drug

The number and percentage of patients experiencing at least one treatment-emergent adverse event resulting in dose modification or discontinuation of any study drug will be summarized by MedDRA system organ class and preferred term for monotherapy of ixazomib or ixazomib in combination.

A by-patient listing of AEs resulting in dose modification or discontinuation of any study drug will be presented.

7.10.7 Deaths

A by-patient listing of the deaths together with the cause of death, will be presented. All deaths occurring on-study and during follow-up will be displayed regardless of AE status for monotherapy of ixazomib or ixazomib in combination.

7.10.8 Clinical Laboratory Evaluations

Laboratory test results from local laboratory will be used. Laboratory test results will be summarized according to scheduled sample collection visit; at baseline and EOS, for monotherapy of ixazomib or ixazomib in combination.

Lab parameters to be analyzed are as follows:

- Hematology: Leukocytes, Erythrocytes, Hemoglobin, Hematocrit, Platelet count (and character descriptors), Lymphocyte count, Monocyte count, Eosinophil count, Basophil count, Neutrophil count, and Blasts.
- Serum Chemistry: Glucose, Blood urea nitrogen, Creatinine, Sodium, Potassium, Chloride, Carbon Dioxide, Urate or Uric acid, Calcium, Magnesium, Phosphate, Albumin, Bilirubin, Aspartate aminotransferase (AST), Alanine aminotransferase (ALT), Alkaline phosphatase, Lactate Dehydrogenase (LDH), Gamma Glutamyl Transferase.
- Serum β-hCG pregnancy test for women of childbearing potential

By-patient listings of scheduled laboratory along with unscheduled test results including hematology, serum chemistry and β-hCG pregnancy test for women of childbearing potential will provided. Unscheduled hematology and chemistry laboratory assessments are performed if clinically indicated.

For the purposes of listings, all laboratory values will be converted to standardized units where appropriate. If a lab value is reported using a non-numeric qualifier (e.g., less than (<) a certain value, or greater than (>) a certain value), the given numeric value will be used in the summary statistics, ignoring the non-numeric qualifier.

7.10.9 Vital Signs

A by-patient listing for the actual values at baseline and changes at end of study from baseline for vital sign parameters including systolic blood pressure, diastolic blood pressure, heart rate, and body weight, will be presented.

7.10.10 12-Lead ECGs

Not applicable

7.10.11 Other Observations Related to Safety

Not applicable

7.11 Interim Analysis

Not applicable

7.12 Changes in the Statistical Analysis Plan

None

8.0 REFERENCES

1. Durie BG, Harousseau JL, Miguel JS, Blade J, Barlogie B, Anderson K, et al. International uniform response criteria for multiple myeloma. Leukemia 2006; 20(9): 1467-73.
2. U.S. Department of Health and Human Services, National Institutes of Health National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE). Version 4.03. 14 June 2010.

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