



Title: A Phase 3, Randomized, Placebo-Controlled, Double-Blind Study of Oral Ixazomib Citrate (MLN9708) Maintenance Therapy in Patients With Multiple Myeloma Following Autologous Stem Cell Transplant

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# **STATISTICAL ANALYSIS PLAN**

*A Phase 3, Randomized, Placebo-Controlled, Double-Blind Study of Oral Ixazomib Citrate (MLN9708) Maintenance Therapy in Patients With Multiple Myeloma Following Autologous Stem Cell Transplant*  
Protocol #: C16019

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## **Approval Signatures**

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**LIST OF ABBREVIATIONS AND GLOSSARY OF TERMS**

<b>Abbreviation</b>	<b>Term</b>
AE	adverse event
AL	light-chain
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ampl	amplification
ASCO	American Society of Clinical Oncology
ASCT	autologous stem cell transplant
AST	aspartate aminotransferase
AUC	area under the curve
BCRP	breast cancer resistance protein
BM	bone marrow
BMA	bone marrow aspirate
BSA	body surface area
BUN	blood urea nitrogen
CBC	complete blood count
CHMP	committee for Medicinal Products for Human Use
CL	clearance
CR	complete response
CT	computed tomography
CYP	cytochrome P450s
del	deletion
DDI	drug-drug interaction
DLT	dose-limiting toxicity
DOR	duration of response
DVT	deep vein thrombosis
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EORTC	European Organization for Research and Treatment of Cancer
EOT	End of Treatment (visit)
EQ-5D	EuroQol 5-Dimensional Health Questionnaire
EQ VAS	EQ visual analogue scale
ESMO	European Society for Medical Oncology
EU	European Union
FA	final analysis
FDA	United States Food and Drug Administration
FFPE	formalin-fixed, paraffin-embedded
FISH	fluorescence in situ hybridization

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<b>Abbreviation</b>	<b>Term</b>
GCP	Good Clinical Practice
GI	gastrointestinal
HDT	high-dose therapy
HRQL	health related quality of life
HU	health utilization
IA	interim analysis
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
IDMC	independent data monitoring committee
IEC	independent ethics committee
IMiD	immunomodulating drugs
IMWG	international Myeloma Working Group
IR	immunophenotype
IRB	institutional review board
IRC	independent review committee
ISC	independent statistical center
ISS	international Staging System
ITT	intent-to-treat
IV	intravenous; intravenously
IXRS	interactive web/voice response system
LenDex	lenalidomide + dexamethasone
MCL	mantle cell lymphoma
MedDRA	Medical Dictionary for Regulatory Activities
Millennium	Millennium Pharmaceuticals, Inc., and its affiliates
MM	multiple myeloma
MP	melphalan prednisone
MRD	minimal residual disease
MRI	magnetic resonance imaging
MRP2	multidrug resistance associated protein
MTD	maximum tolerated dose
QLQ-MY20	Multiple Myeloma Module
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NDMM	newly diagnosed multiple myeloma
NEC	not elsewhere classified
NFKB	nuclear factor kappa-light-chain-enhancer of activated B cells
OS	overall survival
PAD	bortezomib, Adriamycin <sup>®</sup> (doxorubicin), and dexamethasone

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<b>Abbreviation</b>	<b>Term</b>
PD	progressive disease
PE	pulmonary embolism
PFS	progression-free survival
PI	proteasome inhibitor
PK	pharmacokinetic(s)
PN	peripheral neuropathy
PO	<i>per os</i> ; by mouth (orally)
PR	partial response
PSMB1	proteasome (prosome, macropain) subunit, beta type, 1
QLQ-C30	Quality of Life Questionnaire
QOL	quality of life
RISS	revised international staging system stage
RP2D	recommended phase 2 dose
RRMM	relapsed and/or refractory multiple myeloma
SAE	serious adverse event
sCR	stringent complete response
SCT	stem cell transplant/ therapy
SD	stable disease
SMA	Safety Management Attachment (to the Investigator's Brochure)
SNP	single-nucleotide polymorphism
SoC	standard of care
SPEP	serum protein electrophoresis
SPM	second primary malignancies
$t_{1/2}$	terminal disposition phase half-life
TEAE	treatment-emergent adverse event
$T_{max}$	first time of occurrence of maximum (peak) concentration
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TTP	time-to-progression
Tx	treatment
ULN	upper limit of the normal range
UPEP	urine protein electrophoresis
US	United States
VAD	vincristine, doxorubicin, and dexamethasone
VGPR	very good partial response
vs	versus
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 or analytical deficiencies. Specifically, this plan has the following purpose:

To prospectively 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**

This is a randomized, placebo-controlled, double-blind, phase 3 study in patients with newly diagnosed multiple myeloma (NDMM) who have undergone induction therapy according to regional standard of care (SoC), followed by a conditioning regimen containing high-dose melphalan (200 mg/m<sup>2</sup>) and Autologous Stem Cell Transplant (ASCT). Induction therapy must include proteasome inhibitor (PI) and/or immunomodulating drug (IMiD)-based regimens. Vincristine, Adriamycin (doxorubicin), and Dexamethasone (VAD) are not an acceptable induction therapy for this trial.

Patients who have achieved clinical and hematologic recovery following induction, high-dose therapy (HDT), and ASCT will initiate screening for study eligibility no earlier than 75 days after transplant, complete screening within 15 days, and be randomized no later than 115 days after transplant. Eligible patients (those whose complete response [CR], very good partial response [VGPR] or partial response [PR] have been documented during screening and who have met all inclusion/exclusion criteria) will be enrolled and randomized in a 3:2 ratio to ixazomib citrate or placebo. Stratification is based on: induction regimen (PI without an IMiD vs IMiD without a PI vs PI and IMiD); pre-induction International Staging System (ISS) (stage I vs stage II or III); and response after transplantation, defined as the response following induction, HDT, and ASCT measured during screening (CR or VGPR vs PR) on the basis of the International Myeloma Working Group (IMWG) criteria.

Patients will receive blinded study drug (ixazomib citrate capsules or matching placebo capsules) orally on Days 1, 8, and 15 of every 28-day cycle, for a maximum duration of approximately 24 months (26 cycles, to the nearest complete cycle), or until documented disease progression (on the basis of the IMWG criteria) or intolerable toxicities, whichever comes first. To provide patients the opportunity to derive maximum clinical benefit from



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study drug maintenance, the dose of 3 mg will be increased to 4 mg at Cycle 5 provided that during the most recent 2 cycles (Cycle 3 and 4), there have been no nonhematologic AEs  $\geq$  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. Patients who have had any dose reductions will not dose escalate. If dose escalation was inadvertently missed at Cycle 5, escalation may be performed with permission from the Millennium project clinician or designee.

Clinical, laboratory, disease response, and health related quality of life (HRQL) with an emphasis on tolerability and symptom burden, as well as minimal residual disease (MRD) assessments will be made. Following documented disease progression, subsequent therapy will be determined by the investigator/ treating physician.

The primary endpoint of PFS will be supported by prespecified evidence of clinical benefit as measured by the key and other secondary endpoints. There will be 2 interim analyses (IAs) and 1 final analysis (FA) in the study. The first IA will be the FA for PFS for statistical testing purposes.

## **1.2 Study Objectives**

The primary objective is:

- To determine the effect of ixazomib citrate maintenance therapy on PFS, compared to placebo, in patients with NDMM who have had a response (CR, VGPR, or PR) to induction therapy followed by HDT and ASCT

The key secondary objective is:

- To determine the effect of ixazomib citrate maintenance therapy on overall survival (OS) compared to placebo

Other secondary objectives are:

- To determine the effect of ixazomib citrate maintenance therapy on improving best response for patients who enroll in the study at PR or VGPR, as well as maintaining best overall response for patients who enroll in the study at CR.
- To determine the effect of ixazomib maintenance therapy on time to progression (TTP)

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- To determine the effect of ixazomib maintenance therapy on progression-free survival 2 (PFS2), defined as time from the date of randomization to the date of objective disease progression on next-line treatment or death from any cause, whichever comes first.
- To determine the effect of ixazomib maintenance therapy on time to start of the next line of treatment, defined as the time from the date of randomization to the date of the first dose of the next line of antineoplastic therapy for any reason.
- To determine the effect of ixazomib maintenance therapy on time to end of the next line of treatment, defined as the time from the date of randomization to the date of the last dose of the next line of antineoplastic therapy for any reason
- To determine the effect of ixazomib maintenance therapy on duration of the next line of antineoplastic therapy
- To assess the incidence of new primary malignancies in patients receiving ixazomib maintenance therapy compared with placebo following ASCT
- To evaluate the frequency of conversion from MRD positive to MRD negative, or the maintenance of MRD negativity, after 1 and 2 years of therapy in patients treated with ixazomib citrate compared to placebo, using bone marrow aspirates and 8-color flow cytometry or next-generation sequencing.
- To assess the correlation between MRD status (assessed by 8-color flow cytometry and next-generation sequencing) and PFS and OS, using bone marrow aspirates.
- To determine the effects of ixazomib maintenance therapy on PFS and OS in high-risk cytogenetic patient groups characterized by individual or multiple cytogenetic abnormalities, such as del17, t(4:14), t(14:16), ampl 1q, del13, or del1p.
- To determine the long-term safety and tolerability of ixazomib administration to multiple myeloma patients following ASCT.
- To assess overall HRQL, as measured by global health domain of European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30).

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- To collect pharmacokinetic (PK) data to contribute to population PK and exposure response (safety/ efficacy) analysis.
- To evaluate the resolution and improvement of peripheral neuropathy (PN), if it occurs, by grading at each subsequent monthly visit until 1) resolution of PN, 2) the start of an alternative antineoplastic treatment, or 3) 6 months after progression has occurred, whichever comes first.

Exploratory objectives are:

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## **2. POPULATIONS FOR ANALYSIS**

### **2.1 Intent-to-Treat Population**

The Intent-to-Treat (ITT) population is defined as all patients who are randomized and post randomization data are available. Patients will be analyzed according to the treatment they were randomized to receive, regardless of any errors of dosing. Patients who are regarded as screen failure and lack any data post randomization will be excluded from ITT population.

The ITT population will be used for the primary, secondary efficacy analyses, and resource utilization and patient reported outcome analysis.

### **2.2 Safety Population**

The safety population is defined as all patients who receive at least 1 dose of ixazomib or placebo. Patients will be analyzed according to the treatment they actually received. Patients who received any dose of ixazomib will be included in the ixazomib arm, and patients who received only placebo will be included in the placebo arm, regardless of their randomized treatment.

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

### **2.3 Per-Protocol (PP) population**

The PP population consists of all ITT patients who do not violate the terms of the protocol in a way that would impact the study outcome significantly. All decisions to exclude patients from the PP population will be made by the Takeda Project Clinician or designee prior to unblinding the study for IAs or FA purpose.

The PP population will be used as a sensitivity analysis of the ITT population for the primary efficacy endpoint PFS if more than 5% patients are excluded from this analysis.

## **3. HYPOTHESES AND DECISION RULES**

### **3.1 Statistical Hypotheses**

There is one primary endpoint in this study.

The null and alternative hypotheses for PFS are:

$$H_0: \text{PFS in Ixazomib Arm} = \text{PFS in Placebo Arm}$$

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$H_a$ : PFS in Ixazomib Arm > PFS in Placebo Arm

There is one key secondary efficacy endpoint in this study.

The null and alternative hypotheses for OS are:

$H_0$ : OS in Ixazomib Arm = OS in Placebo Arm

$H_a$ : OS in Ixazomib Arm > OS in Placebo Arm

### **3.2 Statistical Decision Rules**

A closed sequential testing procedure will be used to test the primary endpoint of PFS and the key secondary endpoint of OS. First PFS will be tested at the first IA at a 2-sided alpha level of 0.05 at the IA. If 2-sided, stratified log-rank test p value for PFS is  $\geq 0.05$ , the study will be deemed unsuccessful and no further formal hypothesis testing will be conducted. Otherwise, the null hypothesis for PFS will be rejected and the test for PFS is claimed to be statistically significant. In this case, OS will be tested according to the group sequential test method at this IA and subsequent analyses, in which the significance level will be determined by the O'Brien-Fleming alpha spending function (the Lan-DeMets method). Due to the closed sequential testing property, the family-wise type I error is strongly controlled for both PFS and OS.

All other efficacy endpoints will be tested at a 2-sided alpha level of 0.05 unless otherwise specified.

## **4. INTERIM ANALYSIS**

### **4.1 Interim Analysis**

There are two planned interim analyses. The first IA will be performed when approximately 328 PFS events have occurred or 25 months after the last patient has been enrolled, whichever occurs later. The first IA will be the only analysis for PFS for formal statistical testing purpose. After PFS is tested at the first IA, central efficacy and investigator assessments of disease response for protocol purposes will be discontinued (except for investigator assessment of PFS2). The second IA will be conducted for OS when approximately 200 death events have occurred.

The test significance for the IAs of OS will be determined using O'Brien-Fleming boundaries (the Lan-DeMets method) with a total of 260 death events.

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Based on OS results in the second IA, the planned number of OS events needed to trigger the FA may be increased if the observed treatment effect is promising, but not large enough to yield the likely conclusion of statistical significance at the end of the study using the originally planned number of OS events. It is also possible for the entire study design to remain unchanged as a result of the IAs. The Cui-Hung-Wang test statistic will be used in the FA of OS to protect the type I error.

**4.2 Independent Data Monitoring Committee (IDMC)**

An IDMC supported by an independent statistician from independent statistical center (ISC) will review safety and efficacy data at planned interim analyses. The IDMC will provide a recommendation regarding study continuation based on the safety and efficacy parameters. In the event that the study is terminated early based on the IDMC recommendation, the Sponsor will notify the appropriate regulatory authorities.

In addition, the IDMC will periodically review safety data at regularly scheduled meetings pre-specified in the IDMC charter. The first formal safety review will occur after approximately 60 subjects (36 in the ixazomib citrate arm and 24 in the placebo arm) have been randomized and received at least 1 cycle of study treatment. Subsequently, periodic safety reviews will also occur as pre-specified in the IDMC charter.

Study accrual will not be interrupted due to the scheduled safety reviews. The IDMC or ixazomib citrate study team may request an ad-hoc meeting for any reason, including a significant unexpected safety event, unplanned unblinding of study results, follow-up of an observation during a planned IDMC meeting, or a report external to the study, such as publication of study results from a competing product. At each review, subject incidence rates of AEs (including all serious AEs, treatment-related AEs, serious treatment-related events, and events resulting in discontinuation of study drug) will be tabulated. Listings and/or narratives of “on-study” deaths and other serious and significant AEs, including any early withdrawals due to AEs, will be provided. Records of all meetings will be archived. The IDMC will communicate major concerns and recommendations regarding study modification or termination to the sponsor. Further details will be provided in the IDMC charter.

At the 2<sup>nd</sup> IA if OS significance is not claimed, the conditional power based on OS will be calculated. During the closed session of the IDMC meeting at the 2<sup>nd</sup> IA, the IDMC will compare the conditional power for OS based on the interim results with the prespecified effect size adaptation rules, and recommend to the sponsor executive committee the final

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adaptation decision. This recommendation will be documented in the IDMC closed meeting minutes.

### **4.3 Independent Review Committee (IRC)**

An independent review committee (IRC), blinded to treatment arm assignments and investigator determination of response, will review all disease evaluation data (including PFS follow-up period; does not apply to PFS2 assessments) from the study and determine disease status (response and progression), according to IMWG criteria as specified in the IRC charter. Data from the IRC will not be provided back to the investigator during the conduct of the study.

## **5. STATISTICAL METHODOLOGY**

In general, summary tabulations will be presented by treatment arm and control arm, and will be displayed by the number of observations, mean, standard deviation, median, minimum, and maximum for continuous variables, and the number and percent per category for categorical data. The Kaplan-Meier survival curves and 25th, 50th (median), and 75th percentiles will be provided along with their 2-sided 95% CIs for time-to-event data.

### **5.1 Sample Size Justification**

The primary objective of this study is to determine if ixazomib improves PFS compared with placebo in patients with NDMM post HDT and ASCT. The study will not be stopped after the PFS analysis, even if a significant PFS is observed, so that an adequate statistical power for OS can be obtained.

The total sample size is calculated based on maintaining 80% power to test the OS. The study is also adequately powered to test PFS. There are 2 planned IAs and 1 FA. The first IA will be the only analysis for PFS for formal statistical testing purposes. If PFS is significant at the first IA, then OS will be tested at this IA and subsequent analyses.

The FA of PFS, which is also the first IA of OS, will be performed 25 months after the last patient has been enrolled or when approximately 328 PFS events have been observed, whichever occurs later. With projected 328 PFS events, it will have 95% power to detect a hazard ratio of 0.67 (ie, median PFS of 26 months for control versus 39 months for treatment) using a 2-sided log-rank test at a 2-sided alpha level of 0.05 and assuming approximately 15% dropout rate at month 30. This will be the FA for PFS for formal statistical testing purposes, with the opportunity to claim PFS benefit. With projected 328

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PFS events, an observed hazard ratio of 0.802 or better (ie, median PFS of 26 months for control versus 32.4 months for treatment, 25% improvement) will likely to lead to statistical significance for PFS at this analysis. If the test for PFS is not statistically significant, the study will be claimed as unsuccessful and no further formal hypothesis testing will be conducted.

If the test for PFS is statistically significant, OS will be tested. If the OS results are statistically significant at either interim analysis 1 (IA1) or interim analysis 2 (IA2), the study can be stopped early, and this analysis on OS will be the FA for formal hypothesis testing on OS. Otherwise, determination of the number of OS events at FA will occur at IA2.

The total event size calculation for OS is based on the adaptive sample size reassessment approach, which in this study's setting, it is an adaptive event size reassessment approach. The minimum event size of 260 death events is based on an optimistic assumption of a hazard ratio of 0.70 (ie, median OS of 70 months for control versus 100 months for treatment) with 80% power at a 2-sided level of significance. The O'Brien-Fleming alpha spending function (the Lan-Demets method) is used to calculate the significance boundary based on observed number of death events in each IA with a total of 260 OS events for the FA.

The second IA for OS will be performed when approximately 200 death events have been observed, which is expected to occur approximately 60 months after the first patient is enrolled. If OS significance is not claimed, the conditional power based on OS will be calculated. If the conditional power falls in the promising zone, the event size will be determined according to a prespecified event size adaptation rule, with an event cap of approximately 350 death events. No futility analysis will be performed in the study.

The event size adaptation rule is a pre-specified stepwise function to avoid the back calculation problem resulting from one sample size corresponding to either barely promising or highly promising interim results. The event size adaptation rule will be designed by the sponsor's independent design statistician and approved by the sponsor's head of biostatistics. Neither the independent design statistician nor the head of biostatistics is involved in the study conduct.

The adaptation rule will be outlined in a separate document and will not be accessible to the sponsor's study team until completion of the study. The rules will be available only to the sponsor's independent design statistician, the sponsor's head of biostatistics, the IDMC, and



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the statistics' representative on the sponsor's executive committee (if different from the sponsor's head of biostatistics).

## **5.2 Randomization and Stratification**

Randomization scheme will be generated by an independent statistician who is not on the study team. Prior to dosing, a randomization number will be assigned to each patient. The randomization assignment will be implemented by an interactive voice/ web response system (IXRS).

Eligible patients will be randomized in a 3:2 ratio to receive ixazomib arm or placebo arm, stratified by induction regimen (PI without an IMiD vs IMiD without a PI vs PI and IMiD); pre-induction International Staging System (ISS) (stage I vs stage II or III); and response (CR or VGPR vs PR) after transplantation, defined as the response following induction, HDT, and ASCT as assessed by the investigators.

## **5.3 Blinding and Unblinding**

This is a double-blind study: all study personnel including the investigators, site personnel, study clinicians, and the sponsor will be blinded to the treatment assignments. Only the ISC and IDMC will have access to unblinded individual patient level data in the electronic data capture system. The periodic safety analyses will be generated for IDMC by an ISC. The formal IA analyses will also be conducted by ISC for the IDMC. An unblinded submission working group will be formed to prepare submission package and/or work with Agencies for submission purpose at IA.

Refer to section 4.2 for the roles and responsibilities of IDMC.

## **5.4 Data Handling**

### **5.4.1 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 patient reported outcomes data, primarily missing data imputation will be based on published instrument specific methods. Other missing data imputation method such as Last Observation Carry Forward (LOCF) and multiple

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imputation method may be explored as sensitivity analyses for patient reported outcomes data.

**5.4.1.1 Missing/Partial Dates in Screening Visit**

The following rules apply to dates recorded in 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 indicates 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.

**5.4.1.2 Missing/Partial Dates in Adverse Events/Concomitant Therapies/Subsequent Therapies**

**5.4.1.2.1 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 1<sup>st</sup> dose date, then 1<sup>st</sup> dose date will be used instead
  - If year is different than year of 1<sup>st</sup> dose date, then 1<sup>st</sup> of January of the year will be imputed.
- If all is missing, then it is imputed with 1<sup>st</sup> dose date.

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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 31<sup>st</sup> of December will be imputed
  - If YYYY = year of last dose, then 31<sup>st</sup> of December will be imputed
  - If YYYY > year of last dose, then 1<sup>st</sup> of January will be imputed
- If all are missing, then impute date to 31<sup>st</sup> 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.

**5.4.1.2.2 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
  - If year is known, but day and month are missing, then 1<sup>st</sup> of January of the year will be imputed
- If all is missing, then impute date to Date of Birth (DOB)
  - If DOB is not available but age is available, then estimate DOB by using screening date and age (age = screening date – DOB)

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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 31<sup>st</sup> of December will be imputed
  - If YYYY = year of last dose, then 31<sup>st</sup> of December will be imputed
  - If YYYY > year of last dose, then 1<sup>st</sup> 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 the death date will be used 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 dates occurs prior to start date, then the imputed date will be kept the same as the start date.

**5.4.1.2.3 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,
  - 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.
  - 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,
  - 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.

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- 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.

**5.4.2 Definition of Reference Values**

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.

The reference for response 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).

**5.4.3 Windowing of Visits**

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.

**5.4.4 Justification of Pooling**

All data from all sites will be pooled. Study center or treatment-by-center interaction will not be included in any statistical analysis.

**5.4.5 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 (progressive disease/death). Rules for censoring are detailed in section 5.8.

**5.5 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 for discontinuation from the treatment, patients on-going on treatment, patients participating in any follow-up, patients with dose escalation at C5D1,

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patients discontinued from the study, and primary reason for discontinuation from the study. All percentages will be based on the number of patients in the ITT population.

A listing will present data concerning patient disposition.

## **5.6 Demographics and Disease Characteristics at Study Entry**

### **5.6.1 Demographics**

Demographics will be summarized by treatment groups in a descriptive fashion in the ITT population. Demographic data at study entry to be evaluated will include age, sex, race, ethnicity, height, weight, and body surface area. Patient enrollment by region and country will also be summarized by treatment groups.

### **5.6.2 Medical History**

General medical history and prior medications will be listed for all patients by treatment groups. Prior induction regimens will be summarized by PI containing, IMiD containing, corticosteroids containing, cyclophosphamide containing, liposomal doxorubicin containing, platinum containing, akaylator containing, monoclonal antibody containing, busulfan containing, and others.

ASCT procedure will be displayed including type of condition regimen, recovery of ANC > 500 cells/mm<sup>3</sup>, day of recovery to ANC, recovery of platelet count > 20,000 cells/mm<sup>3</sup>, and days of recovery to platelet count. Peripheral blood stem cell mobilization regimen, best response by investigators prior ASCT and post ASCT will also be detailed in summaries.

### **5.6.3 Disease Status at Initial Diagnosis**

Efficacy data including serum M-protein, urine M-protein, and serum involved FLC, serum FLC ratio will be summarized for ITT population. Other characteristics include type of myeloma,  $\beta_2$ -microglobulin, albumin, Durie-Salmon stage, lactate dehydrogenase (LDH), cytogenetics, international staging system stage (ISS), revised international staging system stage (RISS), lytic bone, and extramedullary disease. Time from initial diagnosis to first dose of study treatment, from initial diagnosis to ASCT, and from ASCT to first dose of study treatment will be summarized for all patients.

#### **5.6.4 Disease Status at Study Entry**

Disease characteristics at study entry includes, but are not limited to, Eastern Cooperative Oncology Group (ECOG) performance status, serum M-protein, urine M-protein, serum involved FLC and its ratio,  $\beta_2$  - microglobulin by category (i.e,  $< 3.5$ ,  $\geq 3.5$  and  $< 5.5$ ,  $\geq 5.5$  mg/L), serum creatinine and its category ( $\leq 2$ ,  $> 2$  mg/dL), creatinine clearance by category (ie,  $< 30$ ,  $\geq 30$  and  $< 60$ ,  $\geq 60$  and  $< 90$ ,  $\geq 90$  mL/min), lactate dehydrogenase, serum albumin by category (ie,  $< 35$ ,  $\geq 35$  g/L), corrected calcium, hemoglobin, lytic bone lesions, and extramedullary disease will be summarized for all patients.

A patient's type of myeloma is determined by heavy chain type (IgG, IgA, IgM, IgD, IgE, and other) and light chain type (Kappa, Lambda, and biclonal). In descriptive summaries, myeloma type will be summarized separately for the heavy chain patients (according to IgG, IgA, IgM, IgD, IgE, biclonal, other) and for the light chain patients (according to kappa or lambda or biclonal).

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

For male patients:

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

For female patients:

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

Months from diagnosis to the randomization date for each treatment is calculated by

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

Distribution of stratification factors will also be summarized.

##### **5.6.4.1 Extent of disease at study entry**

The following categories of extent of disease at study entry will be summarized: bone marrow aspirate (number of patients, % plasma cells), bone marrow biopsy (number of

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patients, % plasma cells, marrow cellularity, Kappa/Lambda ratio), combined % plasma cells in bone marrow aspiration and biopsy, and plasmacytomas.

**5.6.5 Bone marrow cytogenetic at initial diagnosis**

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 corresponding to high risk group 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.

**5.7 Treatments and Medications**

**5.7.1 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 generic term for each treatment group in the safety population. Concomitant medication of antibacterials by indication, concomitant medication of antimetetics, and prophylaxis in relation to herpes zoster will be summarized. By-patient listing will also be presented for concomitant medications.

**5.7.2 Study Treatments**

Following the Screening period, eligible patients will be randomized to receive ixazomib or placebo in a double-blind fashion with the randomization ratio of 3:2, respectively.



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**Ixazomib Arm:** Patients will receive ixazomib citrate on Days 1, 8, and 15 of a 28-day cycle.

**Placebo Arm:** Patients will receive placebo capsule on Days 1, 8, and 15 of a 28-day cycle.

In both arms, a starting dose of 3 mg ixazomib or matched placebo 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  $\geq$  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 dose may be escalated to 4 mg at Cycle 5 Day 1. Patients who have had any dose reductions will not get dose escalated. If dose escalation was inadvertently missed at Cycle 5, escalation may be performed with permission from the Millennium project clinician or designee.

Patients will receive study treatment for a maximum duration of approximately 24 months (26 cycles if no delays), or until documented disease progression or intolerable toxicities, whichever comes first.

The number of patients who have been escalated at Cycle 5 Day 1 will be summarized. For those who didn't escalate, their reasons of no escalation will be displayed.

#### **5.7.2.1 Duration of Follow-up**

The duration of OS follow-up is defined as time from the randomization date to the death or last visit of known alive. If a subject is alive, this patient is treated as an event in OS follow-up and the duration equals to the date of a subject is last known to be alive – randomization date + 1. If a subject is dead, this patient is censored for OS follow-up and the duration equals to date of death - randomization date + 1.

The Kaplan Meier (K-M) approach will be used to calculate the median duration of follow up.

#### **5.7.2.2 Extent of Exposure**

A summary of drug exposure to ixazomib/placebo will be characterized by number of treated cycles, numbers and percentages of patients who had  $\geq 1$ ,  $\geq 2$ , ..., and = 26 treated cycles, total amount of dose taken, total number of dose taken, and relative dose intensity (%), by each treatment group in the safety population. Aggregate summary of numbers and percentages of patients who had 1-4, 5-8, 9-12, 13-16, 17-20, 21-24, 25-26 treated cycles

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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.

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

Relative dose intensity (%) is defined as  $100 * (\text{Total amount of dose taken}) / (\text{Total prescribed dose of treated cycles})$ . Total prescribed dose of treated cycles is calculated as: for patients who were treated 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.

Relative dose intensity will also be displayed as <50%, 50% - <= 80%, >80% - < 100%, = 100%, and > 100%. The duration of treatment at 4 mg will be also calculated, from the first date when subjects were dosed with 4 mg till either the last dosing date or the first time they had dose reduced, whichever comes earlier. In addition, relative dose intensity will be calculated for those escalated to 4 mg at cycle 5, counted only for doses starting from cycle 5.

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

## **5.8 Efficacy Analyses**

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

### **5.8.1 Primary Efficacy Endpoint**

There is one primary endpoint, PFS, which is defined as the time from the date of randomization 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 last response assessment that is stable disease (SD) or better. The details regarding the handling of missing assessment and censoring for PFS analysis are presented in [Table 5-1](#).

**Table 5-1 Censoring Rules for PFS Primary Analysis Based on FDA Guidance**

<b>Situation</b>	<b>Date of Progression or Censoring</b>	<b>Outcome</b>
No randomization and/or no post randomization assessment, no subsequent anticancer therapy after study treatment, no death	Date of randomization	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, withdraw consent before any documented death or disease progression	Date of last adequate assessment*	Censored
Death or progression after more than one missed visits	Date of last adequate assessment*	Censored
Alternate antineoplastic therapy started prior to disease progression	Date of last adequate assessment* prior to starting alternate antineoplastic therapy	Censored
Death before first assessment	Date of death	Event
Death between adequate assessment visits	Date of death	Event

\*Adequate disease assessment is defined as there is sufficient data to evaluate a patient’s disease status.

### **5.8.1.1 Primary Efficacy Analysis**

PFS will be analyzed at the first IA, when 25 months after the last patient has been enrolled or approximately 328 (approximately 50%) PFS events have been observed, whichever occurs later. A 2-sided, stratified log-rank test will be used to compare the treatment groups with respect to PFS at a 2-sided alpha level of 0.05. In addition, an unadjusted stratified Cox model will be used to estimate the hazard ratio and its 95% CIs for the treatment effect using the stratification factors. The Kaplan Meier (K-M) survival curves and K-M median PFS (if estimable), along with their 2-sided 95% CIs, will be provided for each treatment group. PFS assessed by IRC in ITT population will be the primary analysis.

Sensitivity analyses for PFS include:

1. PFS assessed by investigator will be analyzed in the ITT population.
2. PFS assessed by IRC will be analyzed in the PP population if more than 5% patients are excluded from this analysis.
3. PFS assessed by IRC using the missing assessment and censoring rules based on EMA guidance with two combined alterations from FDA guidance as presented in [Table 5-2](#).

**Table 5-2 Handling of missing assessment and censoring for PFS Sensitivity Analysis based on EMA guidance**

<b>Situation</b>	<b>Date of Progression or Censoring</b>	<b>Outcome</b>
Alternate antineoplastic therapy started prior to disease progression	Date of documented disease progression	Event
Death or disease progression after more than one missed visit	Date of death or disease progression	Event

PFS assessed by IRC evaluations to which different censoring mechanisms have been applied will be analyzed in the ITT population, for example, not censoring for patients who discontinue treatment and go on alternative antineoplastic therapy. 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.

In addition, a stepwise Cox model will be implemented to identify potential predictive factors using relevant demographic or diagnostic covariates, with the entry level fixed at 0.25 and a stay level fixed at 0.05. Besides treatment and the stratification factors, the model may include the following significant covariates including, but not limited to, treatment arm, age, race (white, non-white), ECOG score at study entry (0 or 1, 2), cytogenetic test (high risk, other), and corrected calcium, ISS(I, II or III), revised ISS (I or II, III), creatinine clearance, etc.

The plan of subgroups for PFS is presented in the [Table 5-3](#) below with a few identified key subgroups:

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**Table 5-3 List of subgroup**

<b>Subgroup</b>	<b>Definition of Group</b>
Age	< 60 years vs. $\geq 60$ and < 75 years
Pre-induction ISS	I vs. II vs. III
Pre-induction ISS	I vs. II or III as one stratification factor
Revised ISS stage at initial diagnosis	I vs. II vs. III
Sex	male vs. female
Race	white vs. black-African American vs. Asian vs. other
Region	APAC vs. EMEA vs. other
Best response post transplant	CR or VGPR vs. PR as one stratification factor
Response at study entry	CR vs. VGPR or less
Cytogenetic risk	high risk group vs. standard risk group corresponding to high risk group vs. unclassifiable group; expanded high risk group vs. standard risk group corresponding to expanded high risk group vs. unclassifiable group
Induction regimen	PI exposed vs. PI naive (IMiD only)
Induction regimen	PI and IMiD vs. PI only vs. IMiD only as one stratification factor

Subgroup testing will be conducted using the two-sided alpha of 0.05. In addition, five prespecified key subgroups (Age: < 60 years; Pre-induction ISS: II or III; Best response post transplant: CR or VGPR; Cytogenetic risk: high risk group and expanded high risk group) will be tested at a 2-sided alpha level of 0.05 with the Hochberg procedure for multiplicity correction.

Additional exploratory analyses may be performed if deemed necessary.

### **5.8.2 Key Secondary Efficacy Endpoint**

There is one key secondary endpoint: OS.

#### Overall Survival

OS is defined as the time from the date of randomization 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. OS will be analyzed based on the ITT population.

### **5.8.2.1 Key Secondary Efficacy Analysis**

#### Overall Survival

A 2-sided, stratified log-rank test will be used to compare the treatment groups with respect to OS. In addition, an unadjusted stratified Cox model will be used to estimate the hazard ratio and its 95% CIs for the treatment effect using the stratification factors. The K-M survival curves and K-M medians (if estimable), along with their 2-sided 95% CIs, will also be provided for each treatment group.

In addition, a stepwise stratified Cox regression model will be used to further evaluate the treatment effects on OS after adjusting for some prognostic factors. Besides treatment and the stratification factors, the model may include, but is not limited to, the following prognostic factors simultaneously: age, race (white, non-white), ECOG score at study entry (0 or 1, 2), cytogenetic test (high risk, other), and corrected calcium, ISS(I, II or III), revised ISS (I or II, III), creatinine clearance, etc.

To adjust for the potential effects of subsequent therapies after patients discontinued study treatment, the following two methods will be used:

- Marginal Structural Models (MSM) by Robin and Finkelstein
- Inverse Probability of Censoring Weighted (IPCW) method by Robins and Finkelstein

In the MSM and IPCW analyses, in order to derive weights adjusting for the time-fixed and time-varying confounding effects due to taking alternative therapies, the covariates affecting disease progression, post-progression treatment, and OS endpoint will be used. Potential time-fixed covariates at study entries are region(APAC, EMEA, other), age(<60, ≥ 60 and <75), race(white, non-white), ECOG score (0 or 1, 2), induction therapy(PI only, IMiD only, PI and IMiD), response at study entry (CR or VGPR, PR), percentage of plasma cells (≤ 30, > 30, missing), presence of extramedullary plasmacytomas (yes, no), presence of lytic bone lesions (yes, no), hemoglobin, platelets, creatinine clearance, albumin, and corrected calcium. Potential time-fixed covariates at initial diagnosis are type of myeloma (IgA, other), ISS (I, II or III), RISS (I or II, III), cytogenetic abnormalities (high risk, others), LDH,  $\beta_2$  microglobulin. Time-varying covariates include duration of exposure, disease progression status at each study visit, hemoglobin value at each study visit and progression/relapse visit, platelets value at each study visit and progression/relapse,

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M-protein value at each study visit and progression/relapse, type of subsequent therapy with proteasome inhibitor, types of subsequent therapy with IMiDs.

The final criteria for selected covariates would need to be statistically have a p-value of less than or equal to 0.1 in the multivariate logistic regression models for weight calculations. If there are more than 5% missing in the covariate, then this covariate will be dropped from the weighting calculation and final OS model. For both MSM and IPCW analyses, logistic regression models on repeated measurements will be used to approximate the Cox models in the weight derivations from which stabilized weights will be derived per subject per observation. Adjusted K-M curves will also be presented along with hazard ratios and 95% confidence intervals, and adjusted p-values based on MSM and IPCW approaches. SAS proc PHREG procedure with counting process type of data input, which takes multiple observations per subject, will be used as the final Cox model for OS for both MSM and IPCW approaches, where robust variance will be used to accommodate covariance introduced by correlated longitudinal observations within each subjects and other extra variabilities due to departure from model assumptions.

Subgroup analyses will be performed for OS following [Table 5-3](#).

### **5.8.3 Other Secondary Efficacy Endpoints and Analyses**

Other secondary efficacy parameters include best response achieved or maintained prior to PD or subsequent therapy, time to progression, PFS2, time to start of the next line of therapy, time to end of the next line of therapy, duration of the next line of therapy, OS and PFS in high-risk population. Conversion of MRD + to MRD-; maintenance of MRD-; correlation between MRD status and PFS and OS.

Disease response-related endpoints prior to PD will be analyzed using IRC-assessed responses.

#### Best Response achieved or maintained prior to PD or subsequent therapy

The time frame for a response is determined from the start of the study treatment until confirmed PD or subsequent therapy, whichever comes earlier.

The percentage of response (PR, VGPR, CR, or sCR) will be determined relative to the ITT population.

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For patients who entered into study with PR response, the percentage of patients maintaining PR as best confirmed response, and converting to VGPR/CR as best confirmed response will be displayed. For patients who entered into study with VGPR response, the percentage of patients maintaining VGPR as best confirmed response, and converting to CR as best confirmed response will be displayed. For patients who entered into study with CR response, the percentage of patients maintaining CR as best confirmed response will be displayed.

For patients entered into study with CR response, the percentage of patients maintaining CR at 12 and 24 months will be displayed; duration of CR will be summarized descriptively using the Kaplan-Meier method.

The IRC-assessed response data will be used for the analysis. Investigator-assessed response data will be used for the sensitivity analysis.

Time to Progression (TTP)

TTP is defined as the time from the date of randomization 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 anti-neoplastic therapy prior to progression, or die during study treatment will also be censored at the date of last response assessment that is SD or better. TTP will be analyzed based on the ITT population using the similar method as PFS. The subgroup analysis of TTP will be analyzed following [Table 5-3](#).

Progression-free survival 2 (PFS2)

Progression-free survival 2 (PFS2) is defined as time from the date of randomization to the date of first documentation of PD (as assessed by investigator) on the next-line treatment following study treatment or death from any cause, whichever occurs first.

PFS2 will be analyzed based on the ITT population as assessed by investigator using the similar method as PFS.

The details of the handling of missing assessment and censoring are presented in [Table 5-4](#) and [Table 5-5](#).



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**Table 5-4 Censoring for PFS2 For Those Who have Received Second line Therapy following Study Treatment**

<b>Situation</b>	<b>Date of Progression or Censoring</b>	<b>Outcome</b>
Documented death or disease progression during second line therapy	Date of death/disease progression	Event
No documented death or disease progression during second line therapy	Date of last assessment	Censored
Lost to follow-up, withdraw consent before any documented death or disease progression during second line therapy	Date of last assessment	Censored
Start of third line therapy prior to the disease progression during second line therapy	Date of last disease assessment prior to starting the third line therapy	Censored

If a patient has no response assessment during second line therapy, it will be censored at first dose of second line therapy.

**Table 5-5 Censoring for PFS2 for Those Who have not received Second Line of Therapy**

<b>Situation</b>	<b>Date of Progression or Censoring</b>	<b>Outcome</b>
No documented death	Date of last visit	Censored
Death	Date of death	Event

In addition, one sensitivity analysis for PFS2 might be conducted on treating start date of 3<sup>rd</sup> line therapy as events if the patients have not experience PD on the second line yet.

Time to start of the next line of therapy

Time to start of the next line of therapy is defined as the time from the date of randomization 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 ITT 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.

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Time to end of the next line therapy

Time to end of next line therapy is defined as the time from the date of randomization 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 ITT population using the similar method as PFS. Patients who have not completed the second line 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 the last dose of the next antineoplastic therapy or death due to any cause, whichever occurs first.

Duration of next line therapy will be analyzed on those patients who actually received next line therapy following the study treatment using the ITT principal. Patients who are still on treatment on the next line of therapy will be censored at date of last known to be alive.

Duration of next line therapy will be summarized using the Kaplan-Meier method.

PFS and OS in Cytogenetic Risk Populations

PFS and OS will be analyzed in high risk group using a similar method as those in the ITT population.

- Cytogenetic high risk group defined as patients carrying any of the following cytogenetic abnormalities: del17, t(4;14), or t(14;16)
- Cytogenetic expanded high-risk group defined as patients carrying any of the following cytogenetic abnormalities: del17, t(4;14), t(14;16) or ampl 1q

In addition, PFS and OS analyses will be summarized by cytogenetics test del17, t(4;14), t(14;16) and ampl 1q if data permit.

**5.9 Pharmacokinetic and Biomarker Analysis**

**5.9.1 Pharmacokinetic Analyses**

Plasma concentration-time data will be presented in listings and summarized by time point in tables.

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PK data collected in this study will contribute to population PK and exposure/response (safety and efficacy) analyses. These analyses may include data from other ixazomib clinical studies. The analysis plan for the population PK and exposure/response analyses will be separately defined and the results of these analyses will be reported separately.

**5.9.2 Biomarker Analysis**

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**5.9.3 Minimal Residual Disease Analysis**

Minimal Residual Disease (MRD) will be assessed at study entry, cycle 12/13 and at the end of treatment (2 years) in all the VGPR and CR patients independent from the arm of the study, unless already done within the most recent 2 cycles. If MRD status is missing or not-evaluable, it will be assumed as MRD positive.

MRD status by response at study entry for each treatment arm and overall population will be summarized. MRD status by response at C12/13, EOT for VGPR and CR patients for each treatment arm and overall population will be summarized. PFS and OS by MRD subgroup analyses will be analyzed according to MRD subgroups listed below.

- For overall population: MRD+ vs. MRD- at study entry
- For patients who were MRD- at study entry: treatment vs. control.
- For patients who were MRD+ at study entry and converted to MRD – at anytime point post study entry: treatment vs. control.
- For patients who were MRD+ at study entry and still maintain MRD+ at anytime point post study entry: treatment vs. control.

The rate of maintaining MRD negativity at Cycle 12/13, EOT and any time point post study entry for patients who were MRD negative at study entry will be compared between

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treatment and control arms. The rate of maintaining MRD negativity at Cycle 12/13, EOT and any time point post study entry for patients who were CR and MRD negative at study entry will be compared between treatment and control arms. The rate of maintaining MRD negativity at Cycle 12/13 and EOT for patients who were MRD negative at study entry may be compared between treatment and control arms in selected subgroups if data permit.

The rate of converting to MRD negative by 3-month interval and any time point post study entry for patients who were MRD positive at study entry will be made between treatment and control arms. The rate of converting to MRD negative at any time point post study entry for patients who were CR and MRD positive at study entry will be made between treatment and control arms. The rate of converting to MRD negative at any time point post study entry for patients who were MRD positive at study entry may be made between treatment and control arms in selected subgroups if data permit.

Time from MRD negative to MRD positive, PD or death will be summarized using the Kaplan-Meier method.

Time from MRD positive at study entry to first MRD negative post study entry will be summarized using the Kaplan-Meier method.

Limit of Detection of MRD will be summarized for all MRD evaluable patients.

MRD analysis on maintenance of MRD negativity, conversion to MRD negativity and correlation with PFS and OS based on different threshold ( $10^{-4}$ ,  $10^{-5}$ ,  $10^{-6}$ ) may be performed if data permit.

## **5.10 Analyses of Patient-Reported Outcomes and Health Economics**

### **5.10.1 Patient Reported Outcomes (PROs)**

#### Descriptive Statistics

Patient-reported outcome (PRO) assessments using the EORTC QLQ-C30 and the EORTC QLQ-MY20 will be analyzed using patients with PRO measurements at study entry and at least one post study entry measurement in the ITT population.

The descriptive statistics of actual value and change from study entry for the subscale scores and summary score of EORTC QLQ-C30 and subscale scores of EORTC QLQ-MY20 will be summarized by treatment group over time. Specifically, two different groupings of

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observations will be used: 1. based on cycle visit and 2. based on 4-week intervals from study entry.

The subscales of EORTC QLQ-C30 and QLQ-MY20 are defined as shown in [Table 5-6](#) and [Table 5-7](#). The summary score of EORTC QLQ-C30 will be calculated from the mean of 13 of the 15 QLQ-C30 scales (the Global Quality of Life scale and the Financial Impact scale are not included).

**Table 5-6 Definition of Subscale Scores of EORTC QLQ-C30**

<b>Subscale</b>	<b>Individual Items</b>
Physical functioning	1-5
Role functioning	6-7
Emotional functioning	21-24
Cognitive functioning	20, 25
Social functioning	26-27
Quality of life	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

**Table 5-7 Definition of Subscale Scores of EORTC QLQ-MY20**

<b>Subscale</b>	<b>Individual Items</b>
Future perspective	18-20
Body image	17
Disease symptoms	1-6
Side effects of treatment	7-16

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Analysis based on minimally important difference (MID)

The number and percentage of patients with either a stable score or an improvement in score from study entry based on a minimally important difference (MID) of 10 will be summarized by treatment group over time. Specifically, patients with a change for the better of  $\geq$ 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”. The number and percentage of patients with “improved” or “stable” subscale scores based on a MID of 5 will also be summarized by treatment group over time.

Analysis based on Linear mixed effects model by incorporating covariates

1. For the summary score and each subscale score of EORTC QLQ-C30 as well as each subscale score of QLQ-MY20, the change in score from study entry to each scheduled treatment cycle visit will be analyzed using repeated measures linear mixed models. These models will include the following covariates: treatment group, score at study entry, stratification factors, visits, and interactions between treatment group and visits. The interaction term between score at study entry and visit may also be considered as a covariate. The estimated mean change in score from study entry with 95% CIs for each treatment group will be provided at each treatment cycle visit. In addition, the mean difference in the changes from study entry between the treatment groups with 95% CIs and p-values will be provided at each treatment cycle visit.
2. For the summary score and each subscale score of EORTC QLQ-C30 as well as each subscale score of QLQ-MY20, the change in score from study entry to a pre-specified time period (e.g., 24, 36, or 48 4-week intervals) will be analyzed using similar linear mixed models to the analyses based on scheduled treatment cycle visit above. Only time periods where at least 50% of patients have the potential to be included will be considered. These models will include the following covariates: treatment group, score at study entry, stratification factors, time from study entry, interactions between treatment group and time from study entry. The interaction term between score at study entry and time from study entry may also be considered as a covariate. The estimated mean change in score from study entry with 95% CIs for each treatment group as well as the mean difference in the changes from study entry between the treatment groups with 95% CIs and p-values will be provided at every three 4-week intervals post study entry.

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Change from study entry scores using cumulative distribution function (CDF) figures

The change in score from study entry to Cycle 26 (or last visit prior to Cycle 26) will be presented using cumulative distribution function (CDF) figures. The x-axis represents the changes in score (range: -100 to 100) and the y-axis represents the cumulative percentage of patients with a given change in score.

An Average Score from the EORTC QLQ-C30 Global Quality of Life domain

For each patient, an average score will be calculated using all available scores from study entry to last measurement prior to PD. For each group, an average score will be calculated from the patient averages. A 2-sample t-test will be used to assess whether the mean average score in the ixazomib arm is noninferior to that in the placebo arm. The noninferiority margin is 12.

Analyses of the global quality of life during the PFS Follow-up period (following EOT until progression), the PD Follow-up period (following progression until start of next-line therapy), and the PFS2 Follow-up period (from the start of next-line therapy until PD2) may be conducted. Comparisons of the average global quality of life during the treatment period or follow-up periods may be also considered.

In addition, the area under the curve (AUC) approach will be used to examine the differential effect of treatment throughout the study as a sensitivity analysis. The AUC approach aggregates the cumulative absolute HRQOL score over time: the y-axis represents the absolute EORTC QLQ-30 global quality of life score (range: 0-100); the x-axis represents the time horizon.

For each individual patient, two AUCs will be calculated: 1. from study entry to last time on-treatment and 2. from study entry to a pre-specified time period (e.g., 24, 36, or 48 4-week intervals). Only time periods where at least 50% of patients have the potential to be included will be considered. In order to calculate the AUCs for each individual, a linear relationship will be assumed between measurements and the worst possible value will be assumed after the last measurement. For each group, the average AUCs will be calculated from the patient averages. A 2-sample t-test will be used to assess whether the mean AUC in the ixazomib arm is noninferior to that in the placebo arm. The noninferiority margin is set to be 12 \* the time period for the AUC analysis. This is consistent with the average score approach, as the time period is fixed.

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Additionally, distribution of individual AUCs in the 2 treatment groups may be described by summary statistics, such as means, standard deviations, medians, etc.

If the noninferiority test is statistically significant, then the superiority test will be performed to further examine the benefit of the differential effect of treatment.

The average score and AUC analyses described above will also apply to other scales of EORTC QLQ-C30 and QLQ-MY20.

Missing data

Details of scoring and initial handling of missing data are included in the EORTC QLQ-C30 and QLQ-MY20 scoring guidelines.

Missing data patterns will be examined. As a sensitivity analysis, different imputation methods for missing data including Last Observation Carry Forward (LOCF) and imputing death as worst possible score, and pattern mixture model may be performed if appropriate after examining missing data patterns.

Compliance for EORTC QLQ-C30 and QLQ-MY20 will also be summarized by number of expected and number and percentage of received by treatment group over time and overall.

**5.10.2 Health Economics Analysis Using Medical Resource Utilization and Utility**

EQ-5D scores will be summarized in descriptive statistics for treatment arms over time.

Compliance for EQ-5D will also be summarized by number of expected and number and percentage of received by treatment group over time and overall.

HU data will be summarized in descriptive statistics of medical encounters (length of hospital stay; number of inpatient, ICU, emergency department and outpatient encounters, and reason for each), number of missing days from work or other activities by patient and care-giver for treatment arms.

Further modeling will be performed separately in post hoc analyses.

**5.11 Safety Analyses**

Safety will be evaluated by the incidence of AEs, severity and type of AEs, and by changes from study entry in the patient's vital signs, weight, and clinical laboratory results using the



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safety population. Exposure to the study drug and reasons for discontinuation will be tabulated.

**5.11.1 Adverse Events**

**5.11.1.1 Adverse Events**

Adverse events will be coded using 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 any study drug and through 30 days after the last dose of any study drug.

AEs will be tabulated according to MedDRA by system organ class, high level terms and preferred terms 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  $\geq 10\%$  of patients in either treatment group)
- Serious AEs (SAEs)
- Drug-related (SAEs)
- AE resulting in discontinuation
- AEs that prevented dose escalation at C5

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.

Treatment-emergent AEs will also be summarized by the National Cancer Institute Common Toxicity Criteria (NCI CTCAE) version 4.03. 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.

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The most commonly reported treatment-emergent AEs (ie, those events reported by  $\geq 10\%$  of any treatment arm) 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 one AE, drug-related AE, grade 3 or higher AE, grade 3 or higher drug-related AE, SAEs, drug-related SAE, AE resulting in discontinuation, and on-study deaths. On-study death is defined as the death that occurs between the first dose of any study drug and within 30 days of the last dose of any study drug.

All concomitant medications collected from screening through the study period will be classified to preferred terms according to the World Health Organization (WHO) drug dictionary.

Additionally, by-patient listings and summary tables of the AE of special interest (AESI) of new primary malignancy and AEs of clinical importance (AECI) of peripheral neuropathy, rash, encephalopathy, liver impairment, hypotension, heart failure, arrhythmias, myocardial infarction, thrombocytopenia, neutropenia, gastrointestinal, and renal impairment will be presented.

Incidence of New Primary Malignancies (NPM)

Two types of incidence rates will be calculated for the safety population based on the new primary malignancy assessment:

- Incidence proportions, defined as the percentage of the subjects reporting any new primary malignancy in the 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 safety population with available information up to the onset of new primary malignancies.

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

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Time to Resolution and Improvement of Peripheral Neuropathy (PN) Events

Peripheral neuropathy 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 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 (meaning that 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.

Time to improvement and time to resolution of PN events will be summarized by outcome (improvement or resolution) using the Kaplan-Meier method. The K-M survival curve 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  $\geq 2$  PN events or those  $\geq 3$  PN events, respectively, if data permit.

**5.11.1.2 Serious Adverse Events**

The number and percentage of patients experiencing at least one treatment-emergent 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).

**5.11.1.3 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).

#### **5.11.1.4 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.

#### **5.11.2 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. However, for the bone marrow plasma cell percentage, the convention as (x-1)% (mainly for < 5% for CR) will be used.

Laboratory test results from the central laboratory will be used when they are available. Laboratory test results from local laboratory will only be used 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 results at study entry 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: lymphocytes, hemoglobin, neutrophils (ANC), platelets counts and leukocytes.
- Serum chemistry: blood urea nitrogen (BUN), creatinine, total bilirubin, urate, lactate dehydrogenase (LDH), albumin, alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), glucose, corrected calcium, sodium, potassium, chloride, carbon dioxide (CO<sub>2</sub>), magnesium, and phosphate.

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

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- Hematology: ANC, hemoglobin, platelets counts, lymphocytes and leukocytes.
- Serum chemistry: ALT, AST, ALP, creatinine, total bilirubin, corrected 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/SGPT, AST/SGOT, alkaline phosphatase, and total bilirubin).

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

### **5.11.3 Electrocardiograms**

Descriptive statistics for the actual values and changes from values at study entry in ECGs will be listed by time point.

QTc interval will be calculated using Bazett's correction and Fridericia's correction, if necessary. The formulas are:

$$QTc \text{ (Bazett)} = QT / (RR^{0.5})$$

$$QTc \text{ (Fridericia)} = QT / (RR^{0.33})$$

where  $RR = 60 / \text{heart rate (bpm)}$

In addition, a categorical analysis of QTc intervals will be performed for each time point. The number and percentage of patients in each QTc interval (< 450 msec, 450-480 msec, > 480- <500 msec, and  $\geq 500$ msec) will be summarized at study entry and each of the subsequent time points. Categories of changes from study entry ( $\geq 30$  msec and  $\geq 60$  msec) will be summarized as well. Maximum QTc intervals and maximum changes from study entry will also be summarized similarly in a separate display.

ECG abnormalities will be presented in a data listing.

### **5.11.4 Vital Signs**

The actual values of vital sign parameters including temperature, blood pressure, heart rate, and body weight, will be summarized over time for each treatment arm. Change from study entry will also be presented.

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A by-patient listing will also be presented.

**5.11.5 Eastern Cooperative Oncology Group (ECOG) Performance Status**

Eastern Cooperative Oncology Group performance status and shifts from study entry to post study entry assessment over time, and ECOG score frequency table over time will be summarized. Shifts from study entry to the worst post study entry score will be tabulated by treatment arm.

**5.11.6 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 MLN9708, e.g. analyses of TEAEs of clinical importance. Tables will be provided with a summary of the patient incidence of all TEAEs of clinical importance by PT, severity, and seriousness for each analysis set within each category of TEAEs of clinical importance.

**6. CHANGES TO PLANNED ANALYSES FROM PROTOCOL**

Reference materials for this statistical plan include Clinical Study Protocol C16019 Amendment 1 (Protocol Amendment dated 05April 2016), and Clinical Study Protocol C16019 Amendment 2 (Protocol Amendment dated 21April 2017).

**7. PROGRAMMING CONSIDERATIONS**

**7.1 Statistical Software**

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

**7.2 Rules and Definitions**

Patient populations are defined in Section 2.

Values at study entry are defined in Section 5.4.2.

**8. 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.

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2. Robins JM, Hernan M, Brumback B. Marginal structural models and causal inference in epidemiology. *Epidemiology* 2000; 11(5): 550-560.
3. Robins JM and Finkelstein DM. Correcting for Noncompliance and Dependent Censoring in an AIDS Clinical Trial with Inverse Probability of Censoring Weighted (IPCW) Log-Rank Tests. *Biometrics* 2000; 56: 779-788.
4. D'Agostino R.B., Lee M.L., Belanger A.J., Cupples L.A., Anderson K., and Kannel W.B. Relation of pooled logistic regression to time dependent Cox regression analysis: the Framingham Heart Study. *Statistics in Medicine*, 9(12): 1501–1515, 1990.
5. Mehta CR, Pocock SJ. Adaptive increase in sample size when interim results are promising: a practical guide with examples. *Stat Med* 2011;30(28):3267-84.
6. Cui L, Hung HM, Wang SJ. Modification of sample size in group sequential clinical trials. *Biometrics* 1999;55(3):853-7.
7. Glimm E, Maurer W, Bretz F. Hierarchical testing of multiple endpoints in group sequential trials. *Stat Med* 2010;29(2):219-28.
8. Liu Y, Hsu J (2009). Testing for efficacy in primary and secondary endpoints by partitioning decision paths. *Journal of the American Statistical Association*, 104: 1661-1670.
9. Huang Y, Hsu J; Hochberg's Step-Up Method: Cutting Corners Off Holm's Step-Down Method. *Biometrika* 2007; 94 (4): 965-975. doi: 10.1093/biomet/asm067