Statistical Analysis Plan

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STATISTICAL ANALYSIS PLAN

A Single-Arm, Open-Label Study of Oral Ixazomib Maintenance Therapy After Initial Therapy in Patients With Newly Diagnosed Multiple Myeloma Not Treated With Stem Cell Transplantation

Protocol #: C16021

Protocol Amendment #: 10 (China Continuation Study)

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Approval Signatures

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LIST OF ABBREVIATIONS AND GLOSSARY OF TERMS

Abbreviation	Term
AE	adverse event
ALC	absolute lymphocyte count
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	area under the curve
BMA	bone marrow aspirate
CDF	cumulative distribution function
CI	confidence interval
CO_2	carbon dioxide
CR	complete response
CT	computed tomography
del	deletion
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
[redacted]	[redacted]
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30
EOT	End of Treatment (visit)
[redacted]	[redacted]
[redacted]	[redacted]
FA	final analysis
GGT	gamma glutamyl transferase
HDT	high-dose therapy
HRQOL	health related quality of life
[redacted]	[redacted]
IA	interim analysis
IDMC	independent data monitoring committee
IRC	independent review committee
ISC	independent statistical center
ISS	International Staging System
ITT	intent-to-treat
IXRS	interactive web/voice response system
K-M	Kaplan-Meier
LDH	lactate dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities

Abbreviation	Term
MID	minimally important difference
MM	multiple myeloma
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NDMM	newly diagnosed multiple myeloma
NEC	not elsewhere classified
NGS	generation sequencing
NK	natural killer (cells)
NPM	new primary malignancy
OS	overall survival
PD	progressive disease
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetic(s)
PN	peripheral neuropathy
PP	per-protocol
PR	partial response
PRO	patient-reported outcome
SAE	serious adverse event
SAP	statistical analysis plan
SCT	stem cell transplant/therapy
SD	stable disease
TTNT	time to next-line therapy
TTP	time to progression
VGPR	very good partial response
[redacted]	[redacted]
WBC	white blood cell (count)
WHO	World Health Organization

1. INTRODUCTION

In general, the purpose of the statistical analysis plan (SAP) is to provide a framework that addresses the protocol objectives in a statistically rigorous fashion, with minimized bias and analytical deficiencies. Specifically, this plan has the following purpose:

To prospectively (a priori) outline the types of analyses and data presentations that will address the study objectives outlined in the protocol, and to explain in detail how the data will be handled and analyzed, adhering to commonly accepted standards and practices of biostatistical analysis in the pharmaceutical industry.

1.1 Study Design

The China Continuation part of Study C16021 was originally designed as a randomized, double-blind, placebo-controlled, multicenter study in patients in China with NDMM who have not undergone SCT. Upon implementation of Amendment 08, the China Continuation will now be a single-arm, open-label study of ixazomib maintenance for patients in China with NDMM who have not undergone SCT. Patients who have not undergone SCT may not have done so because of frailty due to advanced age (eg, ≥65 years) or comorbidity or because they decline SCT for other reasons. Patients enrolled under Amendment 08 will be enrolled based on the same eligibility criteria.

The purpose of the study is to evaluate the role of maintenance therapy with ixazomib in patients who, in their initial therapy before study enrollment, have been treated to achieve a major response category (PR or better) that is judged to be their best response by the investigator/treating physician. Patients must have received initial therapy for 6 to 12 months, according to standard of care, and have met all additional inclusion/exclusion criteria before study enrollment. The initial therapy permitted is any standard of care MM therapy. Upon implementation of Amendment 08, new eligible and consenting patients are to be enrolled no later than 60 days after the last dose of initial therapy. For patients who were previously randomized to the placebo arm who reconsent and cross over to ixazomib, reconsenting more than 60 days after the last dose of initial therapy is permitted. Upon implementation of Amendment 08, all patients received open-label ixazomib.

The Treatment period of the study is defined as the interval during which any enrolled patient is receiving ixazomib; 28-day treatment cycles will be used throughout this period. Patients will have study assessments performed at regular treatment-cycle intervals while they are participating in the study: 3 times during the first cycle (weekly; Days 1, 8, and 15),

twice during the second cycle (Days 1 and 8), and then once per treatment cycle for the remainder of their participation in the Treatment period, for approximately 24 months (equivalent to 26 cycles [if no cycle delays], to the nearest complete cycle) or until they experience PD or unacceptable toxicity, whichever occurs first. The exception to this is patients who have their dose increased at Cycle 5; these patients will have study assessments performed twice during Cycle 5 (on Days 1 and 8).

Prior to implementation of Amendment 08, 10 patients have been randomized and treated in the China Continuation part of Study C16021. Patients who were randomized to study drug (ixazomib or placebo) prior to implementation of Amendment 08 and who are still on study treatment will complete their current cycle of treatment and be unblinded.

Upon implementation of Amendment 08, the study objectives are now focused on long-term tolerability and efficacy of ixazomib in patients in China, so as to evaluate the consistency of the safety and efficacy of ixazomib maintenance between the China population and the C16021 global study population. There will be 1 IA for the safety and efficacy endpoints. This IA will be the primary analysis for the China Continuation and will be performed approximately 12 months after the additional ~20 patients have been enrolled under this amendment. The safety and efficacy endpoints will be assessed in the overall Chinese patient population (patients from China who were enrolled in the ixazomib arm of the C16021 global study, patients in the ixazomib arm of the China Continuation before implementation of Amendment 08, all patients enrolled in the China Continuation under Amendment 08, and patients who were randomized to the placebo arm before implementation of Amendment 08 and who crossed over to the ixazomib arm). The final analysis will be performed when all patients in the China Continuation are off study treatment and have completed the EOT visit, or upon termination of the study by the sponsor, whichever occurs earlier.

1.2 Study Objectives

The primary objective is:

- To determine the long-term safety and tolerability of ixazomib maintenance therapy

The secondary objectives are:

- To determine the progression-free survival (PFS), defined as the time from date of the first dose to PD or death from any cause, in patients in China with NDMM who

have had a major response—defined as CR, VGPR, or PR—to initial therapy and who have not undergone SCT

- To determine overall survival (OS)
- To determine whether response at study entry is improved or maintained
- To determine the time to progression (TTP)
- To determine the time to next-line therapy (TTNT)
- To assess the incidence of new primary malignancy in patients receiving ixazomib maintenance therapy
- To assess health-related quality of life (HRQOL) as measured by the Global Health Status/Quality of Life (QOL) domain of the EORTC QLQ-C30 in patients who receive ixazomib maintenance therapy
- To assess the correlation between frailty status and PFS and OS in patients receiving ixazomib maintenance therapy
- To collect PK data to contribute to population PK and exposure-response (safety/efficacy) analysis
- To evaluate the resolution and improvement of PN, if it occurs, in patients receiving ixazomib maintenance therapy

The exploratory objectives are:

- [redacted]
- [redacted]
- [redacted]

[redacted]

2. POPULATIONS FOR ANALYSIS

All analyses will be performed on the Overall Chinese Patient Population, defined as follows:

- Patients from China who were enrolled in the ixazomib arm of the C16021 global study, PLUS
- Patients in the ixazomib arm of the China Continuation before implementation of Amendment 08, PLUS
- All patients enrolled in the China Continuation under Amendment 08.
- Patients who were randomized to the placebo arm prior to implementation of Amendment 08 and who cross over to the ixazomib arm

All Chinese patients listed in the above bullets constitute the population of interest for this study. Subsets from this population of interest will be derived and used for analysis, as follows:

2.1 Efficacy Population

The Efficacy population is defined as all patients who receive ixazomib treatment for the duration of their study participation. Patients who were randomized to the placebo arm and crossed over to the ixazomib arm upon implementation of Amendment 08 will not be included in the Efficacy population. The Efficacy population will be used for the efficacy analyses, [redacted] and patient-reported outcome (PRO) analyses. Moreover, PRO assessments using the EORTC QLQ-C30 [redacted] will be analyzed using patients with PRO measurements at study entry and at least one post study entry measurement in the Efficacy population.

2.2 Safety Population

Ixazomib Safety population: The Ixazomib Safety population is defined as all patients who receive at least 1 dose of ixazomib. Patients will be analyzed according to the treatment they

actually received; patients who were randomized to the placebo arm prior to implementation of Amendment 08 and who cross over to the ixazomib arm will contribute safety data from the time they initiate ixazomib onward. The primary analysis of safety will focus on the Ixazomib Safety population.

Placebo Safety population: The Placebo Safety population is defined as all patients who receive at least 1 dose of placebo. Patients will be analyzed according to the treatment they actually received; patients who were randomized to the placebo arm prior to implementation of Amendment 08 and who cross over to the ixazomib arm will contribute safety data to this population only during the time they receive placebo. Adverse events data from this patient population will be listed.

The Ixazomib Safety population will be used for all safety-related analyses such as adverse events (AE), concomitant medications, laboratory tests, and vital signs.

2.3 Per-Protocol Population

The Per-Protocol (PP) population is a subset of the Efficacy population and consists of all patients who do not have major protocol violations.

The PP population will be used as a sensitivity analysis of the Efficacy population for the efficacy endpoint, PFS.

2.4 Response-Evaluable Population

The Response-Evaluable population is a subset of the Efficacy population and consists of all patients who have a baseline and at least 1 post-baseline response assessment. The Response-Evaluable population is used for the analyses of disease response related endpoints.

3. HYPOTHESES AND DECISION RULES

Although there will be no formal statistical hypothesis testing performed, this study will be practice-informing, and hence, summary statistics will be employed.

4. STATISTICAL METHODOLOGY

In general, summary tabulations will be displayed by the number of observations, mean, and standard deviation, median, minimum, and maximum for continuous variables, and the

number and percentage per category for categorical data. The Kaplan-Meier (KM) survival curves and 25th, 50th (median), and 75th percentiles will be provided along with their 2-sided 95% confidence intervals (CIs) for time-to-event data.

4.1 Sample Size Justification

The primary objective of the China Continuation is to allow the continued evaluation of any emerging safety signals and efficacy trends in patients in China. Prior to implementation of Amendment 08, 10 patients had been randomized and treated in the China Continuation. An additional ~20 patients are to be enrolled upon implementation of Amendment 08 for a total of approximately 30 patients overall.

With 30 patients, if the true rate for an AE is 10%, the probability of observing at least one patient with that AE is more than 95%. Similarly, if the true rate for an AE is 5%, the probability of observing at least one patient with that AE is more than 79%. Thus, the sample size is enough to give a large probability of observing AEs that are expected to commonly occur (ie, 5% or more) in this population.

4.2 Randomization and Stratification

Upon implementation of Amendment 08, there will be no randomization or stratification of patients. All patients will receive open-label ixazomib.

4.3 Blinding and Unblinding

Upon implementation of Amendment 08, the China Continuation part of Study C16021 will transition from a double-blind, placebo-controlled design to an open-label, single-arm design (ixazomib only). Individual treatment assignments are now available in the IXRS.

4.4 Data Handling

4.4.1 Methods for Handling Missing Data

All available efficacy and safety data will be included in data listings and tabulations. Data that are potentially spurious or erroneous will be examined according to standard data management operating procedures.

In general, missing data will be treated as missing, and no data imputation will be applied, unless otherwise specified. For PRO data, handling of missing data will be based on published instrument specific methods and guidelines.

4.4.1.1 Missing/Partial Dates in Screening Visit

The following rules apply to dates recorded during the Screening visits:

- 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 15th will be used.
- If only a year is present, and it is the same as the year of the first dose of study drug, the 15th 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, unless other data indicate that the date is earlier.
- If only a year is present, and it is not the same as the year of the first dose of study drug, the 15th of June will be used, unless other data indicate that the date is earlier.

4.4.1.2 Missing/Partial Dates in Adverse Events/Concomitant Therapies/Subsequent Therapies

4.4.1.2.1 Missing/Partial Dates in Adverse Events

Adverse events with start dates that are completely or partially missing will be imputed as follows:

- If month and year are known but day is missing
  - If month and year are the same as month and year of first dose date, then impute to first dose date
  - If month and year are different than month and year of first dose date, then impute to first date of the month
- If year is known but day and month are missing
  - If year is same as year of 1st dose date, then 1st dose date will be used instead
  - If year is different than year of 1st dose date, then 1st of January of the year will be imputed.
- If all is missing, then it is imputed with 1st dose date.

Imputing missing AE start date is mandatory. After the imputation, all imputed dates are checked against the start dates to ensure the stop date does not occur before start date. If the imputed stop date occurs prior to start date, then keep the imputed date same as the start date.

Adverse events with stop dates that are completely or partially missing will be imputed as follows:

- If "ongoing" is checked, no imputation is necessary.
- If month and year are known but day is missing, the last day of the month will be imputed
- If year is known, but day and month are missing,
  - If YYYY < year of last dose, then 31st of December will be imputed
  - If YYYY = year of last dose, then 31st of December will be imputed
  - If YYYY > year of last dose, then 1st of January will be imputed
- If all are missing, then impute date to 31st of December, in the year of last dose.

Imputing missing AE stop date is not mandatory if AE is regarded as ongoing. However, if it is to be done, the rules are outlined above. If subject dies, then use death date for AE stop date.

After the imputation, all imputed dates are checked against the start dates to ensure the stop date does not occur before start date. If the imputed stop date occurs prior to start date, then keep the imputed date the same as the start date.

4.4.1.2.2 Missing/Partial Dates in Concomitant Therapies

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

- If month and year are known, but day is missing, then impute day to first of the month
  a. If year is known, but day and month are missing, then 1st of January of the year will be imputed
- If all is missing, then impute date to Date of Birth (DOB)
  a. If DOB is not available but age is available, then estimate DOB by using screening date and age (age = screening date – DOB)

Concomitant therapies with stop dates that are completely or partially missing will be analyzed as follows:

- If "ongoing" is checked, no imputation is necessary.
- If month and year are known but day is missing, the last day of the month will be imputed
- If year is known, but day and month are missing,
  - If YYYY < year of last dose, then 31st of December will be imputed
  - If YYYY = year of last dose, then 31st of December will be imputed
  - If YYYY > year of last dose, then 1st of January will be imputed
- If all is missing, then impute date to 31st of December in the year of last dose

Imputing missing concomitant therapies is optional. However, if it is to be done, the rules are outlined above. If subject dies, then use death date for concomitant therapies stop date. After the imputation, all imputed dates are checked against the start dates to ensure stop date does not occur before start date. If the imputed stop date occurs prior to start date, then keep the imputed date same as the start date.

4.4.1.2.3 Missing/partial dates in subsequent therapies

Subsequent therapies with start dates that are completely or partially missing will be analyzed as follows:

- When month and year are present and the day of the month is missing,
  a. If the onset month and year are the same as the month and year of last dose with study drug, the day of last dose + 1 will be imputed.
  b. If the onset month and year are not the same as the month and year of last dose with study drug, the first day of the month is imputed.
- When only a year is present,
  a. If the onset year is the same as the year of last dose with study drug, the date of last dose + 1 will be imputed.
  b. If the onset year is not the same as the year of last dose with study drug, the first day of the year is imputed.

- If no components of the onset date are present the date of last dose + 1 will be imputed.

4.4.2 Definition of Baseline Values

The baseline for disease assessment during this study will be based on the value collected at the time of initial diagnosis. For the purpose of assessing PD, the disease nadir will be considered as study entry (or sometime later as appropriate).

For subjects that crossed over, baseline for safety data will be defined as the last data collected prior to receiving ixazomib.

4.4.3 Windowing of Visits

All data will be categorized based on the scheduled visit at which they are collected. These visit designators are predefined values that appear as part of the visit tab in the electronic case report form (eCRF).

4.4.4 Justification of Pooling

All data from all sites will be pooled.

4.4.5 Withdrawals, Dropouts, Loss to Follow-up

Time to event parameters will be censored if patients withdraw, drop out, or are lost to follow-up before documentation of the events (PD/death). Rules for censoring are detailed in Section 4.8.

4.5 Patient Disposition

Patient disposition includes the number and percentage of patients for the following categories: patients in each of the study populations, patients discontinued from the treatment, primary reason to discontinue from the treatment, 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 Efficacy population.

A listing will present data concerning patient disposition.

4.6 Demographics and Baseline Disease Characteristics

4.6.1 Disease Status at Study Entry

Study entry disease characteristics including but not limited to (Eastern Cooperative Oncology Group [ECOG]) performance status, type of myeloma, ISS stage, serum M-protein, urine M-protein, β_2-microglobin by category (ie, < 3.5, 3.5-5.5, > 5.5 mg/L), serum creatinine and its category (≤ 2, >2 mg/dL), creatinine clearance by category (ie, < 60, >=60 mL/min and/or , <50, >=50 mL/min), serum albumin by category (ie, < 3.5, ≥ 3.5 g/dL), corrected calcium, hemoglobin, Lytic bone lesions, extramedullary disease will be summarized using Efficacy population.

A patient's type of myeloma is determined by the combination of heavy chain type (IgG, IgA, IgM, IgD, IgE, biclonal, and other) and light chain type (kappa, lambda, and biclonal).

Creatinine clearance is to be calculated using the Cockcroft-Gault formulas as follows:

For male patients:

$$\text{creatinine clearance} = \frac{(140 - \text{Age[years]}) \times \text{weight[kg]}}{72 \times (\text{serum creatinine [mg/dL]})}$$

For female patients:

$$\text{creatinine clearance} = 0.85 \times \frac{(140 - \text{Age[years]}) \times \text{weight[kg]}}{72 \times (\text{serum creatinine [mg/dL]})}$$

Months from diagnosis to the date of first dose is calculated by

$$\frac{\text{first dose date - date of diagnosis}}{365.25/12}$$

Extent of Disease at Baseline

The following categories of extent of disease at baseline will be summarized: number of patients with bone marrow aspirate, bone marrow aspirate results (percentage of plasma cells), number of patients with bone marrow biopsy, bone marrow biopsy results (percentage of plasma cells, percentage of cellularity, type of cellularity, kappa/lambda ratio performed), skeletal survey results and imaging including magnetic resonance imaging/computed

tomography (CT)/positron emission tomography (PET)-CT results (normal, abnormal not clinically significant, abnormal clinically significant, and not done), number and percentage of present lytic bone lesions, number of extramedullary plasmacytoma, and type of extramedullary plasmacytoma.

Percentage for all categorical summarizations for bone marrow biopsy and aspirate is based on patients from the Efficacy population with an adequate sample for the specified test.

4.6.2 Demographics

Demographics will be summarized in a descriptive fashion in the Efficacy population. Baseline demographic data to be evaluated will include age, sex, weight, and other parameters as appropriate.

4.6.3 Medical History

General medical history and prior medications will be listed for all patients.

Medical history will be summarized (frequency and percentage) by the disease categories recorded in the database. A patient is counted only once within a category. Percentages are based on the number of patients in the Ixazomib Safety population.

Prior induction regimens will be summarized by PI containing, IMiD containing, corticosteroids containing, akaylator containing, monoclonal antibody, as appropriate.

The duration of prior induction regimens will be summarized using descriptive statistics.

4.6.4 Disease Status at Initial Diagnosis

Efficacy data including serum M-protein (g/L), urine M-protein (g/24h), and FLC will be summarized using Efficacy population. Other characteristics at initial diagnosis include β_2-microglobin, Durie-Salmon stage, ISS stage, Lytic bone, extramedullary disease, type of myeloma.

4.6.5 Bone Marrow Cytogenetics

High risk cytogenetic categories are defined as (1) del17 group: patients with del17 alone (2) Cytogenetic high-risk group: patients with any of the following cytogenetic abnormalities: del17, t(4;14) , t(14;16). The standard risk group in the high-risk category is defined as patients for whom the test del17, t(4;14) , t(14;16) are normal. “Unclassifiable” is defined as

patients who do not have cytogenetic data that can be categorized to high risk or standard risk corresponding to high risk group, either because of missing, unknown or indeterminate results. (3) Cytogenetic Expanded high-risk group: patients with any of the following abnormalities: del17, t(4;14) , t(14;16), or ampl 1q. The standard risk group corresponding to expanded high risk group is defined as patients for whom del17, t(4;14) , t(14;16) and ampl 1q are normal. "Unclassifiable" is defined as patients who do not have cytogenetic data that can be categorized to expanded high risk or standard risk corresponding to expanded high risk group, either because of missing, unknown or indeterminate results. The percentage of each category will be summarized.

4.7 Treatments and Medications

4.7.1 Concomitant Medications

Concomitant medications will be coded by preferred term using the World Health Organization (WHO) Drug Dictionary. The number and percentage of patients taking concomitant medications from the first dose through the end of the on-treatment period will be tabulated by Anatomical Therapeutic Chemical (ATC) classification pharmacological subgroup and WHO drug preferred term in the Ixazomib Safety population. Concomitant medication of antibacterials by indication, concomitant medication of antimetics, and prophylaxis in relation to herpes zoster will be summarized. A by-patient listing will also be presented for concomitant medications.

Concomitant procedures will not be coded but will be presented in a data listing for the Ixazomib Safety population.

4.7.2 Study Treatments

Following the Screening period, eligible patients will be enrolled and receive ixazomib. Patients will receive ixazomib capsules (hereafter referred to as "study drug") orally on Days 1, 8, and 15 of every 28-day cycle. A starting dose of 3 mg of study drug will be used for all patients through Cycle 4. Upon evaluation of toxicities at the completion of Cycle 4, if during the most recent 2 cycles (Cycle 3 and 4), there have been no nonhematologic AEs ≥ Grade 2 related to study drug, no dose interruptions related to study drug toxicities, and no delays of greater than 1 week in starting a cycle due to study drug toxicities, the study drug dose will be escalated to 4 mg beginning with Cycle 5 Day 1. Patients who have had *any* dose reductions will not dose escalate. If dose escalation was inadvertently missed at Cycle

5, escalation at a later cycle may be performed with permission from the Takeda project clinician or designee.

The Treatment period will be approximately 24 months (equivalent to 26 cycles [if no cycle delays], to the nearest complete cycle) or until patients experience PD or unacceptable toxicity, whichever occurs first.

4.7.2.1 Duration of Follow-up

The duration of follow-up is defined as time from the date of first dose to the death or last known visit. If a subject dies, the duration equal to date of death minus date of first dose + 1 and treated as censored for follow up. If a subject is alive, the duration equal to the date subject last known to be alive minus date of first dose + 1 and treated as event for follow up.

4.7.2.2 Extent of Exposure

An overall summary of drug exposure will be presented including number of treated cycles, numbers and percentages of patients who had ≥ 1, ≥ 2, …, and ≥ 26 treated cycles, in the Ixazomib Safety population. An aggregate summary of numbers and percentages of patients who had 1 to 4, 5 to 8, 9 to 12, 13 to 16, 17 to 20, 21 to 24, and ≥25 treated cycles will also be presented in the same table. 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.

Additionally, exposure to ixazomib will be characterized by total amount of dose taken in mg, total number of dose taken, number of treated cycles, numbers and percentages of patients who had ≥ 1, ≥ 2, …, and ≥ 26 treated cycles, and relative dose intensity (%) in the Ixazomib Safety population.

A treated cycle is defined as a cycle in which the patient received any amount of any study drug.

$$\text{relative dose intensity (\%)} = 100 \times \frac{\text{total dose received}}{\text{sum of prescribed dose over treated cycles}}$$

Sum prescribed dose over treated cycles is calculated as: for patients who were escalated at or after C5D1, it equals number of prescribed doses per cycles * dose prescribed at enrollment (3mg) * 4 cycles + dose prescribed at C5D1 (4mg) * number of prescribed doses

per cycle * (number of treated cycles - 4). For patients who were not treated more than 4 cycles, it equals dose prescribed at enrollment (3mg) * number of prescribed doses per cycle * number of treated cycles. The number of patients with 100% relative dose intensity, 80% to <= 100%, 50% to < =80%, and < =50% will be summarized using Safety population.

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

4.7.2.3 Treatment Modifications

Dose modification on each study drug due to adverse event will be summarized by Cycle 1 - 26, Cycles 1- 4, 5 - 8, 9- 12, 13 - 16, 17 -20, 21 -24, and 25 - 26 and total in the Ixazomib Safety population. Action on drug will be summarized using similar manner.

4.8 Efficacy Analyses

All efficacy evaluations will be conducted using the Efficacy population unless otherwise specified.

Secondary efficacy parameters include PFS, OS, best response achieved or maintained prior to PD or subsequent therapy, duration of CR, TTP, TTNT, time to end of next-line therapy, duration of the next line of therapy, OS and PFS in high-risk cytogenetic patient groups characterized by individual or multiple cytogenetic abnormalities, including but not limited to del(17) and translocations t(4;14) ort(14;16), and correlation between frailty status and PFS and OS.

Progression-free survival

Progression-free survival , PFS, is defined as the time from the date of first dose to the date of first documentation of PD or death due to any cause, whichever occurs first. Patients without documentation of PD will be censored at the date of their last adequate assessment. The details regarding the handling of missing assessments and censoring for PFS analysis are presented in Table 4-1.

Table 4-1 Handling of Missing Assessments and Censoring for PFS Primary Analysis Based on FDA Guidance

Situation	Date of Progression or Censoring	Outcome
No baseline and/or no postbaseline assessment	Date of first dose	Censored
Disease progression documented between scheduled visits	Date of documented disease progression	Event
No documented death or disease progression	Date of last adequate assessment*	Censored
Lost to follow-up, withdrawal of consent before any documented death or disease progression	Date of last adequate assessment*	Censored
Death or progression after more than 1 missed visit	Date of last adequate assessment*	Censored
Alternate antineoplastic therapy including HDT-SCT started before disease progression	Date of last adequate assessment before starting alternate antineoplastic therapy including HDT-SCT	Censored
Death before first assessment	Date of death	Event
Death between adequate assessment visits	Date of death	Event

Abbreviations: HDT-SCT = high-dose therapy/stem cell transplant; PFS = progression-free survival.
* Adequate disease assessment is defined as there are sufficient data to evaluate a patient's disease status.

Progression-free survival will be analyzed using PFS events reported in China (pooled from patients enrolled in the global study and the China continuation). A sensitivity analysis of PFS, as assessed by the investigator, in the Per-Protocol population may also be conducted. The Kaplan-Meier (K-M) survival curve and K-M median (if estimable), along with their 2-sided 95% CIs, will be provided. The K-M estimates along with 95% CI will be provided by 6-month interval at 6 months, 12 months, 18 months, and so on. The final analysis (FA) will be performed when all patients in the China Continuation are off treatment and have completed the EOT visit, or upon termination of the study by the sponsor, whichever occurs earlier. Descriptive statistics will be used to summarize patient data collected after the IA.

PFS assessed by investigator using different censoring mechanisms will be analyzed in the Efficacy population, for example, not censoring for patients who discontinue treatment and go on transplant or alternative antineoplastic therapy. The other details of the handling of missing assessment and censoring for additional sensitivity analyses are presented in Table 4-2. Sensitivity analyses will be performed on the basis of one alteration at a time, not on combined alterations unless specified otherwise. Additional sensitivity analysis for PFS might be conducted on treating start date of alternate antineoplastic therapy as events.

Table 4-2 Handling of Missing Assessments and Censoring for PFS Sensitivity Analysis Based on EMA guidance

Situation	Date of Progression or Censoring	Outcome
Alternate antineoplastic therapy including HDT-SCT started before disease progression	Date of documented disease progression	event
Death or disease progression after more than 1 missed visit	Date of death or disease progression	event

Abbreviations: HDT-SCT = high-dose therapy/stem cell transplant; PFS = progression-free survival.

The subgroup analysis will be based on baseline factors: initial therapy (proteasome-inhibitor–containing or not); International Staging System (ISS) stage before initial therapy (stage I or II vs stage III); age (< 75 vs ≥ 75 years); and response to initial therapy, as measured during screening (CR or VGPR vs PR), demographic data such as sex and age, and other factors, as appropriate depending on the number of PFS events in a subgroup.

Overall Survival

Overall survival (OS) is defined as the time from the date of first to the date of death. Patients without documentation of death at the time of analysis will be censored at the date last known to be alive. Patients who withdraw, drop out, or are lost to follow-up are censored at the date of last visit. Overall survival will be analyzed based on the Efficacy population.

The K-M survival curve and K-M median (if estimable), along with their 2-sided 95% CIs, will also be provided. The K-M estimates along with 95% CI will be provided by 6-month interval at 6 months, 12 months, 18 months, and so on.

The subgroup analysis will be based on baseline factors: initial therapy (proteasome-inhibitor–containing or not); International Staging System (ISS) stage before initial therapy (stage I or II vs stage III); age (< 75 vs ≥ 75 years); and response to initial therapy, as measured during screening (CR or VGPR vs PR), demographic data such as sex and age, and other factors, as appropriate depending on the number of OS events in a subgroup.

Best Response achieved or maintained prior to PD or subsequent therapy

The percentage of each response category (PR, VGPR, and CR) will be determined relative to the Response-Evaluable population. In addition, the improvement of response for patients who enroll in the study at PR or VGPR will be analyzed.

Duration of Complete Response

Duration of CR is defined as the time from the date of first dose for those who had a CR at study entry or the date of CR for those in whom CR was achieved during the treatment period to the date of first documentation of PD. Responders without documentation of PD will be censored at the date of last assessed CR. Duration of CR will be summarized descriptively using the K-M method.

Time to Progression

Time to progression (TTP) is defined as the time from the date of first dose to the date of first documentation of PD. Patients without documentation of PD at the time of analysis will be censored at the date of last response assessment that is SD or better. Patients who take alternative antineoplastic therapy, or initiation of ASCT, or die during treatment will also be censored at the date of last response assessment. TTP will be analyzed based on the Efficacy population using similar method as PFS.

Time to Start of Next-Line Therapy

Time to start of the next line of therapy is defined as the time from the date of first dose to the date of the first dose of the next line of antineoplastic therapy, for any reason.

Time to start of next line therapy will be analyzed based on the Efficacy population using the similar method as PFS. Patients who have not started the second line therapy will be censored at date of last known to be alive.

Time to End of Next-Line Therapy

Time to end of next-line therapy is defined as the time from the date of first dose to the date of last dose of next antineoplastic therapy following study treatment or death due to any cause, whichever occurs first.

Time to end of next-line therapy will be analyzed based on the Efficacy population using the similar method as PFS. Patients who have not completed the next line of therapy will be censored at date of last known to be alive.

Duration of Next-Line Therapy

Duration of next-line therapy is defined as the time from the date of first dose of next-line therapy to the date of discontinuation of next antineoplastic therapy following study treatment or death due to any cause, whichever occurs first.

Duration of next-line therapy will be analyzed in those patients who actually received next-line therapy following the study treatment using the Efficacy population. Patients who are still on treatment on the next line of therapy will be censored at their last visit. Duration of next-line therapy will be summarized descriptively using the K-M method.

Correlation Between Frailty Status and Progression-Free Survival and Overall Survival

The K-M survival curves and K-M median PFS or OS (if estimable), along with their 2-sided 95% CIs, will be provided for each frailty status. An unadjusted Cox model including frailty status (fit, unfit, or frail) will be used to estimate the hazard ratio and 95% CIs for the frailty for both PFS and OS, if data permit. A status of fit will be compared with a status of unfit or frail. The analysis will be based on the Efficacy population.

4.9 Pharmacokinetic

4.9.1 Pharmacokinetic Analyses

Plasma ixazomib concentration-time data may be presented in listings. Pharmacokinetic data will be used to perform population PK analysis using a nonlinear mixed effects modeling approach and to assess the effect of various covariates on ixazomib PK, and may include data from other studies as appropriate. The analysis plan for the population PK analysis will be separately defined, and the results of these analyses will be reported separately.

Further exploratory analyses may be carried out based on emerging scientific knowledge.

4.10 Analyses of Patient-Reported Outcomes [redacted]

4.10.1 Patient-Reported Outcomes

Descriptive Statistics

Patient-reported outcome assessments using the EORTC QLQ-C30 [redacted] will be analyzed using patients with PRO measurements at study entry and at least one post study entry measurement in the Efficacy population.

Descriptive statistics of actual values and change from baseline in the subscale scores and summary score of the EORTC QLQ-C30 [redacted] will be summarized over time.

The EORTC QLQ-C30 contains 30 items across 5 functional subscales (physical functioning, role functioning, emotional functioning, cognitive functioning, and social functioning), 1 global health status/QoL subscale, and 9 symptom subscales (fatigue, nausea and vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). Items 1 - 28 have 4 response levels (not at all, a little, quite a bit, and very much) and items 29 and 30 rely on a 7-point numeric rating scale. The summary score of EORTC QLQ-C30 is calculated from the mean of 13 of the 15 EORTC QLQ-C30 scales (the Global Health Status/QOL and the Financial Impact scale are not included). [redacted] The recall period for both instruments is 1 week. All subscales were linearly transformed to a 0–100 scale based on EORTC scoring manuals. High scores for the global health status/QoL and functional subscales indicate higher QoL or functioning, while high scores on the symptom subscales indicate higher levels of symptomatology or problems. The subscales of the EORTC QLQ-C30 [redacted] are defined as shown in Table 4-3 and Table 4-4.

Table 4-3 Definition of Subscale Scores of EORTC QLQ-C30

Subscale	Individual Items
Physical functioning	1-5
Role functioning	6-7
Emotional functioning	21-24
Cognitive functioning	20, 25
Social functioning	26-27
Global Health Status/QOL	29-30
Fatigue	10, 12, 18
Nausea and vomiting	14-15
Pain	9, 19
Dyspnea	8
Insomnia	11
Appetite loss	13
Constipation	16
Diarrhea	17
Financial difficulties	28

Abbreviations: EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30.

Table 4-4 [redacted]

[redacted]

Analysis Based on Minimally Important Difference

For the summary score and each subscale score of EORTC QLQ-C30 [redacted], the number and percentage of patients with either a stable score or an improvement in score from study entry based on minimally important differences (MIDs) of 10 (primary analyses) [1] - [3] and 5 (sensitivity analyses) [4] will be summarized over time. Specifically, patients with a change from study entry for the better of ≥MID will be classified as "improved". Those with no change in score from study entry or a change in score within MID will be classified as "stable".

Missing Data

Details of scoring and handling of missing data are included in the EORTC QLQ-C30 [redacted] scoring guidelines.

PRO Compliance

Compliance for EORTC QLQ-C30 [redacted] will be summarized by number of expected and number and percentage of received over time.

4.10.2 [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

4.11 Safety Analyses

Safety will be evaluated by the incidence of adverse events (AEs), severity and type of AEs, and by changes from baseline in the patient's vital signs, weight, and clinical laboratory results using the Ixazomib Safety population. Exposure to the study drug regimen and reasons for discontinuation will be tabulated.

4.11.1 Adverse Events

4.11.1.1 Adverse Events

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). All AEs will be presented in a by-patient listing. Treatment-emergent AEs are AEs that occur after administration of the first dose of study drug (Ixazomib for Ixazomib Safety population, placebo for placebo safety population) and through 30 days after the last dose of any study drug. Safety summaries will be provided for Ixazomib Safety population. Listings of all the AE's for the placebo subjects and for the AE's that occurred prior to crossover will be provided.

Adverse events will be tabulated according to MedDRA by System Organ Class, High Level Term, and Preferred Term and will include the following categories:

- Treatment-emergent AEs
- Drug-related treatment-emergent AEs
- Grade 3 or higher treatment-emergent AEs (also report Grade 3 and 4 separately)

- Grade 3 or higher drug-related treatment-emergent AEs (also report Grade 3 and 4 separately)

- The most commonly reported treatment-emergent AEs (ie, those events reported by ≥ 10% of patients in Ixazomib Safety population)

- SAEs

Patients with the same AE more than once will have that event counted only once within each body system, once within each High Level Term, and once within each Preferred Term.

Drug-related treatment-emergent AEs will also be summarized by the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03. Given that this study involves an initial therapy followed by ixazomib, if a treatment-emergent AE is related to study drug, it will be considered drug related. Patients with the same AE more than once will have the maximum intensity of that event counted within each body system, once within each High Level Term, and once within each Preferred Term.

The most commonly reported treatment-emergent AEs (ie, those events reported by ≥ 10% of Ixazomib Safety population) will be tabulated by Preferred Term. Patients with the same AE more than once will have that event counted only once within each Preferred Term.

An overall summary AE table will include numbers and percentages of patients who had at least 1 AE, drug-related AE, Grade 3 or higher AE (also Grade 3 and 4 AEs), Grade 3 or higher drug-related AE (also Grade 3 and 4 drug-related AEs), SAE, drug-related SAE, AE resulting in discontinuation, and on-study death. On-study death is defined as a death that occurs between the first dose of any study drug and within 30 days of the last dose of study drug.

Additional safety analyses may be performed to most clearly enumerate rates of toxicities and to further define the safety profile of ixazomib.

Additionally, summary tables and by-patient listings of the AEs of clinical importance will be presented including rash, PN, thrombocytopenia, and gastrointestinal disorders if appropriate.

Incidence of New Primary Malignancies

Two types of incidence rates will be calculated for the Ixazomib Safety population based on the new primary malignancy (NPM) assessment:

- Incidence proportions, defined as the percentage of the subjects reporting any new primary malignancy in the Ixazomib Safety population with available information
- Incidence rates, defined by the number of the subjects reporting any new primary malignancy divided by the total duration of follow-up (patient-years = pt-yrs) in the Ixazomib Safety population with available information up to the onset of NPMs

Due to the distinct nature of hematologic and nonhematologic neoplasms, and the emerging signals of NPMs for immunomodulating agents, analyses of NPMs may be performed separately for hematologic and nonhematologic malignancies.

Time to Resolution and Improvement of Peripheral Neuropathy Events

Peripheral neuropathy is defined as the treatment emergent AE in the High Level Term of Peripheral neuropathies NEC (not elsewhere classified) according to MedDRA.

A PN event is considered as 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; that is, all the grades recorded after the maximum grade are less than the maximum grade.

Time to resolution and time to improvement are to be defined for each PN event. Time to resolution is defined as the time from the initial onset date (inclusive) to the resolution date for resolved events. Time to improvement is defined as the time from the initial onset date (inclusive) of the maximum grade to the first onset date that the toxicity grade is below the maximum grade with no higher grade thereafter, or the resolution date, whichever occurs first. Subjects with a PN event without a resolution will be censored at the time of last visit. Subjects with a PN event without an improvement will be censored at the time of last visit.

Time to improvement and time to resolution of PN events will be summarized by outcome (improvement or resolution) using the K-M method. The K-M survival curves and K-M medians (if estimable), along with their 2-sided 95% CIs, will be presented. This analysis is

event based; thus, 1 subject could contribute multiple observations if the subject has more than 1 PN event.

The analysis may be conducted for patients with any PN events or those with ≥ 2 PN events or those ≥ 3 PN events, respectively, if data permit.

4.11.1.2 Serious Adverse Events

The number and percentage of patients experiencing at least 1 treatment-emergent serious AE (SAE) will be summarized by MedDRA primary System Organ Class, High Level Term, and Preferred Term. Drug-related SAEs will be summarized similarly.

In addition, a by-patient listing of the SAEs will be presented (the patient listing will contain all SAEs regardless of treatment-emergent AE status).

4.11.1.3 Deaths

A by-patient listing of the deaths will be presented. All deaths occurring on study will be displayed (regardless of treatment-emergent AE status).

4.11.1.4 Adverse Events Resulting in Discontinuation of Study Drug

A by-patient listing of treatment-emergent AEs resulting in discontinuation of study drug will be presented.

4.11.2 Laboratory Data

For the purposes of summarization in both the tables and listings, all laboratory values will be converted to standardized units. If a lab value is reported using a non-numeric qualifier (eg, 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. Laboratory test results from the central laboratory will be used when they are available. Laboratory test results from local laboratories will be used only when no central laboratory test results exist at the same scheduled sample collection time point.

If a patient has repeated laboratory values for a given time point, the value from the last evaluation will be used.

Laboratory test results will be summarized according to the scheduled sample collection time point. Change from baseline will also be presented. Unscheduled laboratory test

results will be listed and included in laboratory shift tables. The parameters to be analyzed are as follows:

- Hematology: hemoglobin, hematocrit, absolute neutrophil count (ANC), absolute lymphocyte count (ALC), monocytes, eosinophils, basophils, platelets, and white blood cell (WBC) count

- Serum chemistry: blood urea nitrogen, creatinine, total bilirubin, urate, lactate dehydrogenase (LDH), albumin, alkaline phosphatase, aspartate aminotransferase (AST), alanine aminotransferase (ALT), glucose, calcium, sodium, potassium, chloride, carbon dioxide (CO_2), magnesium, phosphate, and gamma glutamyl transferase (GGT)

[redacted]

Shift tables will be constructed for laboratory parameters to tabulate changes in NCI CTCAE for toxicity (version 4.03) from baseline to postbaseline worst CTCAE grade. Parameters to be tabulated will include:

- Hematology: ALC, ANC, hemoglobin, platelets, WBC

- Serum chemistry: ALT, AST, alkaline phosphatase, creatinine, total bilirubin, calcium, magnesium, potassium, sodium, and phosphate

Mean laboratory values and box plots over time for key lab parameters will be produced, including but not limited to ANC, platelets, and liver function tests (ALT, AST, alkaline phosphatase, and total bilirubin).

By-patient listings to be presented include hematology, serum chemistry, [redacted] urinalysis, urine total protein, and urine creatinine.

4.11.3 Electrocardiograms

Descriptive statistics for the actual in electrocardiograms (ECGs) will be listed.

Corrected QT interval (QTc) will be calculated, if necessary.

Electrocardiogram abnormalities will be presented in a data listing.

4.11.4 Vital Signs

The actual values of vital sign parameters including temperature, blood pressure, heart rate, respiratory rate, and body weight, will be summarized over time. Change from baseline will also be presented.

A by-patient listing will also be presented.

4.11.5 Eastern Cooperative Oncology Group Performance Status

Eastern Cooperative Oncology Group Performance Status and shifts from baseline to postbaseline assessment over time, and ECOG score frequency tables over time will be summarized. Shifts from baseline to the worst postbaseline score will be tabulated.

4.11.6 Other Safety Assessments

Pregnancy testing results will be presented in a by-patient listing.

Additional safety analyses may be performed to most clearly enumerate rates of toxicities and to further define the safety profile of ixazomib.

5. CHANGES TO PLANNED ANALYSES FROM PROTOCOL

Reference materials for this statistical plan include Clinical Study Protocol C16021 Amendment 10 (Protocol dated 15 June 2022).

6. PROGRAMMING CONSIDERATIONS

6.1 Statistical Software

SAS version 9.2 (or higher) will be used for all analyses.

6.2 Rules and Definitions

Patient populations are defined in Section 2.

Baseline values are defined in Section 4.4.2.

7. REFERENCES

1. Osoba D, Rodrigues G, Myles J, Zee B, Pater J. Interpreting the significance of changes in health-related quality-of-life scores. J Clin Oncol 1998;16:139–44.

2. Cella D, Pickard AS, Duh MS, et al. Health-related quality of life in patients with advanced renal cell carcinoma receiving pazopanib or placebo in a randomized phase III trial. Eur J Cancer. 2012 Feb;48(3):311-23.

[redacted]

4. Stewart AK, Dimopoulos MA, Masszi T, et al. Health-Related Quality-of-Life Results From the Open-Label, Randomized, Phase III ASPIRE Trial Evaluating Carfilzomib, Lenalidomide, and Dexamethasone Versus Lenalidomide and Dexamethasone in Patients With Relapsed Multiple Myeloma. J Clin Oncol. 2016 Nov 10;34(32):3921-3930.

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
[redacted]	Biostatistics Approval	26-Sep-2022 15:39 UTC