Title: A Phase 2, Open-Label, Multicenter Study of Ixazomib Plus Lenalidomide and Dexamethasone in Adult Japanese Patients With Relapsed and/or Refractory Multiple Myeloma

NCT Number: NCT02917941

Statistical analysis plan Approve Date: 19-SEP-2018

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STATISTICAL ANALYSIS PLAN

STUDY NUMBER: C16028

A Phase 2, Open-Label, Multicenter Study of Ixazomib Plus Lenalidomide and Dexamethasone in Adult Japanese Patients With Relapsed and/or Refractory Multiple Myeloma

PHASE 2

Version: 2

Date: 19 September 2018

Prepared by:

PPD

PPD

Based on:

Protocol Version: Amendment 1

Protocol Date: 25 November 2016

1.1 Approval Signatures

Study Title: A Phase 2, Open-Label, Multicenter Study of Ixazomib Plus Lenalidomide and Dexamethasone in Adult Japanese Patients With Relapsed and/or Refractory Multiple Myeloma

Approvals:

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2.0 TABLE OF CONTENTS

3.0 LIST OF ABBREVIATIONS

5-HT3	5-hydroxytryptamine 3 serotonin receptor
ADL	activities of daily living
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
BUN	blood urea nitrogen
CBC	complete blood count
CI	confidence interval
CO_2	carbon dioxide
CR	complete response
CRO	contract research organization
CT	computed tomography
CYP	cytochrome P450
Del	deletion
DNA	deoxyribonucleic acid
DOR	duration of response
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EOT	End of Treatment (visit)
FAS	full analysis set
FCBP	female patients of childbearing potential
FDA	United States Food and Drug Administration
FISH	fluorescent in situ hybridization
FLC	free light chain
GCP	Good Clinical Practice
G-CSF	granulocyte colony stimulating factor
GVHD	graft-versus-host disease
HBcAb	hepatitis B core antibody
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
IMiD	immunomodulatory drugs
IMWG	International Myeloma Working Group
IRB	institutional review board
ISS	international staging system
IUD	intrauterine device
IV	intravenous; intravenously
LenDex	lenalidomide and dexamethasone
LDH	lactate dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities

MHRA	Medicines and Healthcare products Regulatory Agency
MM	multiple myeloma
MRI	magnetic resonance imaging
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NDMM	newly diagnosed multiple myeloma
ORR	overall response rate
OS	overall survival
PD	progressive disease (disease progression)
PET	positron emission tomography
PFS	progression-free survival
PMDA	Pharmaceuticals and Medical Devices Agency
PML	progressive multifocal leukoencephalopathy
POEMS	polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes
PR	partial response
PRES	posterior reversible encephalopathy syndrome
PTE	pretreatment event
RNA	ribonucleic acid
RRMM	relapsed and/or refractory multiple myeloma
SAE	serious adverse event
SAP	statistical analysis plan
sCR	stringent complete response
SD	stable disease
SPEP	serum protein electrophoresis
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
TEN	toxic epidermal necrolysis
T_{max}	time to first occurrence of maximum (peak) concentration
TSH	thyroid stimulating hormone
TTP	time to progression
ULN	upper limit of the normal range
UPEP	urine protein electrophoresis
VGPR	very good partial response
WBC	white blood cell
WHO	World Health Organization

4.0 OBJECTIVES

4.1 Primary Objectives

To determine VGPR or better (VGPR + CR) rate in response-evaluable analysis set*

*Defined as patients who received at least one dose of ixazomib and had measurable disease at baseline, and at least one post baseline response assessment.

4.2 Secondary Objectives

- To determine progression-free survival (PFS)
- To determine overall response rate (ORR) (partial response [PR] or better)
- To determine duration of response (DOR)
- To determine time to progression (TTP)
- To determine safety
- To determine overall survival (OS)

4.3 Additional Objectives

Not applicable

4.4 Study Design

This is a phase 2, open-label, single arm, multicenter study to evaluate the efficacy and safety of ixazomib plus lenalidomide and dexamethasone in Japanese patients with relapsed and/or refractory multiple myeloma (MM). The patient population will consist of adult men and women who have a confirmed diagnosis of MM, who have received 1 to 3 prior lines of therapy, and who meet other outlined eligibility criteria (see Section 7.0). Approximately 30 patients will be enrolled in the study.

General eligibility criteria may be assessed prior to the formal Screening period if it is part of standard clinical practice. However, per the Schedule of Events, formal screening will occur during the Screening period, which may last for up to 28 days prior to enrollment. A Takeda clinician will confirm patient eligibility prior to enrollment. Determination of disease progression as an entry criterion may be based on patient data obtained during or following the patient's most recent prior antineoplastic therapy.

Patients will receive study drug (ixazomib 4.0 mg) on Days 1, 8, and 15 plus lenalidomide (25 mg) on Days 1 through 21 and dexamethasone (40 mg) on Days 1, 8, 15, and 22 of a 28-day cycle. Patients may continue to receive treatment until progressive disease (PD) or unacceptable toxicity, whichever comes first. Dose modifications may be made based on toxicities. Patients with a low creatinine clearance < 60 mL/min will receive a reduced lenalidomide dose of 10 mg. The lenalidomide dose may be escalated to 15 mg after 2 cycles if the patient is not responding to treatment and is tolerating the treatment. If renal function normalizes (ie, creatinine clearance ≥ 60 mL/min) and the patient continues to tolerate this treatment, lenalidomide may then be escalated to 25 mg.

Patients will be seen at regular treatment cycle intervals while they are participating in the study: four times a treatment cycle for the first 2 cycles, twice a treatment cycle for the 3rd

cycle, and then once a treatment cycle for the remainder of their participation in the active treatment and, if applicable, the PFS (every 4 weeks) and OS (every 12 weeks) follow-up phases of the study.

Response will be assessed by investigator according to the IMWG criteria for all patients every 4 weeks until PD. Central laboratory data will be used for serum M-protein, urine M-protein and serum free light chain. All patients will be followed for survival after progression. Patients will be contacted every 12 weeks until death or termination of the study by the sponsor.

Patients will attend an End of Treatment (EOT) visit approximately 30 days after receiving their last dose of study treatment (ixazomib, lenalidomide or dexamethasone) and will continue to be followed for other follow-up assessments specified in the Schedule of Events. Patients discontinuing study treatment prior to PD will continue to be assessed for PD during the PFS follow-up portion of the study.

Analysis is planned to be performed twice during the study. The primary analysis is planned to be performed using the data obtained at approximately 12 months from the enrollment of the last patient. The final analysis is planned to be performed after the final database lock using the data obtained at approximately 24 months from the enrollment of the last patient. The timing of analysis may be changed or additional analysis may be added upon request of the regulatory authorities.

5.0 ANALYSIS ENDPOINTS

Primary Efficacy Endpoint

VGPR or better rate in response-evaluable analysis set

Secondary Efficacy Endpoints

- PFS, defined as the time from the date of first study drug administration to the date of first documentation of PD or death from any cause, whichever occurs first
- ORR
- DOR, defined as the time from the date of first documentation of response to the date of first documentation of PD
- TTP, defined as the time from the date of first study drug administration to the date of first documentation of PD
- Safety including treatment-emergent adverse events (TEAEs), laboratory parameters, and vital signs
- OS, defined as the time from the date of first study drug administration to the date of death

6.0 DETERMINATION OF SAMPLE SIZE

Assuming the expected VGPR or better rate is 48.1% and the threshold rate is 39.0% based on the results of Study C16010, a sample size of 27 would be necessary to provide a point estimate of VGPR or better rate higher than the threshold rate with 80% probability. Assuming a drop-out ratio of 10%, the target number of patients has been set to 30. The expected response rate and the threshold assumptions are based on VGPR or better rate in ixazomib + LenDex arm and placebo + LenDex arm in Study C16010 (intent-to-treat population, primary analysis).

7.0 METHODS OF ANALYSIS AND PRESENTATION

7.1 General Principles

7.1.1 Study Definitions

The following definitions and calculation formulas will be used.

- Descriptive statistics: Number of subjects, mean, standard deviation, maximum, minimum, and quartiles
- Frequency distributions: Number of subjects and percentage (of nonmissing) per category
- Baseline body surface area (m^2): square root of (baseline height * baseline weight / 3600)
- Time since initial diagnosis to first dose at study entry (months): (first dose date - date of initial diagnosis + 1) / (365.25 / 12)
- Relapsed patients: Patients who relapsed from at least 1 previous treatment but were not refractory to any previous treatment. Patients who progress after 60 days from the last dose of a given therapy will be considered relapsed.
- Refractory patients: Patients who were refractory to at least 1 previous treatment but were not relapsed to any previous treatment. Refractory disease is defined as disease progression on treatment or progression within 60 days after the last dose of a given therapy.
- Refractory and relapsed patients: Patients who were relapsed from at least 1 previous treatment and additionally were refractory to at least 1 previous treatment.
- Primary refractory patients: Patients who are refractory to all lines of previous therapy (i.e., best response to prior therapy is SD or disease progression on all lines of therapy).
- Time since last transplant to first dose at study entry (months): (first dose date – start date of prior transplant) / (30.4375)
- Relative dose intensity: 100 * (total amount of dose taken) / (total prescribed dose of treated cycles), where total prescribed dose equals [dose prescribed at enrollment * number of prescribed doses per cycle * the number of treated cycles]
- Extent of Exposure (cycles) is based on the number of treated cycles.
- Extent of Exposure (days): date of last dose – date of first dose + 1
- Percent drug compliance (%): (study drug taken in mg) / (study drug expected to be taken in mg) *100%
- Treatment-emergent adverse event (TEAE): Any adverse event that occurs after administration of the first dose of any study drug through 30 days after the last dose of any study drug
- If corrected calcium is not reported directly, it can be calculated using the following formula:
  - Corrected Calcium (mmol/L): serum calcium (mmol/L) + 0.0200 * (40 – serum albumin (g/L))

7.1.2 Definition of Study Visit Windows

Unless otherwise specified, the baseline value is defined as the value collected at the time closest to, but before, the start of study drug administration.

All data will be categorized on the basis of the scheduled visit at which they are collected.

7.1.3 Significance Level and Confidence Coefficient

- Confidence coefficient: 95% (two-sided)

7.2 Analysis Sets

In this study, the following three analysis sets are defined.

- FAS: All subjects who received at least one dose of the study drug during the treatment period. Subjects will be excluded from FAS if the following criterion is met:
  - No study drug received
- Response-evaluable analysis set: All FAS subjects with measurable disease at baseline, and at least one post baseline response assessment. Measurable disease is defined by at least 1 of the following 3 measurements based on central laboratory data: serum M-protein ≥1 g/dL (≥ 10 g/L), urine M-protein ≥200 mg/24 hours, and serum free light chain assay where involved free light chain level ≥10 mg/dL (≥ 100 mg/L), provided that the serum free light chain ratio is abnormal.

  Subjects will be excluded from the response-evaluable analysis set if any of the following criteria are met:
  - No measurable disease at baseline
  - No post-baseline assessment
  - No study drug received
- Safety analysis set: All subjects who received at least one dose of the study drug during the treatment period. Subjects will be excluded from the safety analysis set if the following criterion is met:
  - No study drug received

7.3 Disposition of Subjects

7.3.1 Study Information

Analysis Set:	All Subjects Who Signed the Informed Consent Form	
Analysis Variable(s) :	Date First Subject Signed Informed Consent Form Date of Last Subject's Last Visit/Contact MedDRA Version WHO Drug Version SAS Version Used for Creating the Datasets	
Analytical Method(s) :	(1) Study Information Study information shown in the analysis variables section will be provided.	

7.3.2 Number of Subjects Who Entered the Treatment Period by Site

Analysis Set:	All Subjects Who Entered the Treatment Period	
Analysis Variable(s) :	Status of Entrance into the Treatment Period	[Entered]
Stratum:	Site	[Site numbers will be used as categories]
Analytical Method(s) :	(1) Number of Subjects Who Entered the Treatment Period by Site Frequency distribution will be provided for each stratum.	

7.3.3 Disposition of Subjects

Analysis Set:	All Subjects Who Entered the Treatment Period	
Analysis Variable(s) :	Study Drug Completion Status	[Ongoing on Treatment, Prematurely Discontinued Study Drug]
	Reason for Discontinuation of Study Drug	[Adverse Event, Lost to Follow-up, Progressive Disease, Protocol Violation, Study Terminated by Sponsor, Withdrawal by Subject, Other]

	Subjects that have Participated in OS Follow-up	
	Subjects that have Participated in PFS Follow-up	[Yes, No]
	Completion Status of the Follow-up Period	[Completed Follow-up Period, Prematurely Discontinued Follow-up Period]
	Reason for Discontinuation of the Follow-up Period	[Lost to Follow-up, Study Terminated by Sponsor, Withdrawal by Subject, Other]

Analytical Method(s) : (1) Disposition of Subjects
Frequency distributions will be provided.

7.3.4 Protocol Deviations and Analysis Sets

7.3.4.1 Protocol Deviations

Analysis Set:	All Subjects Who Entered the Treatment Period	
Analysis Variable(s) :	Significant Protocol Deviation	[Entry Criteria, Concomitant Medication, Procedure Not Performed Per Protocol, Study Medication, Withdrawal Criteria, Good Clinical Practice]

Analytical Method(s) : (1) Protocol Deviations
Frequency distribution will be provided for each deviation category. A subject who has several deviations will be counted once in each appropriate category. A subject who has several deviations that can be classified into the same category will be counted only once.

7.3.4.2 Analysis Sets

Analysis Set:	All Subjects Who Entered the Treatment Period	
Analysis Variable(s) :	Handling of Subjects	[Categories are based on the specifications in Section 7.2

		"Analysis Sets"]
	Analysis Sets	
	Full Analysis Set	[Included]
	Response-evaluable Analysis Set	[Included]
	Safety Analysis Set	[Included]
Analytical Method(s) :	(1) Subjects Excluded from Analysis Sets (2) Analysis Sets Frequency distributions will be provided. For (1), a subject who has several reasons for exclusion will be counted once in each appropriate category. A subject who has several reasons for exclusion that can be classified into the same category will be counted only once.	

7.4 Demographic and Other Baseline Characteristics

7.4.1.1 Demographic and Other Baseline Characteristics

Analysis Set:	Full Analysis Set	
Analysis Variable(s) :	Age (years)	[Min<= - <=65, 65< - <=75, 75< - <=Max]
	Sex	[Male, Female]
	Ethnicity	[Hispanic or Latino, Not Hispanic or Latino, Not Reported]
	Race	[White, Black or African American, Native Hawaiian or Other Pacific Islander, Asian (Asian Indian), Asian (Chinese), Asian (Japanese), Asian (Korean), Asian (Other), Asian (Not Reported), American Indian or Alaska Native, Not Reported, Other]
	Baseline Height (cm)	
	Baseline Weight (kg)	
	Baseline Body Surface Area (m^2)	
	Time Since Initial Diagnosis to First Dose at Study Entry (months)	
	ISS Stage at Initial Diagnosis	[I, II, III, Unknown]

Patient Population Categories	[Relapsed Patients, Refractory Patients, Refractory and Relapsed Patients]
Type of Myeloma at Initial Diagnosis	
IgG	[Kappa, Lambda, Biclonal, Unknown]
IgA	[Kappa, Lambda, Biclonal, Unknown]
IgD	[Kappa, Lambda, Biclonal, Unknown]
IgE	[Kappa, Lambda, Biclonal, Unknown]
IgM	[Kappa, Lambda, Biclonal, Unknown]
Biclonal	[Kappa, Lambda, Biclonal, Unknown]
Unknown	[Kappa, Lambda, Biclonal, Unknown]
Other	[Kappa, Lambda, Biclonal, Unknown]
Durie-Salmon Stage at Initial Diagnosis	[IA, IB, IIA, IIB, IIIA, IIIB, Unknown]
Lines of Prior Therapy	[1, 2, 3]
Evidence of Lytic Bone Disease at Initial Diagnosis	[Yes, No, Unknown]
Evidence of Extramedullary Disease at Initial Diagnosis	[Yes, No, Unknown]
Patients with a Bone Marrow Transplant or Stem Cell Transplant	
Type of Transplant Procedure	[Allogenic, Autologous, Both, Unknown]
Time Since Last Transplant to First Dose at Study Entry (months)	
Type of Prior Regimens	[Velcade Contained, Thalidomide Contained, Thalidomide Refractory,

	Lenalidomide Contained, Corticosteroids Contained, Dexamethasone, Prednisone, Other, Carfilzomib Contained, Melphalan Contained, Other]
Type of Last Prior Regimen	[Velcade Contained, Thalidomide Contained, Thalidomide Refractory, Lenalidomide Contained, Corticosteroids Contained, Dexamethasone, Prednisone, Other, Carfilzomib Contained, Melphalan Contained, Other]
Patient was Relapsed on Last Prior Therapy	[Yes, No]
Patient was Refractory on Last Prior Therapy	[Yes, No]
Time Since Last Dose of Prior Therapy to First Dose at Study Entry (months)	
Best Response to Prior Therapy	[Complete Response, Partial Response, Stable Disease, Progressive Disease, Unable to Assess, Unknown]
Time Since Disease Progression on Prior Therapy to First Dose at Study Entry (months)	
Patients with Prior Radiation	
Time Since Last Prior Radiation to First Dose at Study Entry (months)	

Patients with Prior Surgery or Non-Radiation Procedures	
Time Since Last Prior Surgery or Non-Radiation Procedure to First Dose at Study Entry (months)	
Prior IMiD Therapy	[Exposed, Thalidomide, Lenalidomide, Pomalidomide, Naive]
Patient was Refractory to Any Prior IMiD Therapy	[Yes, No]
Prior Proteasome Inhibitor Therapy	[Exposed, Velcade, Carfilzomib, Naive]
Patient was Refractory to Any Prior Proteasome Inhibitor Therapy	[Yes, No]
Primary Refractory Patients	[Progression Disease, Stable Disease]
ISS Stage for Myeloma at Study Entry	[I, II, III]
Evidence of Lytic Bone Disease	[Present, Absent, Unknown]
Extramedullary Disease at Study Entry	[Yes, No, Unknown]
Serum M-Protein (g/L)	
Urine M-Protein (g/24h)	
Serum Creatinine (mg/dL)	[Min<= - <=2, 2< - <=Max]
Serum Albumin (g/L)	[Min<= - <35, 35<= - <=Max]
β_2-microglobulin (mg/L)	[Min<= - <3.5, 3.5<= - <5.5, 5.5<= - <=Max]
Creatinine Clearance (mL/min)	[Min<= - <30, 30<= - <60, 60<= - <90, 90<= - <=Max]
Corrected Calcium (mmol/L)	
Baseline ECOG Performance Status	[0, 1, 2, 3, 4]
Baseline Hemoglobin (g/L)	

Analytical

Method(s) : (1) Summary of Demographics and Baseline Characteristics
Frequency distributions for categorical variables and descriptive statistics for continuous variables will be provided.

7.4.1.2 Baseline Bone Marrow Evaluation and Extramedullary Disease Assessment

Analysis Set: Full Analysis Set
Analysis

Variable(s) :		
Bone Marrow Aspiration		
	Number of Patients with Bone Marrow Aspiration	
	Number of Patients with Adequate Sample for Interpretation	
	% Plasma Cells	[Available, Unable to Detect, Not Available]
Bone Marrow Biopsy		
	Number of Patients with Bone Marrow Biopsy	
	Number of Patients with Adequate Sample for Interpretation	
	% Plasma Cells	[Available, Unable to Detect, Not Available]
	% Marrow Cellularity	[Available, Not Available]
	Marrow Cellularity Status	[Hypocellular, Hypercellular, Normocellular, Unable to Assess]
Immunohistochemistry or Immunofluorescence for Kappa/Lambda Ratio Performed		[Yes, No, Not Applicable]
Ratio Determined by Analysis of a Minimum of 100 Plasma Cells		[Yes, No, Not Applicable]
% Plasma Cells in Bone Marrow		
Kappa/Lambda Ratio		
Bone Marrow Cytogenetic Results		
	Sample Collected?	[Yes, No, Not Applicable]
	Method of Assessment	[Conventional/Karotype, Molecular/FISH, Both]

Cytogenetic Results (Conventional/Karotype)	[Normal, Abnormal, Indeterminate]
Cytogenetic Results (Molecular/FISH)	[Normal, Abnormal, Indeterminate]
Abnormality of Chromosomal Aberrations	
Subjects with Any Chromosomal Abnormalities	[Del 13 or -13q, Del 17 or -17p, t(4;14), t(6;14), t(8;14), t(11;14), t(12;14), t(14;16), t(14;20), Hyperdiploidy, Hypodiploidy, Non-hyperdiploidy, 1q amplification, 1q deletion, Other]
Cytogenetic Results	[High Risk, Standard, Not Available]
Skeletal Survey	
Result	[Within Normal Limits, Abnormal]
Lytic Bone Lesions Present	[Yes, No, Indeterminate]
Imaging (Computed Tomography)	
Result	[Within Normal Limits, Abnormal]
Plasmacytomas Present	[Yes, No, Indeterminate]
Imaging (Magnetic Resonance Imaging)	
Result	[Within Normal Limits, Abnormal]
Plasmacytomas Present	[Yes, No, Indeterminate]
Imaging (Positron Emission Tomography)	
PET Activity	[FDG Positive, FDG Negative, Indeterminate]
Subjects with Plasmacytomas	[Liver (Visceral), Lung (Visceral), Node, Soft Tissue, Lytic Bone, Other]
Number of Plasmacytomas	[1, 2, >=3]
Soft Tissue Plasmacytomas Total Size (cm^2)	
Lytic Bone Plasmacytomas Total Size (cm^2)	

Analytical

Method(s) : (1) Baseline Bone Marrow Evaluation and Extramedullary Disease Assessment

Frequency distributions for categorical variables and descriptive statistics for continuous variables will be provided.

7.4.1.3 Baseline Bone Marrow Cytogenetic Results

Analysis Set: Full Analysis Set

Analysis Variable(s) : Cytogenetics [Del 13, Del 17, t(4;14), t(14;16), 1q amplification]

Analytical Method(s) : Frequency distributions will be provided by the laboratory (central laboratory, local lab and total).

7.4.1.4 Disease Specific History – IMiD and Proteasome Inhibitor

Analysis Set: Full Analysis Set

Analysis Variable(s) : Exposed to Prior IMiD Therapy

Lenalidomide

Lenalidomide Refractory

Best Response [CR, PR, SD, PD, Unable to Assess, Unknown]

Thalidomide

Thalidomide Refractory

Best Response [CR, PR, SD, PD, Unable to Assess, Unknown]

Pomalidomide

Pomalidomide Refractory

Best Response [CR, PR, SD, PD, Unable to Assess, Unknown]

Exposed to Prior Proteasome Inhibitor Therapy

Velcade

Velcade Refractory

Best Response [CR, PR, SD, PD, Unable to Assess,

Unknown]

Carfilzomib

Carfilzomib Refractory

Best Response [CR, PR, SD, PD, Unable to Assess, Unknown]

Analytical Method(s) : (1) Disease Specific History – IMiD and Proteasome Inhibitor

Frequency distributions for categorical variables will be provided. For the analysis variables "Exposed to Prior IMiD Therapy", "Lenalidomide", "Thalidomide", "Pomalidomide", "Exposed to Prior Proteasome Inhibitor Therapy", "Velcade", and "Carfilzomib", the denominators for the percentages will be the number of subjects in FAS. For the analysis variables "Lenalidomide Refractory", "Thalidomide Refractory", "Pomalidomide Refractory", "Velcade Refractory", and "Carfilzomib Refractory", the denominators for the percentages will be the number of subjects who were exposed to the specified therapy (Lenalidomide, Thalidomide, Pomalidomide, Velcade, or Carfilzomib). For the analysis variable "Best Response", the denominators for the percentages will be the number of subjects who were refractory to the specified therapy (Lenalidomide, Thalidomide, Pomalidomide, Velcade, or Carfilzomib).

7.4.1.5 Summary of Baseline Measurable Status in Subjects with only Abnormal Baseline Free Light Chain

Analysis Set: Full Analysis Set

Analysis Variable(s) : Free Light Chains (no Heavy Chain)

Measureable

Measureable by FLC only

Non-measureable

Analytical Method(s) : (1) Summary of Baseline Measurable Status in Subjects with only Abnormal Baseline Free Light Chain

Frequency distributions for categorical variables will be provided.

7.4.1.6 Summary of New Primary Malignancy

Analysis Set:	Full Analysis Set	
Analysis Variable(s) :	Subjects with any New Primary Malignancy	
	New Primary Malignancy Disease Type (On Treatment)	[Categories will be based on actual data]
	New Primary Malignancy Disease Type (Follow-up)	[Myelodysplastic syndrome, Acute myeloid leukaemia or related precursor neoplasm, Precursor lymphoid neoplasm, Mature B-cell neoplasm, Mature T-cell and NK-cell neoplasm, Hodgkin lymphoma, Solid Tumor, Other]
Analytical Method(s) :	(1) Summary of New Primary Malignancy Frequency distributions will be provided. Summaries will be provided using the new primary malignancy disease type and its detailed categories, where the detailed categories will be sorted alphabetically.	

7.5 Medical History and Concurrent Medical Conditions

Analysis Set:	Safety Analysis Set
Analysis Variable(s) :	Medical History Concurrent Medical Conditions
Analytical Method(s) :	(1) Medical History by Verbatim Term (2) Concurrent Medical Conditions by Verbatim Term Frequency distributions will be provided. Summary will be provided using verbatim terms. A subject with multiple occurrences of medical history within a verbatim term will be counted only once in that verbatim term.

7.6 Medication History and Concomitant Medications

Analysis Set: Safety Analysis Set

Analysis Variable(s): Concomitant Medications

Analytical Method(s): (1) Concomitant Medications by ATC Pharmacological Subgroup and WHO Generic Term

Frequency distributions will be provided. Concomitant medications are defined as medications with start dates occurring on or after date of first dose and before date of last dose + 30 days. WHO Drug dictionary will be used for coding. Summaries will be provided using ATC pharmacological subgroup and WHO generic term. ATC pharmacological subgroup will be sorted alphabetically and WHO generic term will be sorted in decreasing frequency based on the number of reports. A subject who has been administered several medications with the same WHO generic term will be counted only once for that WHO generic term.

7.7 Study Drug Exposure and Compliance

7.7.1.1 Study Drug Exposure and Compliance

Analysis Set: Safety Analysis Set

Analysis Variable(s):

Total Amount of Doses Taken (mg)	
Total Number of Doses Taken	
Number of Treated Cycles	[>=1, >=2, >=3, >=4, >=5, >=6, >=7, >=8, >=9, >=10, >=11, >=12, >=13, >=14, >=15, >=16, >=17, >=18, >=19, >=20, >=21, >=22, >=23, >=24]
Relative Dose Intensity (%)	[Min<= - <50, 50<= - <80, 80<= - <100, 100, 100< - <=Max]
Extent of Exposure (cycles)	[1<= - <=3, 4<= - <=6, 7<= -<=9, 10<= - <=12, 13<= - <=15,

		16<= - <=18, 19<= - <=21, 22<= - <=24, 24< - <=Max]
	Extent of Exposure (days)	
	Percent Drug Compliance (%)	[Min<= - <50, 50<= - <=65, 65< - <=80, 80< - <=100, 100< - <=Max]

Analytical Method(s) :

(1) Study Drug Exposure and Compliance – Ixazomib
(2) Study Drug Exposure and Compliance – Lenalidomide
(3) Study Drug Exposure and Compliance – Dexamethasone
(4) Study Drug Exposure and Compliance – Combination (Ixazomib, Lenalidomide, Dexamethasone)

Frequency distributions for categorical variables and descriptive statistics for continuous variables will be provided. For (4), only the number of treated cycles, extent of exposure (cycles), and extent of exposure (days) will be provided.

Mean and 95% CI plots of changes over time will be provided for the relative dose intensity. A treated cycle is defined as a cycle in which the patients received any amount of Ixazomib for (1), Lenalidomide for (2), Dexamethasone for (3), and any of Ixazomib, Lenalidomide, Dexamethasone for (4).

7.7.1.2 Dose Modifications

Analysis Set: Safety Analysis Set

Analysis Variable(s) :

Dose Modification	
Cycle Delayed	
Action on Drug	[No Action Taken, Reduced Prescribed, Reduced Non-Prescribed, Increased Prescribed, Increased non-Prescribed, Held, Missed, Delayed, Discontinued Permanently]
Number of Subjects with at least 1 Dose Reduction	
Number of Subjects with at least 2 Dose Reduction	

Analytical

Method(s) : (1) Dose Modifications – Ixazomib
(2) Dose Modifications – Lenalidomide
(3) Dose Modifications – Dexamethasone

Frequency distributions will be provided for overall, for every cycle from Cycle 1 to 18, and for Cycles 1-6, 7-12, 13-18, 19-21, 22-24, >=25. The analysis variable "dose modification" includes reduced prescribed, reduced non-prescribed, increased prescribed, increased non-prescribed, delayed, and discontinued permanently. For the analysis variable "Action on Drug", a subject will be counted once for each unique reason for dose modification that they have had over the course of the study. For "Action on Drug", the numerators for the percentages are the number of subjects with a dosing modification and the denominators are the total number of subjects with non-missing dosing data. Dose reduction is defined as a prescribed reduction in dose over consecutive scheduled dosing days.

7.8 Efficacy Analysis

7.8.1 Primary Efficacy Endpoint(s)

7.8.1.1 Primary Analysis

Analysis Set: Response-evaluable Analysis Set

Analysis Variable(s): CR
sCR
PR
VGPR
Overall Response (CR+PR (including sCR and VGPR))
VGPR or better (CR+VGPR)
SD
PD

Analytical Method(s): The VGPR or better (CR + VGPR) rate and the 2-sided 95% confidence intervals will be provided in the response-evaluable analysis set as the primary analysis. The response rate and the 2-sided 95% confidence intervals will be provided for each analysis variable based on the confirmed best response.
The response rates and the 2-sided 95% confidence intervals will also be summarized based on the unconfirmed best response and the best response (confirmed or unconfirmed) at the end of each cycle (from Cycle 1 to Cycle 24).
The ORR is defined as the proportion of patients who achieved PR or better.
Stacked bar graph will be provided for ORR (confirmed or unconfirmed) and ORR (confirmed) at the end of each cycle and overall.

7.8.1.2 Sensitivity Analysis

Analysis Set: Full Analysis Set

Analysis Variable(s): CR
sCR
PR
VGPR

Overall Response (CR+PR (including sCR and VGPR))
VGPR or better (CR + VGPR)
SD
PD
Not Evaluable

Analytical Method(s): To check the robustness of the results, the same analyses as those in Section 7.8.1.1 will be performed using FAS, except for the summary based on the best response (confirmed or unconfirmed) at the end of each cycle and the stacked bar graphs for ORR. Non-evaluable subjects in FAS will only be included in the denominator when calculating the response rates.
The VGPR or better (CR + VGPR) rate and the 2-sided 95% confidence intervals will be provided in FAS as the sensitivity analysis for the primary analysis. Non-evaluable subjects in FAS will be included in the analysis as not VGPR or CR.

7.8.2 Secondary Efficacy Endpoint(s)

7.8.2.1 Progression-free Survival

Analysis Set: Full Analysis Set

Analysis Variable(s): PFS

Analytical Method(s): For the PFS, the Kaplan-Meier curve [and the 25th, 50th (median), and 75th percentiles, if estimable] will be calculated with their 2-sided 95% CIs in FAS. Kaplan-Meier estimates will also be calculated at 6 months, 9 months, 12 months, 18 months, and 24 months with their 2-sided 95% CIs. The median follow-up time in months and its 2-sided 95% CI will also be provided.
PFS is defined as the time from the date of first study drug administration to the date of first documentation of PD or death from any cause, whichever occurs first. The number of subjects with events and the number of subjects censored will be provided as well as the reason for censoring. Patients without documentation of PD will be censored at the date of the last response assessment that is SD or better. The details regarding the handling of missing assessments and censoring are presented in the table below.

Situation	Date of Progression or Censoring	Outcome
No baseline and/or no post baseline assessment, no subsequent anticancer therapy after study treatment, no death	Date of first dose	Censored
Disease progression documented between scheduled visits	Date of next scheduled visit	Progressed
No documented death or disease progression	Date of last adequate assessment[1]	Censored
Lost to follow-up, withdraw consent before any documented death or disease progression	Date of last adequate assessment[1]	Censored
Death or progression after more than 1 missed visit[2]	Date of last adequate assessment[1]	Censored
Alternate antineoplastic therapy started prior to disease progression	Date of last adequate assessment prior to starting alternate antineoplastic therapy	Censored
Death before first post baseline assessment	Date of death	Progressed
Death between adequate assessment visits	Date of death	Progressed

[1]: Adequate disease assessment is defined as there is sufficient data to evaluate a subject's disease status.

[2]: Death or progression occurs more than 90 days from previous adequate assessment.

7.8.2.2 Duration of Response

Analysis Set: Responders in the Full Analysis Set

Analysis Variable(s): DOR

Analytical Method(s): For the DOR, the Kaplan-Meier curve [and the 25th, 50th (median), and 75th

percentiles, if estimable] will be calculated with their 2-sided 95% CIs for the subjects who responded to the study treatment among the FAS. Kaplan-Meier estimates will also be calculated at 6 months, 12 months, 18 months, and 24 months with their 2-sided 95% CIs.
DOR is defined as the time from the date of first documentation of response to the first documentation of PD. Responders without documentation of PD will be censored at the date of their last response assessment that is SD or better. The number of subjects with events and the number of subjects censored will be provided as well as the reason for censoring.
For the analysis of DOR, "response" will be defined as (1) VGPR or better (2) ORR (3) CR and the same analysis will be performed for each type of response.

7.8.2.3 Time to Progression

Analysis Set:	Full Analysis Set
Analysis Variable(s):	TTP
Analytical Method(s):	For the TTP, the Kaplan-Meier curve [and the 25th, 50th (median), and 75th percentiles, if estimable] will be calculated with their 2-sided 95% CIs in FAS. Kaplan-Meier estimates will also be calculated at 6 months, 9 months, 12 months, 18 months, and 24 months with their 2-sided 95% CIs. TTP is defined as the time from the date of first study drug administration 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 their last response assessment that is SD or better. Patients with no response assessment will be censored at the first day of administration. Patients who do not experience progression and start new systemic therapy for multiple myeloma will be censored at the date of their last response assessment that is SD or better. The number of subjects with events and the number of subjects censored will be provided as well as the reason for censoring.

7.8.2.4 Overall Survival

Analysis Set: Full Analysis Set

Analysis Variable(s): OS

Analytical Method(s): For the OS, the Kaplan-Meier curve [and the 25th, 50th (median), and 75th percentiles, if estimable] will be calculated with their 2-sided 95% CIs in FAS. Kaplan-Meier estimates will also be calculated at 6 months, 9 months, 12 months, 18 months, and 24 months with their 2-sided 95% CIs. The median follow-up time in months and its 2-sided 95% CI will also be provided.

OS is defined as the time from the date of first study drug administration to the date of death. Subjects without documentation of death at the time of the analysis will be censored at the date when they were last known to be alive. The number of deaths and the number censored will be provided as well as the reason for censoring.

7.8.3 Additional Efficacy Endpoint(s)

7.8.3.1 Best M-Protein Response to Treatment

Analysis Set: Response-evaluable Analysis Set

Analysis Variable(s): Best M-Protein Response

Categories: Response Category

[100% Reduction,
Immunofixation Negative,
>=90% Reduction,
>=50% Reduction]
[90 - <100% Reduction,
75 - <90% Reduction,
50 - <75% Reduction,
25 - <50% Reduction]
[<25% Reduction to <25% Increase,
>=25% Increase]
No Post-Baseline Assessment of Measurable M-Protein

Analytical

Method(s): Frequency distribution will be provided. For subjects with measurable serum M-protein at baseline, the best M-protein response is the percent change from baseline to best (lowest) value post-baseline in serum M-protein. For subjects with non-measurable serum M-protein, but measurable urine M-protein, the best M-protein response is the percent change from baseline to best (lowest) value post-baseline in urine M-protein. Mean and standard deviation plots of changes over time of serum M-protein will be provided for observed values and percent changes from baseline. A waterfall plot of serum M-protein will be provided for the percent changes from baseline.

7.8.3.2 Time to Response

Analysis Set: Responders in the Response-evaluable Analysis Set
Full Analysis Set

Analysis Variable(s): VGPR or better (CR + VGPR)
Overall Response

Analytical Method(s): For the time to response, the Kaplan-Meier curve [and the 25th, 50th (median), and 75th percentiles, if estimable] will be calculated with their 2-sided 95% CIs, showing as cumulative distribution function. Kaplan-Meier estimates will also be calculated at 6 months, 9 months, 12 months, 18 months, and 24 months with their 2-sided 95% CIs.
Time to response is defined as the time from the date of first study drug administration to the date of first documentation of the confirmed response indicated in the analysis variable. Responders are defined as subjects with documentation of a confirmed response of the analysis variable. The number of subjects with events and the number of subjects censored will be provided. The same analyses will be performed using FAS.

7.8.3.3 Duration of Follow-up

Analysis Set: Full Analysis Set

Analysis Variable(s): Duration of Follow-up

Analytical Method(s): For the duration of follow-up, the Kaplan-Meier estimates [the 25th, 50th

(median), and 75th percentiles, if estimable] will be calculated with their 2-sided 95% CIs. Kaplan-Meier estimates of the follow-up rate will also be calculated at 6 months, 9 months, 12 months, 18 months, and 24 months with their 2-sided 95% CIs. The median follow-up time in months and its 2-sided 95% CI will also be provided.

Duration of follow-up is defined as time from the date of first study drug administration to the date of death or last known visit. The number of subjects with events and the number of subjects censored will be provided as well as the reason for censoring.

7.8.4 Statistical/Analytical Issues

7.8.4.1 Adjustments for Covariates

Not applicable.

7.8.4.2 Handling of Dropouts or Missing Data

Censoring rules have been described in each applicable section. For M-protein, values below the lower limit of quantification will be treated as zero.

7.8.4.3 Multicenter Studies

Treatment-by-center interaction will not be explored since this study is a single-arm study.

7.8.4.4 Multiple Comparison/Multiplicity

Not applicable.

7.8.4.5 Use of an "Efficacy Subset" of Subjects

In addition to analyses on the primary endpoint using the response-evaluable analysis set, a secondary analysis will also be performed using the FAS to examine the robustness of the results.

7.8.4.6 Active-Control Studies Intended to Show Equivalence or Non-Inferiority

Not applicable.

7.8.4.7 Examination of Subgroups

Analysis Set: Response-evaluable Analysis Set
Full Analysis Set

Analysis Variable(s): CR
sCR

	PR	
	VGPR	
	Overall Response (CR+PR (including sCR and VGPR))	
	VGPR or better (CR + VGPR)	
	SD	
	PD	
Subgroup(s):	Age (years)	[Min<= - <=65, 65< - <=75, 75< - <=Max]
	Sex	[Male, Female]
	Cytogenetic Risk	[High Risk {(del17); t(4;14); t(14;16)}, Non-High Risk]
	ISS Stage for Myeloma at Study Entry	[I, II, III]
	Lines of Prior Therapy	[1, 2 or 3]
	Prior Proteasome Inhibitor Therapy	[Exposed, Naive]
	Prior IMiD Therapy	[Exposed, Naive]
	Thalidomide Refractory	[Yes, No]
	Refractory to Any Line of Prior Therapy	[Yes, No]
	Patient was Refractory on Last Prior Therapy	[Yes, No]
	Relapsed and/or Refractory	[Relapsed, Refractory, Relapsed and Refractory]
	Prior Velcade Therapy	[Exposed, Naive]
	Creatinine Clearance (mL/min)	[Min<= - <60, 60<= - <=Max]
	Baseline ECOG Performance Status	[0 or 1, 2]
	Prior Lenalidomide Therapy	[Exposed, Naive]
	Prior Thalidomide Therapy	[Exposed, Naive]
Analytical Method(s):	The same analyses as those in Sections 7.8.1.1 and 7.8.1.2 will be performed with the confirmed best response for each subgroup. A forest plot will be produced using the VGPR or better (CR+VGPR) rate and the 2-sided 95% confidence intervals.	

7.8.4.8 Examination of Subgroups – Summary Table

Analysis Set:	Response-evaluable Analysis Set	
	Full Analysis Set	
Analysis Variable(s):	ORR	
	VGPR or better	
	CR or better	
Subgroup(s):	Age (years)	[Min<= - <=65, 65< - <=75, 75< - <=Max]
	Sex	[Male, Female]
	Cytogenetic Risk	[Not Available, Standard Risk, High Risk, High Risk (del17), High Risk t(4;14), High Risk t(14;16)]
	Baseline ECOG Performance Status	[0, 1, 2]
	Prior Lines of Therapy per Takeda review	[1, with SCT, without SCT, 2, with SCT, without SCT, 3, with SCT, without SCT]
	Relapsed/Refractory Type	[Relapsed, Refractory, Relapsed and Refractory, Primary Refractory]
	Prior Proteasome Inhibitor	[Exposed, Naive, Refractory (Takeda), Vc-Refractory (Takeda), CFZ-Refractory (Takeda)]
	Prior IMiD	[Exposed, Naive, Refractory (Takeda), Thal-Refractory (Takeda), Len-Refractory (Takeda)]
	ISS stage at Study Entry	[I, II, III]
	Best Response	[>=CR, >=VGPR, >=PR, SD, PD]
	Creatinine Clearance (mL/min)	[Min<= - <60, 60<= - <=Max]
	1 Prior Line with SCT	
	High Risk	

ISS 3	
Prior IMiD	[Exposed, Naive]
Thalidomide	[Exposed, Naive]
Lenalidomide	[Exposed, Naive]
Maintenance Therapy (Takeda)	[Yes, No]
Time from Last SCT to First Dose (Months)	[0<= - <12, 12<= - <24, 24<= - <36, 36<= - <=Max]
Prior PI	[Exposed, Naive]
1 Prior Line with SCT	
Single vs. Double SCT	[Single SCT, Double SCT]
With Velcade + Thalidomide	[Yes, No]
With Velcade + Lenalidomide	[Yes, No]
Best Response on Prior SCT	[CR, PR, SD or PD]
ECOG	[0, 1]
Low Bone Marrow Cellularity	[Yes, No, Missing]
Cytogenetic Risk	[Not Available, 1 Line with SCT, Others]

Analytical Method(s): Frequency distributions for each analysis variable will be provided for each subgroup.

7.9 Pharmacokinetic/Pharmacodynamic Analysis

7.9.1 Pharmacokinetic Analysis

Not applicable.

7.9.2 Pharmacodynamic Analysis

Not applicable.

7.10 Other Outcomes

Not applicable.

7.11 Safety Analysis

7.11.1 Adverse Events

7.11.1.1 Overview of Treatment-Emergent Adverse Events

Analysis Set: Safety Analysis Set

Analysis Variable(s): TEAE

Analytical Method(s): The following summaries will be provided.

(1) Overview of Treatment-Emergent Adverse Events
   1) Any adverse event
   2) Grade 3 or higher adverse event
   3) Drug-related adverse event
   4) Drug-related grade 3 or higher adverse event
   5) Serious adverse event
   6) Drug-related serious adverse event
   7) Adverse events resulting in any study drug dose reduction
   8) Adverse events resulting in any study drug dose modification
   9) Adverse events resulting in any study drug discontinuation
   10) On-study deaths

For summary 8), dose modification will include dose reduction, dose increase, dose delay, and dose discontinuation.

TEAEs will be counted according to the rules below.

Number of subjects

- Summaries for 3), 4), and 6)
  A subject with occurrences of TEAE in both categories (i.e., Related and Not Related) will be counted once in the Related category.
- Summaries for 2) and 4)
  A subject with multiple occurrences of TEAE will be counted once for the TEAE with the maximum intensity.
- Summaries other than 2), 3), 4), and 6)
  A subject with multiple occurrences of TEAE will be counted only once.

7.11.1.2 Overview of Treatment-Emergent Adverse Events by Subgroups

Analysis Set:	Safety Analysis Set	
Analysis Variable(s) :	TEAE	
Subgroup(s):	Cycles	[1-6, 7-12, 13-18, >=19]
	Sex	[Male, Female]
	Creatinine Clearance (mL/min)	[Min<= - <60, 60<= - <=Max]

Analytical Method(s) : The same overview summary as Section 7.11.1.1 will be provided for each subgroup category.

(1) Overview of Treatment-Emergent Adverse Events by Cycle in Subjects with >= 12 Cycles Exposure
(2) Overview of Treatment-Emergent Adverse Events by Sex
(3) Overview of Treatment-Emergent Adverse Events by Creatinine Clearance

The summary in (1) will be based on subjects who have completed 12 cycles or more of the study drug.

7.11.1.3 Displays of Treatment-Emergent Adverse events

Analysis Set:	Safety Analysis Set	
Analysis Variable(s) :	TEAE	
Categories:	Intensity	[Grade 1, Grade 2, Grade 3, Grade 4, Grade 5]
	Time of Onset (Cycle)	[1 –3, 4 – 6, 7 – 9, 10 – 12, 13 – 15, 16 – 18, 19 – 21, 22 – 24]

Analytical Method(s) : The following summaries will be provided using frequency distribution. TEAEs will be coded using the MedDRA and will be summarized using SOC, HLT, and PT.

SOC, HLT, and PT will be sorted in decreasing frequency for tables provided by SOC, HLT, and PT. SOC will be sorted alphabetically and PT will be sorted in decreasing frequency for tables provided by SOC and PT. PT will be sorted in decreasing frequency for tables provided by PT only.

(1) Treatment-Emergent Adverse Events by System Organ Class, High

Level Term, and Preferred Term

(2) Treatment-Emergent Adverse Events by Preferred Term

(3) Treatment-Emergent Drug-Related Adverse Events by System Organ Class, High Level Term, and Preferred Term

(4) Treatment-Emergent Grade 3 or Higher Adverse Events by System Organ Class, High Level Term, and Preferred Term

(5) Treatment-Emergent Grade 3 or Higher Adverse Events by Preferred Term

(6) Treatment-Emergent Drug-Related Grade 3 or Higher Adverse Events by System Organ Class, High Level Term, and Preferred Term

(7) Treatment-Emergent Grade 4 Adverse Events by System Organ Class, High Level Term, and Preferred Term

(8) Intensity of Treatment-Emergent Adverse Events by System Organ Class, High Level Term, and Preferred Term

(9) Intensity of Treatment-Emergent Drug-Related Adverse Events by System Organ Class, High Level Term, and Preferred Term

(10) Treatment-Emergent Adverse Events Leading to Study Drug Discontinuation by System Organ Class, High Level Term, and Preferred Term

(11) Treatment-Emergent Serious Adverse Events by System Organ Class, High Level Term, and Preferred Term

(12) Treatment-Emergent Drug-Related Serious Adverse Events by System Organ Class, High Level Term, and Preferred Term

(13) Treatment-Emergent Adverse Events by System Organ Class, High Level Term, and Preferred Term Over Time

(14) Most Frequent Non Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(15) Summary of Treatment-Emergent Adverse Events which Resulted in Dose Reduction by System Organ Class and Preferred Term

(16) Summary of Treatment-Emergent Adverse Events which Resulted in Dose Held by System Organ Class and Preferred Term

(17) Summary of Treatment-Emergent Adverse Events which Resulted in Dose Discontinuation by System Organ Class and Preferred Term

The frequency distribution will be provided according to the rules below.

Number of subjects

- Summary tables other than (4) to (9) and (13)

A subject with multiple occurrences of TEAE within a SOC will be counted only once in that SOC. A subject with multiple occurrences of TEAE within an HLT will be counted only once in that HLT. A subject with multiple occurrences of TEAE within a PT will be counted only once in that PT. Percentages will be based on the number of subjects in the safety analysis set.

- Summary tables for (4) to (9)
  A subject with multiple occurrences of TEAE within a SOC, an HLT, or a PT will be counted only once for the TEAE with the maximum intensity. Percentages will be based on the number of subjects in the safety analysis set.
- Summary table for (13)
  A subject with a TEAE that occurs in more than one interval is counted in all the intervals that the TEAE occurs. For each time interval, a subject with multiple occurrences of TEAE within a SOC, an HLT, or a PT will be counted only once in that SOC, HLT, or PT.
  When calculating percentages for each time interval, the number of subjects at risk (i.e., subjects who either have an exposure or have an occurrence of TEAE, during or after the corresponding time interval) will be used as the denominator. The number of subjects whose onset of any one of the TEAEs is within the time interval will be used as the numerator.
- Summary table for (14)
  Most frequent non-serious TEAEs refer to PTs that are not serious whose percentages are at least 5%.
- Summary table for (15)
  TEAEs which resulted in dose reduction in Ixazomib, in Lenalidomide, and in Dexamethasone will each be displayed, as well as the TEAEs which resulted in dose reduction in any of Ixazomib, Lenalidomide, or Dexamethasone.
- Summary table for (16)
  TEAEs which resulted in dose held in Ixazomib, in Lenalidomide, and in Dexamethasone will each be displayed, as well as the TEAEs which resulted in dose held in any of Ixazomib, Lenalidomide, or Dexamethasone.
- Summary table for (17)
  TEAEs which resulted in dose discontinuation in Ixazomib, in

Lenalidomide, and in Dexamethasone will each be displayed.

7.11.1.4 Displays of Treatment-Emergent Adverse Events of Clinical Importance and Haemorrhage

Analysis Set:	Safety Analysis Set
Analysis Variable(s) :	TEAE of clinical importance Treatment-emergent haemorrhage adverse events
Categories:	NCI CTCAE Grade [Grade 1, Grade 2, Grade 3, Grade 4, Grade 5]
Analytical Method(s) :	Adverse events of clinical importance will include diarrhea, rash, neutropenia, thrombocytopenia, nausea, peripheral neuropathy, vomiting, arrhythmias, renal, liver impairment, hypotension, heart failure, new primary malignancy, myocardial infarction, and encephalopathy. The following summaries will be provided using frequency distribution. For (2) and (3), descriptive statistics will be provided. For (3), time to resolution from the first onset of the AE will be summarized. If no date of resolution is recorded, then the last date of visit will be used as the date of resolution. TEAEs will be coded using the MedDRA and will be summarized using PT for (1) to (6). For (1), PT will be sorted in decreasing frequency. For (4) to (6), AECI and PT will both be sorted alphabetically. A subject with multiple occurrences of TEAE within a PT will be counted only once for the TEAE with the maximum intensity. For (4), TEAEs of clinical importance which resulted in dose reduction in Ixazomib, in Lenalidomide, and in Dexamethasone will each be displayed, as well as TEAEs of clinical importance which resulted in dose reduction in any of Ixazomib, Lenalidomide, or Dexamethasone. For (5), TEAEs of clinical importance which resulted in dose held in Ixazomib, in Lenalidomide, and in Dexamethasone will each be displayed, as well as TEAEs of clinical importance which resulted in dose held in any of Ixazomib, Lenalidomide, or Dexamethasone. For (6), TEAEs of clinical importance which resulted in dose discontinuation in Ixazomib, in Lenalidomide, and in Dexamethasone will each be displayed, as well as TEAEs of clinical importance which resulted in dose discontinuation in any of Ixazomib, Lenalidomide, or Dexamethasone. For (7), TEAEs will be summarized using SOC, HLT, and

PT, where SOC, HLT, and PT will be sorted in decreasing frequency.
TEAEs will be graded using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) (Version 4.03).

(1) Treatment-Emergent Adverse Events of Clinical Importance by Preferred Term and NCI CTCAE Grade
(2) Summary of Time to First Onset in Treatment-Emergent Adverse Events of Clinical Importance
(3) Summary of Time to Resolution in Treatment-Emergent Adverse Events of Clinical Importance
(4) Treatment-Emergent Adverse Events of Clinical Importance which Resulted in Dose Reduction by Preferred Term
(5) Treatment-Emergent Adverse Events of Clinical Importance which Resulted in Dose Held by Preferred Term
(6) Treatment-Emergent Adverse Events of Clinical Importance which Resulted in Dose Discontinuation by Preferred Term
(7) Treatment-Emergent Haemorrhage Adverse Events by System Organ Class, High Level Term, and Preferred Term
(8) Treatment-Emergent Adverse Events of Clinical Importance, Grades and Concomitant Medications by ATC Pharmacological Subgroup and WHO Generic Term

7.11.1.5 Summary of Treatment-Emergent Adverse Events Overall, and by Toxicity, Seriousness, Relatedness, Discontinuation, and Dose Modification

Analysis Set: Safety Analysis Set

Analysis Variable(s) : TEAE
TEAE of clinical importance

Analytical Method(s) : The following summaries will be provided using frequency distribution. The summaries will include the number and percentages of subjects who had any TEAEs, drug-related TEAEs, Grade 3 or higher TEAEs, Grade 3 or higher drug-related TEAEs, serious TEAEs, TEAEs resulting in death, TEAEs leading to study drug discontinuation, TEAEs which resulted in dose reduction, dose held, and dose delayed in any of Ixazomib, Lenalidomide, or Dexamethasone. TEAEs will be coded using the MedDRA and will be

summarized using SOC and PT. SOC and PT will be sorted in decreasing frequency.

(1) Summary of Treatment-Emergent Adverse Events Overall, and by Toxicity, Seriousness, Relatedness, Discontinuation, and Dose Modification

(2) Summary of Treatment-Emergent Adverse Events of Clinical Importance Overall, and by Toxicity, Seriousness, Relatedness, Discontinuation, and Dose Modification

7.11.2 Clinical Laboratory Evaluations

7.11.2.1 Hematology and Blood Chemistry

Analysis Set: Safety Analysis Set

Analysis Variable(s) :

Hematology		
Hemoglobin	Hematocrit	Platelet Count
WBC Count	Neutrophils	Lymphocytes
Serum Chemistry		
Blood Urea Nitrogen	Creatinine	Total Bilirubin
Uric Acid	Lactate dehydrogenase (LDH)	Alkaline Phosphatase
AST	ALT	Albumin
Glucose	Sodium	Potassium
Chloride	Carbon dioxide	Magnesium
Calcium	Phosphate	Thyroid Stimulating Hormone (TSH)

Categories: Intensity [Grade 0, Grade 1, Grade 2, Grade 3, Grade 4]

Visit: Hematology: Screening, Baseline, Cycle 1 Day 1, Cycle 1 Day 7, Cycle 1 Day 14, Cycle 1 Day 21, Cycle 2 Day 1, Cycle 2 Day 7, Cycle 2 Day 14, Cycle 2 Day 21, Cycle 3 Day 1, Cycle 3 Day 14, Cycle 4 Day 1, Cycle 5 Day 1, Cycle 6 Day 1, ... (up to the maximum cycle), End of Treatment, Last Assessment

Serum Chemistry: Screening, Baseline, Cycle 1 Day 1, Cycle 2 Day 1, Cycle 3 Day 1, Cycle 4 Day 1, Cycle 5 Day 1, Cycle 6 Day 1, ... (up to the maximum cycle), End of Treatment, Last Assessment

Analytical

Method(s) : For each variable, (1) will be provided.
For applicable variables, (2), (3), and (4) will be provided.
NCI CTCAE (Version 4.03) will be used for grading. Last Assessment is defined as the last measurement prior to or on the last visit conducted 30 days after the last dose of study drug regimen.
Laboratory test results from the central laboratory will be used when they are available. Laboratory test results from local laboratory will be used only when no central laboratory test result exists at the same scheduled sample collection time point.

(1) Summary of Laboratory Test Results and Change from Baseline by Visit
Descriptive statistics for observed values for each visit and changes from baseline will be provided.

(2) Case Plots
Plots over time for each subject will be presented for platelet count.

(3) Line Plot of Platelet Count Over Time
For the platelet count, the overall median over time will be presented.

(4) Maximum Grade Shift from Baseline of Laboratory Parameters
The maximum (worst) post-baseline grade will be determined for each subject. Shift tables showing the number of subjects in each grade category at baseline and post-baseline visit will be provided using evaluable data.

7.11.3 Vital Signs and Weight

Analysis Set: Safety Analysis Set

Analysis Variable(s) : Systolic Blood Pressure (mmHg)
Diastolic Blood Pressure (mmHg)
Heart Rate (bpm)
Respiratory Rate (bpm)
Temperature (C)
Weight (kg)

Visit: Screening, Baseline, Cycle 1 Day 1, Cycle 2 Day 1, Cycle 3 Day 1, Cycle 4 Day 1, ... (up to the maximum cycle), End of Treatment, Last Assessment

Analytical

Method(s) : For each variable, the following summaries will be provided.
Last Assessment is defined as the last measurement prior to or on the last visit conducted 30 days after the last dose of study drug regimen.

(1) Summary of Vital Signs Parameters and Change from Baseline by Visit
Descriptive statistics for observed values for each visit and changes from baseline will be provided.

7.11.4 12-Lead ECGs

Not applicable.

7.11.5 Other Observations Related to Safety

7.11.5.1 ECOG Performance Status

Analysis Set: Safety Analysis Set
Analysis
Variable(s) : ECOG Performance Status
Categories: ECOG Score [0, 1, 2, 3, 4]
Visit: Screening, Baseline, Cycle 2 Day 1, Cycle 3 Day 1, ... (up to the maximum cycle), End of Treatment, Last Assessment
Analytical
Method(s) : For each variable, the following summaries will be provided.
Last Assessment is defined as the last measurement prior to or on the last visit conducted 30 days after the last dose of study drug regimen.

(1) ECOG Performance Status Data Measured Over Time
Descriptive statistics for observed values for each visit and changes from baseline will be provided.

(2) ECOG Performance Score Shift from Baseline to Post-Baseline Assessments Over Time
Shift tables showing the number of subjects in each ECOG score category at baseline and each post-baseline visit will be provided.

7.11.5.2 Subsequent Anti-Cancer Therapy

Analysis Set: Safety Analysis Set
Analysis
Variable(s) : Subsequent Anti-Cancer Therapy
Analytical

Method(s) : (1) Subsequent Anti-Cancer Therapy by Class of Agent and WHO Generic Term

Frequency distributions will be provided.

7.12 Interim Analysis

Analysis is planned to be performed twice during the study. The primary analysis is planned to be performed using the data obtained at approximately 12 months from the enrollment of the last patient. The final analysis is planned to be performed after the final database lock using the data obtained at approximately 24 months from the enrollment of the last patient. The timing of analysis may be changed or additional analysis may be added upon request of the regulatory authorities.

7.13 Changes in the Statistical Analysis Plan

The analyses in the statistical analysis plan do not differ from the analyses specified in the protocol.

Changes from the previous version of SAP are listed below.

Page 20, Section 7.4.1.3 Baseline Bone Marrow Cytogenetic Results

Added Text

Analysis Set: Full Analysis Set

Analysis Variable(s) : Cytogenetics [Del 13, Del 17, t(4;14), t(14;16), 1q amplification]

Analytical Method(s) : Frequency distributions will be provided by the laboratory (central laboratory, local lab and total).

Rationale for Amendment

This section has been added.

Page 22, Section 7.5 Medical History and Concurrent Medical Conditions

Existing Text

(2) Concurrent Medical Conditions by System Organ Class and Preferred Term

Frequency distributions will be provided.

For (1), summary will be provided using verbatim terms. A subject with multiple occurrences of medical history within a verbatim term will be counted only once in that verbatim term.

For (2), MedDRA dictionary will be used for coding. Summary will be provided using SOC and PT, where SOC and PT will be sorted in decreasing frequency. A subject with multiple occurrences of concurrent medical condition within a SOC will be counted only once in that SOC. A subject with multiple occurrences of concurrent medical condition within a PT will be counted only once in that PT.

Revised Text

(2) Concurrent Medical Conditions by Verbatim Term

Frequency distributions will be provided.

Summary will be provided using verbatim terms. A subject with multiple occurrences of medical history within a verbatim term will be counted only once in that verbatim term.

Rationale for Amendment

Concurrent Medical Conditions has not been coded by MedDRA.

Page 30, Section 7.8.3.1 Best M-Protein Response to Treatment

Existing Text

Mean and standard deviation plots of changes over time will be provided for observed values and percent changes from baseline. A waterfall plot of will be provided for the percent changes from baseline.

Revised Text

Mean and standard deviation plots of changes over time of serum M-protein will be provided for observed values and percent changes from baseline. A waterfall plot of serum M-protein will be provided for the percent changes from baseline.

Rationale for Amendment

To clarify the analytical method.

Page 31, Section 7.8.3.2 Time to Response

Existing Text

For the time to response, the Kaplan-Meier curve [and the 25th, 50th (median), and 75th percentiles, if estimable] will be calculated with their 2-sided 95% CIs.

Revised Text

For the time to response, the Kaplan-Meier curve [and the 25th, 50th (median), and 75th percentiles, if estimable] will be calculated with their 2-sided 95% CIs, showing as cumulative distribution function.

Rationale for Amendment

To clarify the analytical method.

Page 31, Section 7.8.3.2 Time to Response

Existing Text

The number of subjects with events and the number of subjects censored will be provided as well as the reason for censoring.

Revised Text

The number of subjects with events and the number of subjects censored will be provided.

Rationale for Amendment

To clarify the analytical method.

Page 31, Section 7.8.3.3 Duration of Follow-up

Existing Text

For the duration of follow-up, the Kaplan-Meier curve [and the 25th, 50th (median), and 75th percentiles, if estimable] will be calculated with their 2-sided 95% CIs. Kaplan-Meier estimates will also be calculated at 6 months, 9 months, 12 months, 18 months, and 24 months with their 2-sided 95% CIs.

Revised Text

For the duration of follow-up, the Kaplan-Meier estimates [the 25th, 50th (median), and 75th percentiles, if estimable] will be calculated with their 2-sided 95% CIs. Kaplan-Meier estimates of the follow-up rate will also be calculated at 6 months, 9 months, 12 months, 18 months, and 24 months with their 2-sided 95% CIs.

Rationale for Amendment

To clarify the analytical method.

Page 32, Section 7.8.4.2 Handling of Dropouts or Missing Data

Adding Text

For M-protein, values below the lower limit of quantification will be treated as zero.

Rationale for Amendment

There have been the values "below the lower limit of quantification".

Page 32, Section 7.8.4.7 Examination of Subgroups

Existing Text

Creatinine Clearance (mL/min)	[Min<= - <60, 60<= - <=Max]
	[Min<= - <50, 50<= - <=Max]

Revised Text

Creatinine Clearance (mL/min)	[Min<= - <60, 60<= - <=Max]

Rationale for Amendment

This subgroup has not been needed.

Page 34, Section 7.8.4.8 Examination of Subgroups – Summary Table

Existing Text

Prior Proteasome Inhibitor	[Exposed, Naive, Refractory, Vc-Refractory (Takeda), CFZ-Refractory (Takeda)]
Prior IMiD	[Exposed, Naive, Refractory, Thal-Refractory (Takeda), Len-Refractory (Takeda)]

Revised Text

Prior Proteasome Inhibitor	[Exposed, Naive, Refractory <u>(Takeda)</u>, Vc-Refractory (Takeda), CFZ-Refractory (Takeda)]
Prior IMiD	[Exposed, Naive, Refractory <u>(Takeda)</u>, Thal-Refractory (Takeda), Len-Refractory (Takeda)]

Rationale for Amendment

To correct the miswritings.

Page 34, Section 7.8.4.8 Examination of Subgroups – Summary Table

Existing Text

Creatinine Clearance (mL/min)	<u>[Min<= - <50, 50<= - <=Max]</u> <u>[Min<= - <50, 50<= - <60,</u> <u>60<= - <=Max]</u> [Min<= - <60, 60<= - <=Max]

Revised Text

Creatinine Clearance (mL/min)	[Min<= - <60, 60<= - <=Max]

Rationale for Amendment

These subgroups have not been needed.

Page 34, Section 7.8.4.8 Examination of Subgroups – Summary Table

Existing Text

Maintenance Therapy	[Yes, No]
Time from SCT to First Dose (Months)	[0<= - <12, 12<= - <24, 24<= - <36, 36<= - <=Max]

Revised Text

Maintenance Therapy (Takeda)	[Yes, No]
Time from Last SCT to First Dose (Months)	[0<= - <12, 12<= - <24, 24<= - <36, 36<= - <=Max]

Rationale for Amendment

To clarify the analytical method.

Page 37, Section 7.11.1.2 Overview of Treatment-Emergent Adverse Events by Subgroups

Existing Text

Creatinine Clearance (mL/min)	[Min<= - <30, 30<= - <60, 60<= - <90, 90<= - <=Max]

Revised Text

Creatinine Clearance (mL/min)	[Min<= - <60, 60<= - <=Max]

Rationale for Amendment

This subgroup has been changed.

Page 40, Section 7.11.1.3 Displays of Treatment-Emergent Adverse events

Existing Text

Summary table for (17)

TEAEs which resulted in dose discontinuation in Ixazomib, in Lenalidomide, and in Dexamethasone will each be displayed, as well as the TEAEs which resulted in dose discontinuation in any of Ixazomib, Lenalidomide, or Dexamethasone.

Revised Text

Summary table for (17)

TEAEs which resulted in dose discontinuation in Ixazomib, in Lenalidomide, and in Dexamethasone will each be displayed.

Rationale for Amendment

The deleted portion has been duplicated.

Page 40, Section 7.11.1.4 Displays of Treatment-Emergent Adverse Events of Clinical Importance and Haemorrhage

Adding Text

(9) Treatment-Emergent Adverse Events of Clinical Importance, Grades and Concomitant Medications by ATC Pharmacological Subgroup and WHO Generic Term

Rationale for Amendment

This analysis has been added.

Page 43, Section 7.11.2.1 Hematology and Blood Chemistry

Existing Text

(2) Case Plots

Plots over time for each subject will be presented for platelet count and neutrophils.

Revised Text

(2) Case Plots

Plots over time for each subject will be presented for platelet count.

Rationale for Amendment

The case plot of neutrophils has not been needed.

8.0 REFERENCES

Not applicable.

STATISTICAL ANALYSIS PLAN

STUDY NUMBER: C16028

A Phase 2, Open-Label, Multicenter Study of Ixazomib Plus Lenalidomide and Dexamethasone in Adult Japanese Patients With Relapsed and/or Refractory Multiple Myeloma

PHASE 2

Version: 1

Date: 16 August 2017

Prepared by:

PPD

PPD

Based on:

Protocol Version: Amendment 1

Protocol Date: 25 November 2016

1.1 Approval Signatures

Study Title: A Phase 2, Open-Label, Multicenter Study of Ixazomib Plus Lenalidomide and Dexamethasone in Adult Japanese Patients With Relapsed and/or Refractory Multiple Myeloma

Approvals:

PPD
PPD

PPD

PPD
PPD

PPD

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2.0 TABLE OF CONTENTS

3.0 LIST OF ABBREVIATIONS

5-HT3	5-hydroxytryptamine 3 serotonin receptor
ADL	activities of daily living
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
BUN	blood urea nitrogen
CBC	complete blood count
CI	confidence interval
CO_2	carbon dioxide
CR	complete response
CRO	contract research organization
CT	computed tomography
CYP	cytochrome P450
Del	deletion
DNA	deoxyribonucleic acid
DOR	duration of response
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EOT	End of Treatment (visit)
FAS	full analysis set
FCBP	female patients of childbearing potential
FDA	United States Food and Drug Administration
FISH	fluorescent in situ hybridization
FLC	free light chain
GCP	Good Clinical Practice
G-CSF	granulocyte colony stimulating factor
GVHD	graft-versus-host disease
HBcAb	hepatitis B core antibody
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
IMiD	immunomodulatory drugs
IMWG	International Myeloma Working Group
IRB	institutional review board
ISS	international staging system
IUD	intrauterine device
IV	intravenous; intravenously
LenDex	lenalidomide and dexamethasone
LDH	lactate dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities

MHRA	Medicines and Healthcare products Regulatory Agency
MM	multiple myeloma
MRI	magnetic resonance imaging
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NDMM	newly diagnosed multiple myeloma
ORR	overall response rate
OS	overall survival
PD	progressive disease (disease progression)
PET	positron emission tomography
PFS	progression-free survival
PMDA	Pharmaceuticals and Medical Devices Agency
PML	progressive multifocal leukoencephalopathy
POEMS	polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes
PR	partial response
PRES	posterior reversible encephalopathy syndrome
PTE	pretreatment event
RNA	ribonucleic acid
RRMM	relapsed and/or refractory multiple myeloma
SAE	serious adverse event
SAP	statistical analysis plan
sCR	stringent complete response
SD	stable disease
SPEP	serum protein electrophoresis
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
TEN	toxic epidermal necrolysis
T_{max}	time to first occurrence of maximum (peak) concentration
TSH	thyroid stimulating hormone
TTP	time to progression
ULN	upper limit of the normal range
UPEP	urine protein electrophoresis
VGPR	very good partial response
WBC	white blood cell
WHO	World Health Organization

4.0 OBJECTIVES

4.1 Primary Objectives

To determine VGPR or better (VGPR + CR) rate in response-evaluable analysis set*

*Defined as patients who received at least one dose of ixazomib and had measurable disease at baseline, and at least one post baseline response assessment.

4.2 Secondary Objectives

- To determine progression-free survival (PFS)
- To determine overall response rate (ORR) (partial response [PR] or better)
- To determine duration of response (DOR)
- To determine time to progression (TTP)
- To determine safety
- To determine overall survival (OS)

4.3 Additional Objectives

Not applicable

4.4 Study Design

This is a phase 2, open-label, single arm, multicenter study to evaluate the efficacy and safety of ixazomib plus lenalidomide and dexamethasone in Japanese patients with relapsed and/or refractory multiple myeloma (MM). The patient population will consist of adult men and women who have a confirmed diagnosis of MM, who have received 1 to 3 prior lines of therapy, and who meet other outlined eligibility criteria (see Section 7.0). Approximately 30 patients will be enrolled in the study.

General eligibility criteria may be assessed prior to the formal Screening period if it is part of standard clinical practice. However, per the Schedule of Events, formal screening will occur during the Screening period, which may last for up to 28 days prior to enrollment. A Takeda clinician will confirm patient eligibility prior to enrollment. Determination of disease progression as an entry criterion may be based on patient data obtained during or following the patient's most recent prior antineoplastic therapy.

Patients will receive study drug (ixazomib 4.0 mg) on Days 1, 8, and 15 plus lenalidomide (25 mg) on Days 1 through 21 and dexamethasone (40 mg) on Days 1, 8, 15, and 22 of a 28-day cycle. Patients may continue to receive treatment until progressive disease (PD) or unacceptable toxicity, whichever comes first. Dose modifications may be made based on toxicities. Patients with a low creatinine clearance < 60 mL/min will receive a reduced lenalidomide dose of 10 mg. The lenalidomide dose may be escalated to 15 mg after 2 cycles if the patient is not responding to treatment and is tolerating the treatment. If renal function normalizes (ie, creatinine clearance ≥ 60 mL/min) and the patient continues to tolerate this treatment, lenalidomide may then be escalated to 25 mg.

Patients will be seen at regular treatment cycle intervals while they are participating in the study: four times a treatment cycle for the first 2 cycles, twice a treatment cycle for the 3rd

cycle, and then once a treatment cycle for the remainder of their participation in the active treatment and, if applicable, the PFS (every 4 weeks) and OS (every 12 weeks) follow-up phases of the study.

Response will be assessed by investigator according to the IMWG criteria for all patients every 4 weeks until PD. Central laboratory data will be used for serum M-protein, urine M-protein and serum free light chain. All patients will be followed for survival after progression. Patients will be contacted every 12 weeks until death or termination of the study by the sponsor.

Patients will attend an End of Treatment (EOT) visit approximately 30 days after receiving their last dose of study treatment (ixazomib, lenalidomide or dexamethasone) and will continue to be followed for other follow-up assessments specified in the Schedule of Events. Patients discontinuing study treatment prior to PD will continue to be assessed for PD during the PFS follow-up portion of the study.

Analysis is planned to be performed twice during the study. The primary analysis is planned to be performed using the data obtained at approximately 12 months from the enrollment of the last patient. The final analysis is planned to be performed after the final database lock using the data obtained at approximately 24 months from the enrollment of the last patient. The timing of analysis may be changed or additional analysis may be added upon request of the regulatory authorities.

5.0 ANALYSIS ENDPOINTS

Primary Efficacy Endpoint

VGPR or better rate in response-evaluable analysis set

Secondary Efficacy Endpoints

- PFS, defined as the time from the date of first study drug administration to the date of first documentation of PD or death from any cause, whichever occurs first
- ORR
- DOR, defined as the time from the date of first documentation of response to the date of first documentation of PD
- TTP, defined as the time from the date of first study drug administration to the date of first documentation of PD
- Safety including treatment-emergent adverse events (TEAEs), laboratory parameters, and vital signs
- OS, defined as the time from the date of first study drug administration to the date of death

6.0 DETERMINATION OF SAMPLE SIZE

Assuming the expected VGPR or better rate is 48.1% and the threshold rate is 39.0% based on the results of Study C16010, a sample size of 27 would be necessary to provide a point estimate of VGPR or better rate higher than the threshold rate with 80% probability. Assuming a drop-out ratio of 10%, the target number of patients has been set to 30. The expected response rate and the threshold assumptions are based on VGPR or better rate in ixazomib + LenDex arm and placebo + LenDex arm in Study C16010 (intent-to-treat population, primary analysis).

7.0 METHODS OF ANALYSIS AND PRESENTATION

7.1 General Principles

7.1.1 Study Definitions

The following definitions and calculation formulas will be used.

- Descriptive statistics: Number of subjects, mean, standard deviation, maximum, minimum, and quartiles
- Frequency distributions: Number of subjects and percentage (of nonmissing) per category
- Baseline body surface area (m^2): square root of (baseline height * baseline weight / 3600)
- Time since initial diagnosis to first dose at study entry (months): (first dose date - date of initial diagnosis + 1) / (365.25 / 12)
- Relapsed patients: Patients who relapsed from at least 1 previous treatment but were not refractory to any previous treatment. Patients who progress after 60 days from the last dose of a given therapy will be considered relapsed.
- Refractory patients: Patients who were refractory to at least 1 previous treatment but were not relapsed to any previous treatment. Refractory disease is defined as disease progression on treatment or progression within 60 days after the last dose of a given therapy.
- Refractory and relapsed patients: Patients who were relapsed from at least 1 previous treatment and additionally were refractory to at least 1 previous treatment.
- Primary refractory patients: Patients who are refractory to all lines of previous therapy (i.e., best response to prior therapy is SD or disease progression on all lines of therapy).
- Time since last transplant to first dose at study entry (months): (first dose date – start date of prior transplant) / (30.4375)
- Relative dose intensity: 100 * (total amount of dose taken) / (total prescribed dose of treated cycles), where total prescribed dose equals [dose prescribed at enrollment * number of prescribed doses per cycle * the number of treated cycles]
- Extent of Exposure (cycles) is based on the number of treated cycles.
- Extent of Exposure (days): date of last dose – date of first dose + 1
- Percent drug compliance (%): (study drug taken in mg) / (study drug expected to be taken in mg) *100%
- Treatment-emergent adverse event (TEAE): Any adverse event that occurs after administration of the first dose of any study drug through 30 days after the last dose of any study drug
- If corrected calcium is not reported directly, it can be calculated using the following formula:
  - Corrected Calcium (mmol/L): serum calcium (mmol/L) + 0.0200 * (40 – serum albumin (g/L))

7.1.2 Definition of Study Visit Windows

Unless otherwise specified, the baseline value is defined as the value collected at the time closest to, but before, the start of study drug administration.

All data will be categorized on the basis of the scheduled visit at which they are collected.

7.1.3 Significance Level and Confidence Coefficient

- Confidence coefficient: 95% (two-sided)

7.2 Analysis Sets

In this study, the following three analysis sets are defined.

- FAS: All subjects who received at least one dose of the study drug during the treatment period. Subjects will be excluded from FAS if the following criterion is met:
  - No study drug received
- Response-evaluable analysis set: All FAS subjects with measurable disease at baseline, and at least one post baseline response assessment. Measurable disease is defined by at least 1 of the following 3 measurements based on central laboratory data: serum M-protein ≥1 g/dL (≥ 10 g/L), urine M-protein ≥200 mg/24 hours, and serum free light chain assay where involved free light chain level ≥10 mg/dL (≥ 100 mg/L), provided that the serum free light chain ratio is abnormal.

  Subjects will be excluded from the response-evaluable analysis set if any of the following criteria are met:
  - No measurable disease at baseline
  - No post-baseline assessment
  - No study drug received
- Safety analysis set: All subjects who received at least one dose of the study drug during the treatment period. Subjects will be excluded from the safety analysis set if the following criterion is met:
  - No study drug received

7.3 Disposition of Subjects

7.3.1 Study Information

Analysis Set:	All Subjects Who Signed the Informed Consent Form	
Analysis Variable(s) :	Date First Subject Signed Informed Consent Form	
	Date of Last Subject's Last Visit/Contact	
	MedDRA Version	
	WHO Drug Version	
	SAS Version Used for Creating the Datasets	
Analytical Method(s) :	(1) Study Information	
	Study information shown in the analysis variables section will be provided.	

7.3.2 Number of Subjects Who Entered the Treatment Period by Site

Analysis Set:	All Subjects Who Entered the Treatment Period	
Analysis Variable(s) :	Status of Entrance into the Treatment Period	[Entered]
Stratum:	Site	[Site numbers will be used as categories]
Analytical Method(s) :	(1) Number of Subjects Who Entered the Treatment Period by Site	
	Frequency distribution will be provided for each stratum.	

7.3.3 Disposition of Subjects

Analysis Set:	All Subjects Who Entered the Treatment Period	
Analysis Variable(s) :	Study Drug Completion Status	[Ongoing on Treatment, Prematurely Discontinued Study Drug]
	Reason for Discontinuation of Study Drug	[Adverse Event, Lost to Follow-up, Progressive Disease, Protocol Violation, Study Terminated by Sponsor, Withdrawal by Subject, Other]

	Subjects that have Participated in OS Follow-up	
	Subjects that have Participated in PFS Follow-up	[Yes, No]
	Completion Status of the Follow-up Period	[Completed Follow-up Period, Prematurely Discontinued Follow-up Period]
	Reason for Discontinuation of the Follow-up Period	[Lost to Follow-up, Study Terminated by Sponsor, Withdrawal by Subject, Other]

Analytical Method(s) : (1) Disposition of Subjects
Frequency distributions will be provided.

7.3.4 Protocol Deviations and Analysis Sets

7.3.4.1 Protocol Deviations

Analysis Set:	All Subjects Who Entered the Treatment Period	
Analysis Variable(s) :	Significant Protocol Deviation	[Entry Criteria, Concomitant Medication, Procedure Not Performed Per Protocol, Study Medication, Withdrawal Criteria, Good Clinical Practice]

Analytical Method(s) : (1) Protocol Deviations
Frequency distribution will be provided for each deviation category. A subject who has several deviations will be counted once in each appropriate category. A subject who has several deviations that can be classified into the same category will be counted only once.

7.3.4.2 Analysis Sets

Analysis Set:	All Subjects Who Entered the Treatment Period	
Analysis Variable(s) :	Handling of Subjects	[Categories are based on the specifications in Section 7.2

		"Analysis Sets"]
	Analysis Sets	
	Full Analysis Set	[Included]
	Response-evaluable Analysis Set	[Included]
	Safety Analysis Set	[Included]

Analytical Method(s) :
(1) Subjects Excluded from Analysis Sets
(2) Analysis Sets

Frequency distributions will be provided. For (1), a subject who has several reasons for exclusion will be counted once in each appropriate category. A subject who has several reasons for exclusion that can be classified into the same category will be counted only once.

7.4 Demographic and Other Baseline Characteristics

7.4.1.1 Demographic and Other Baseline Characteristics

Analysis Set:	Full Analysis Set	
Analysis Variable(s) :	Age (years)	[Min<= - <=65, 65< - <=75, 75< - <=Max]
	Sex	[Male, Female]
	Ethnicity	[Hispanic or Latino, Not Hispanic or Latino, Not Reported]
	Race	[White, Black or African American, Native Hawaiian or Other Pacific Islander, Asian (Asian Indian), Asian (Chinese), Asian (Japanese), Asian (Korean), Asian (Other), Asian (Not Reported), American Indian or Alaska Native, Not Reported, Other]
	Baseline Height (cm)	
	Baseline Weight (kg)	
	Baseline Body Surface Area (m^2)	
	Time Since Initial Diagnosis to First Dose at Study Entry (months)	
	ISS Stage at Initial Diagnosis	[I, II, III, Unknown]

Patient Population Categories	[Relapsed Patients, Refractory Patients, Refractory and Relapsed Patients]
Type of Myeloma at Initial Diagnosis	
IgG	[Kappa, Lambda, Biclonal, Unknown]
IgA	[Kappa, Lambda, Biclonal, Unknown]
IgD	[Kappa, Lambda, Biclonal, Unknown]
IgE	[Kappa, Lambda, Biclonal, Unknown]
IgM	[Kappa, Lambda, Biclonal, Unknown]
Biclonal	[Kappa, Lambda, Biclonal, Unknown]
Unknown	[Kappa, Lambda, Biclonal, Unknown]
Other	[Kappa, Lambda, Biclonal, Unknown]
Durie-Salmon Stage at Initial Diagnosis	[IA, IB, IIA, IIB, IIIA, IIIB, Unknown]
Lines of Prior Therapy	[1, 2, 3]
Evidence of Lytic Bone Disease at Initial Diagnosis	[Yes, No, Unknown]
Evidence of Extramedullary Disease at Initial Diagnosis	[Yes, No, Unknown]
Patients with a Bone Marrow Transplant or Stem Cell Transplant	
Type of Transplant Procedure	[Allogenic, Autologous, Both, Unknown]
Time Since Last Transplant to First Dose at Study Entry (months)	
Type of Prior Regimens	[Velcade Contained, Thalidomide Contained, Thalidomide Refractory,

	Lenalidomide Contained, Corticosteroids Contained, Dexamethasone, Prednisone, Other, Carfilzomib Contained, Melphalan Contained, Other]
Type of Last Prior Regimen	[Velcade Contained, Thalidomide Contained, Thalidomide Refractory, Lenalidomide Contained, Corticosteroids Contained, Dexamethasone, Prednisone, Other, Carfilzomib Contained, Melphalan Contained, Other]
Patient was Relapsed on Last Prior Therapy	[Yes, No]
Patient was Refractory on Last Prior Therapy	[Yes, No]
Time Since Last Dose of Prior Therapy to First Dose at Study Entry (months)	
Best Response to Prior Therapy	[Complete Response, Partial Response, Stable Disease, Progressive Disease, Unable to Assess, Unknown]
Time Since Disease Progression on Prior Therapy to First Dose at Study Entry (months)	
Patients with Prior Radiation	
Time Since Last Prior Radiation to First Dose at Study Entry (months)	

Patients with Prior Surgery or Non-Radiation Procedures	
Time Since Last Prior Surgery or Non-Radiation Procedure to First Dose at Study Entry (months)	
Prior IMiD Therapy	[Exposed, Thalidomide, Lenalidomide, Pomalidomide, Naive]
Patient was Refractory to Any Prior IMiD Therapy	[Yes, No]
Prior Proteasome Inhibitor Therapy	[Exposed, Velcade, Carfilzomib, Naive]
Patient was Refractory to Any Prior Proteasome Inhibitor Therapy	[Yes, No]
Primary Refractory Patients	[Progression Disease, Stable Disease]
ISS Stage for Myeloma at Study Entry	[I, II, III]
Evidence of Lytic Bone Disease	[Present, Absent, Unknown]
Extramedullary Disease at Study Entry	[Yes, No, Unknown]
Serum M-Protein (g/L)	
Urine M-Protein (g/24h)	
Serum Creatinine (mg/dL)	[Min<= - <=2, 2< - <=Max]
Serum Albumin (g/L)	[Min<= - <35, 35<= - <=Max]
β_2-microglobulin (mg/L)	[Min<= - <3.5, 3.5<= - <5.5, 5.5<= - <=Max]
Creatinine Clearance (mL/min)	[Min<= - <30, 30<= - <60, 60<= - <90, 90<= - <=Max]
Corrected Calcium (mmol/L)	
Baseline ECOG Performance Status	[0, 1, 2, 3, 4]
Baseline Hemoglobin (g/L)	

Analytical

Method(s) : (1) Summary of Demographics and Baseline Characteristics
Frequency distributions for categorical variables and descriptive statistics for continuous variables will be provided.

7.4.1.2 Baseline Bone Marrow Evaluation and Extramedullary Disease Assessment

Analysis Set: Full Analysis Set
Analysis
Variable(s) :

Bone Marrow Aspiration	
Number of Patients with Bone Marrow Aspiration	
Number of Patients with Adequate Sample for Interpretation	
% Plasma Cells	[Available, Unable to Detect, Not Available]
Bone Marrow Biopsy	
Number of Patients with Bone Marrow Biopsy	
Number of Patients with Adequate Sample for Interpretation	
% Plasma Cells	[Available, Unable to Detect, Not Available]
% Marrow Cellularity	[Available, Not Available]
Marrow Cellularity Status	[Hypocellular, Hypercellular, Normocellular, Unable to Assess]
Immunohistochemistry or Immunofluorescence for Kappa/Lambda Ratio Performed	[Yes, No, Not Applicable]
Ratio Determined by Analysis of a Minimum of 100 Plasma Cells	[Yes, No, Not Applicable]
% Plasma Cells in Bone Marrow	
Kappa/Lambda Ratio	
Bone Marrow Cytogenetic Results	
Sample Collected?	[Yes, No, Not Applicable]
Method of Assessment	[Conventional/Karotype, Molecular/FISH, Both]

Cytogenetic Results (Conventional/Karotype)	[Normal, Abnormal, Indeterminate]
Cytogenetic Results (Molecular/FISH)	[Normal, Abnormal, Indeterminate]
Abnormality of Chromosomal Aberrations	
Subjects with Any Chromosomal Abnormalities	[Del 13 or -13q, Del 17 or -17p, t(4;14), t(6;14), t(8;14), t(11;14), t(12;14), t(14;16), t(14;20), Hyperdiploidy, Hypodiploidy, Non-hyperdiploidy, 1q amplification, 1q deletion, Other]
Cytogenetic Results	[High Risk, Standard, Not Available]
Skeletal Survey	
Result	[Within Normal Limits, Abnormal]
Lytic Bone Lesions Present	[Yes, No, Indeterminate]
Imaging (Computed Tomography)	
Result	[Within Normal Limits, Abnormal]
Plasmacytomas Present	[Yes, No, Indeterminate]
Imaging (Magnetic Resonance Imaging)	
Result	[Within Normal Limits, Abnormal]
Plasmacytomas Present	[Yes, No, Indeterminate]
Imaging (Positron Emission Tomography)	
PET Activity	[FDG Positive, FDG Negative, Indeterminate]
Subjects with Plasmacytomas	[Liver (Visceral), Lung (Visceral), Node, Soft Tissue, Lytic Bone, Other]
Number of Plasmacytomas	[1, 2, >=3]
Soft Tissue Plasmacytomas Total Size (cm^2)	
Lytic Bone Plasmacytomas Total Size (cm^2)	

Analytical

Method(s) : (1) Baseline Bone Marrow Evaluation and Extramedullary Disease Assessment

Frequency distributions for categorical variables and descriptive statistics for continuous variables will be provided.

7.4.1.3 Disease Specific History – IMiD and Proteasome Inhibitor

Analysis Set: Full Analysis Set

Analysis Variable(s) : Exposed to Prior IMiD Therapy

- Lenalidomide
  - Lenalidomide Refractory
    - Best Response [CR, PR, SD, PD, Unable to Assess, Unknown]
- Thalidomide
  - Thalidomide Refractory
    - Best Response [CR, PR, SD, PD, Unable to Assess, Unknown]
- Pomalidomide
  - Pomalidomide Refractory
    - Best Response [CR, PR, SD, PD, Unable to Assess, Unknown]

Exposed to Prior Proteasome Inhibitor Therapy

- Velcade
  - Velcade Refractory
    - Best Response [CR, PR, SD, PD, Unable to Assess, Unknown]
- Carfilzomib
  - Carfilzomib Refractory
    - Best Response [CR, PR, SD, PD, Unable to Assess, Unknown]

Analytical Method(s) : (1) Disease Specific History – IMiD and Proteasome Inhibitor

Frequency distributions for categorical variables will be provided. For the analysis variables "Exposed to Prior IMiD Therapy", "Lenalidomide",

"Thalidomide", "Pomalidomide", "Exposed to Prior Proteasome Inhibitor Therapy", "Velcade", and "Carfilzomib", the denominators for the percentages will be the number of subjects in FAS. For the analysis variables "Lenalidomide Refractory", "Thalidomide Refractory", "Pomalidomide Refractory", "Velcade Refractory", and "Carfilzomib Refractory", the denominators for the percentages will be the number of subjects who were exposed to the specified therapy (Lenalidomide, Thalidomide, Pomalidomide, Velcade, or Carfilzomib). For the analysis variable "Best Response", the denominators for the percentages will be the number of subjects who were refractory to the specified therapy (Lenalidomide, Thalidomide, Pomalidomide, Velcade, or Carfilzomib).

7.4.1.4 Summary of Baseline Measurable Status in Subjects with only Abnormal Baseline Free Light Chain

Analysis Set: Full Analysis Set

Analysis Variable(s): Free Light Chains (no Heavy Chain)
- Measureable
  - Measureable by FLC only
- Non-measureable

Analytical Method(s): (1) Summary of Baseline Measurable Status in Subjects with only Abnormal Baseline Free Light Chain

Frequency distributions for categorical variables will be provided.

7.4.1.5 Summary of New Primary Malignancy

Analysis Set: Full Analysis Set

Analysis Variable(s): Subjects with any New Primary Malignancy

New Primary Malignancy Disease Type (On Treatment) [Categories will be based on actual data]

New Primary Malignancy Disease Type (Follow-up) [Myelodysplastic syndrome,

Acute myeloid leukaemia or related precursor neoplasm,
Precursor lymphoid neoplasm,
Mature B-cell neoplasm,
Mature T-cell and NK-cell neoplasm,
Hodgkin lymphoma, Solid Tumor,
Other]

Analytical Method(s) : (1) Summary of New Primary Malignancy

Frequency distributions will be provided. Summaries will be provided using the new primary malignancy disease type and its detailed categories, where the detailed categories will be sorted alphabetically.

7.5 Medical History and Concurrent Medical Conditions

Analysis Set: Safety Analysis Set

Analysis Variable(s) : Medical History
Concurrent Medical Conditions

Analytical Method(s) :
(1) Medical History by Verbatim Term
(2) Concurrent Medical Conditions by System Organ Class and Preferred Term

Frequency distributions will be provided.

For (1), summary will be provided using verbatim terms. A subject with multiple occurrences of medical history within a verbatim term will be counted only once in that verbatim term.

For (2), MedDRA dictionary will be used for coding. Summary will be provided using SOC and PT, where SOC and PT will be sorted in decreasing frequency. A subject with multiple occurrences of concurrent medical condition within a SOC will be counted only once in that SOC. A subject with multiple occurrences of concurrent medical condition within a PT will be counted only once in that PT.

7.6 Medication History and Concomitant Medications

Analysis Set: Safety Analysis Set

Analysis Variable(s): Concomitant Medications

Analytical Method(s): (1) Concomitant Medications by ATC Pharmacological Subgroup and WHO Generic Term

Frequency distributions will be provided. Concomitant medications are defined as medications with start dates occurring on or after date of first dose and before date of last dose + 30 days. WHO Drug dictionary will be used for coding. Summaries will be provided using ATC pharmacological subgroup and WHO generic term. ATC pharmacological subgroup will be sorted alphabetically and WHO generic term will be sorted in decreasing frequency based on the number of reports. A subject who has been administered several medications with the same WHO generic term will be counted only once for that WHO generic term.

7.7 Study Drug Exposure and Compliance

7.7.1.1 Study Drug Exposure and Compliance

Analysis Set: Safety Analysis Set

Analysis Variable(s):

Total Amount of Doses Taken (mg)	
Total Number of Doses Taken	
Number of Treated Cycles	[>=1, >=2, >=3, >=4, >=5, >=6, >=7, >=8, >=9, >=10, >=11, >=12, >=13, >=14, >=15, >=16, >=17, >=18, >=19, >=20, >=21, >=22, >=23, >=24]
Relative Dose Intensity (%)	[Min<= - <50, 50<= - <80, 80<= - <100, 100, 100< - <=Max]
Extent of Exposure (cycles)	[1<= - <=3, 4<= - <=6, 7<= -<=9, 10<= - <=12, 13<= - <=15, 16<= - <=18, 19<= - <=21, 22<= - <=24, 24< - <=Max]
Extent of Exposure (days)	

	Percent Drug Compliance (%)	[Min<= - <50, 50<= - <=65, 65< - <=80, 80< - <=100, 100< - <=Max]

Analytical Method(s) :

(1) Study Drug Exposure and Compliance – Ixazomib
(2) Study Drug Exposure and Compliance – Lenalidomide
(3) Study Drug Exposure and Compliance – Dexamethasone
(4) Study Drug Exposure and Compliance – Combination (Ixazomib, Lenalidomide, Dexamethasone)

Frequency distributions for categorical variables and descriptive statistics for continuous variables will be provided. For (4), only the number of treated cycles, extent of exposure (cycles), and extent of exposure (days) will be provided.

Mean and 95% CI plots of changes over time will be provided for the relative dose intensity. A treated cycle is defined as a cycle in which the patients received any amount of Ixazomib for (1), Lenalidomide for (2), Dexamethasone for (3), and any of Ixazomib, Lenalidomide, Dexamethasone for (4).

7.7.1.2 Dose Modifications

Analysis Set: Safety Analysis Set

Analysis Variable(s) :

Dose Modification	
Cycle Delayed	
Action on Drug	[No Action Taken, Reduced Prescribed, Reduced Non-Prescribed, Increased Prescribed, Increased non-Prescribed, Held, Missed, Delayed, Discontinued Permanently]
Number of Subjects with at least 1 Dose Reduction	
Number of Subjects with at least 2 Dose Reduction	

Analytical Method(s) :

(1) Dose Modifications – Ixazomib
(2) Dose Modifications – Lenalidomide
(3) Dose Modifications – Dexamethasone

Frequency distributions will be provided for overall, for every cycle from Cycle 1 to 18, and for Cycles 1-6, 7-12, 13-18, 19-21, 22-24, >=25. The analysis variable "dose modification" includes reduced prescribed, reduced non-prescribed, increased prescribed, increased non-prescribed, delayed, and discontinued permanently. For the analysis variable "Action on Drug", a subject will be counted once for each unique reason for dose modification that they have had over the course of the study. For "Action on Drug", the numerators for the percentages are the number of subjects with a dosing modification and the denominators are the total number of subjects with non-missing dosing data. Dose reduction is defined as a prescribed reduction in dose over consecutive scheduled dosing days.

7.8 Efficacy Analysis

7.8.1 Primary Efficacy Endpoint(s)

7.8.1.1 Primary Analysis

Analysis Set: Response-evaluable Analysis Set

Analysis Variable(s): CR
sCR
PR
VGPR
Overall Response (CR+PR (including sCR and VGPR))
VGPR or better (CR+VGPR)
SD
PD

Analytical Method(s): The VGPR or better (CR + VGPR) rate and the 2-sided 95% confidence intervals will be provided in the response-evaluable analysis set as the primary analysis. The response rate and the 2-sided 95% confidence intervals will be provided for each analysis variable based on the confirmed best response.
The response rates and the 2-sided 95% confidence intervals will also be summarized based on the unconfirmed best response and the best response (confirmed or unconfirmed) at the end of each cycle (from Cycle 1 to Cycle 24).
The ORR is defined as the proportion of patients who achieved PR or better.
Stacked bar graph will be provided for ORR (confirmed or unconfirmed) and ORR (confirmed) at the end of each cycle and overall.

7.8.1.2 Sensitivity Analysis

Analysis Set: Full Analysis Set

Analysis Variable(s): CR
sCR
PR
VGPR

Overall Response (CR+PR (including sCR and VGPR))
VGPR or better (CR + VGPR)
SD
PD
Not Evaluable

Analytical Method(s): To check the robustness of the results, the same analyses as those in Section 7.8.1.1 will be performed using FAS, except for the summary based on the best response (confirmed or unconfirmed) at the end of each cycle and the stacked bar graphs for ORR. Non-evaluable subjects in FAS will only be included in the denominator when calculating the response rates.
The VGPR or better (CR + VGPR) rate and the 2-sided 95% confidence intervals will be provided in FAS as the sensitivity analysis for the primary analysis. Non-evaluable subjects in FAS will be included in the analysis as not VGPR or CR.

7.8.2 Secondary Efficacy Endpoint(s)

7.8.2.1 Progression-free Survival

Analysis Set: Full Analysis Set

Analysis Variable(s): PFS

Analytical Method(s): For the PFS, the Kaplan-Meier curve [and the 25th, 50th (median), and 75th percentiles, if estimable] will be calculated with their 2-sided 95% CIs in FAS. Kaplan-Meier estimates will also be calculated at 6 months, 9 months, 12 months, 18 months, and 24 months with their 2-sided 95% CIs. The median follow-up time in months and its 2-sided 95% CI will also be provided.
PFS is defined as the time from the date of first study drug administration to the date of first documentation of PD or death from any cause, whichever occurs first. The number of subjects with events and the number of subjects censored will be provided as well as the reason for censoring. Patients without documentation of PD will be censored at the date of the last response assessment that is SD or better. The details regarding the handling of missing assessments and censoring are presented in the table below.

Situation	Date of Progression or Censoring	Outcome
No baseline and/or no post baseline assessment, no subsequent anticancer therapy after study treatment, no death	Date of first dose	Censored
Disease progression documented between scheduled visits	Date of next scheduled visit	Progressed
No documented death or disease progression	Date of last adequate assessment[1]	Censored
Lost to follow-up, withdraw consent before any documented death or disease progression	Date of last adequate assessment[1]	Censored
Death or progression after more than 1 missed visit[2]	Date of last adequate assessment[1]	Censored
Alternate antineoplastic therapy started prior to disease progression	Date of last adequate assessment prior to starting alternate antineoplastic therapy	Censored
Death before first post baseline assessment	Date of death	Progressed
Death between adequate assessment visits	Date of death	Progressed

[1]: Adequate disease assessment is defined as there is sufficient data to evaluate a subject's disease status.

[2]: Death or progression occurs more than 90 days from previous adequate assessment.

7.8.2.2 Duration of Response

Analysis Set: Responders in the Full Analysis Set

Analysis Variable(s): DOR

Analytical Method(s): For the DOR, the Kaplan-Meier curve [and the 25th, 50th (median), and 75th

percentiles, if estimable] will be calculated with their 2-sided 95% CIs for the subjects who responded to the study treatment among the FAS. Kaplan-Meier estimates will also be calculated at 6 months, 12 months, 18 months, and 24 months with their 2-sided 95% CIs.
DOR is defined as the time from the date of first documentation of response to the first documentation of PD. Responders without documentation of PD will be censored at the date of their last response assessment that is SD or better. The number of subjects with events and the number of subjects censored will be provided as well as the reason for censoring.
For the analysis of DOR, "response" will be defined as (1) VGPR or better (2) ORR (3) CR and the same analysis will be performed for each type of response.

7.8.2.3 Time to Progression

Analysis Set: Full Analysis Set

Analysis Variable(s): TTP

Analytical Method(s): For the TTP, the Kaplan-Meier curve [and the 25th, 50th (median), and 75th percentiles, if estimable] will be calculated with their 2-sided 95% CIs in FAS. Kaplan-Meier estimates will also be calculated at 6 months, 9 months, 12 months, 18 months, and 24 months with their 2-sided 95% CIs.
TTP is defined as the time from the date of first study drug administration 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 their last response assessment that is SD or better. Patients with no response assessment will be censored at the first day of administration. Patients who do not experience progression and start new systemic therapy for multiple myeloma will be censored at the date of their last response assessment that is SD or better. The number of subjects with events and the number of subjects censored will be provided as well as the reason for censoring.

7.8.2.4 Overall Survival

Analysis Set: Full Analysis Set

Analysis Variable(s): OS

Analytical Method(s): For the OS, the Kaplan-Meier curve [and the 25th, 50th (median), and 75th percentiles, if estimable] will be calculated with their 2-sided 95% CIs in FAS. Kaplan-Meier estimates will also be calculated at 6 months, 9 months, 12 months, 18 months, and 24 months with their 2-sided 95% CIs. The median follow-up time in months and its 2-sided 95% CI will also be provided.

OS is defined as the time from the date of first study drug administration to the date of death. Subjects without documentation of death at the time of the analysis will be censored at the date when they were last known to be alive. The number of deaths and the number censored will be provided as well as the reason for censoring.

7.8.3 Additional Efficacy Endpoint(s)

7.8.3.1 Best M-Protein Response to Treatment

Analysis Set: Response-evaluable Analysis Set

Analysis Variable(s): Best M-Protein Response

Categories: Response Category

[100% Reduction,
Immunofixation Negative,
>=90% Reduction,
>=50% Reduction]
[90 - <100% Reduction,
75 - <90% Reduction,
50 - <75% Reduction,
25 - <50% Reduction]
[<25% Reduction to <25% Increase,
>=25% Increase]
No Post-Baseline Assessment of Measurable M-Protein

Analytical

Method(s): Frequency distribution will be provided. For subjects with measurable serum M-protein at baseline, the best M-protein response is the percent change from baseline to best (lowest) value post-baseline in serum M-protein. For subjects with non-measurable serum M-protein, but measurable urine M-protein, the best M-protein response is the percent change from baseline to best (lowest) value post-baseline in urine M-protein. Mean and standard deviation plots of changes over time will be provided for observed values and percent changes from baseline. A waterfall plot will be provided for the percent changes from baseline.

7.8.3.2 Time to Response

Analysis Set: Responders in the Response-evaluable Analysis Set
Full Analysis Set

Analysis Variable(s): VGPR or better (CR + VGPR)
Overall Response

Analytical Method(s): For the time to response, the Kaplan-Meier curve [and the 25th, 50th (median), and 75th percentiles, if estimable] will be calculated with their 2-sided 95% CIs. Kaplan-Meier estimates will also be calculated at 6 months, 9 months, 12 months, 18 months, and 24 months with their 2-sided 95% CIs.
Time to response is defined as the time from the date of first study drug administration to the date of first documentation of the confirmed response indicated in the analysis variable. Responders are defined as subjects with documentation of a confirmed response of the analysis variable. The number of subjects with events and the number of subjects censored will be provided as well as the reason for censoring.
The same analyses will be performed using FAS.

7.8.3.3 Duration of Follow-up

Analysis Set: Full Analysis Set

Analysis Variable(s): Duration of Follow-up

Analytical Method(s): For the duration of follow-up, the Kaplan-Meier curve [and the 25th, 50th

(median), and 75th percentiles, if estimable] will be calculated with their 2-sided 95% CIs. Kaplan-Meier estimates will also be calculated at 6 months, 9 months, 12 months, 18 months, and 24 months with their 2-sided 95% CIs. The median follow-up time in months and its 2-sided 95% CI will also be provided.

Duration of follow-up is defined as time from the date of first study drug administration to the date of death or last known visit. The number of subjects with events and the number of subjects censored will be provided as well as the reason for censoring.

7.8.4 Statistical/Analytical Issues

7.8.4.1 Adjustments for Covariates

Not applicable.

7.8.4.2 Handling of Dropouts or Missing Data

Censoring rules have been described in each applicable section.

7.8.4.3 Multicenter Studies

Treatment-by-center interaction will not be explored since this study is a single-arm study.

7.8.4.4 Multiple Comparison/Multiplicity

Not applicable.

7.8.4.5 Use of an "Efficacy Subset" of Subjects

In addition to analyses on the primary endpoint using the response-evaluable analysis set, a secondary analysis will also be performed using the FAS to examine the robustness of the results.

7.8.4.6 Active-Control Studies Intended to Show Equivalence or Non-Inferiority

Not applicable.

7.8.4.7 Examination of Subgroups

Analysis Set: Response-evaluable Analysis Set
Full Analysis Set

Analysis Variable(s): CR
sCR
PR

	VGPR	
	Overall Response (CR+PR (including sCR and VGPR))	
	VGPR or better (CR + VGPR)	
	SD	
	PD	
Subgroup(s):	Age (years)	[Min<= - <=65, 65< - <=75, 75< - <=Max]
	Sex	[Male, Female]
	Cytogenetic Risk	[High Risk {(del17); t(4;14); t(14;16)}, Non-High Risk]
	ISS Stage for Myeloma at Study Entry	[I, II, III]
	Lines of Prior Therapy	[1, 2 or 3]
	Prior Proteasome Inhibitor Therapy	[Exposed, Naive]
	Prior IMiD Therapy	[Exposed, Naive]
	Thalidomide Refractory	[Yes, No]
	Refractory to Any Line of Prior Therapy	[Yes, No]
	Patient was Refractory on Last Prior Therapy	[Yes, No]
	Relapsed and/or Refractory	[Relapsed, Refractory, Relapsed and Refractory]
	Prior Velcade Therapy	[Exposed, Naive]
	Creatinine Clearance (mL/min)	
		[Min<= - <60, 60<= - <=Max]
		[Min<= - <50, 50<= - <=Max]
	Baseline ECOG Performance Status	[0 or 1, 2]
	Prior Lenalidomide Therapy	[Exposed, Naive]
	Prior Thalidomide Therapy	[Exposed, Naive]
Analytical Method(s):	The same analyses as those in Sections 7.8.1.1 and 7.8.1.2 will be performed with the confirmed best response for each subgroup. A forest plot will be produced using the VGPR or better (CR+VGPR) rate and the 2-sided 95% confidence intervals.	

7.8.4.8 Examination of Subgroups – Summary Table

Analysis Set:	Response-evaluable Analysis Set	
	Full Analysis Set	
Analysis Variable(s):	ORR	
	VGPR or better	
	CR or better	
Subgroup(s):	Age (years)	[Min<= - <=65, 65< - <=75, 75< - <=Max]
	Sex	[Male, Female]
	Cytogenetic Risk	[Not Available, Standard Risk, High Risk, High Risk (del17), High Risk t(4;14), High Risk t(14;16)]
	Baseline ECOG Performance Status	[0, 1, 2]
	Prior Lines of Therapy per Takeda review	[1, with SCT, without SCT, 2, with SCT, without SCT, 3, with SCT, without SCT]
	Relapsed/Refractory Type	[Relapsed, Refractory, Relapsed and Refractory, Primary Refractory]
	Prior Proteasome Inhibitor	[Exposed, Naive, Refractory, Vc-Refractory (Takeda), CFZ-Refractory (Takeda)]
	Prior IMiD	[Exposed, Naive, Refractory, Thal-Refractory (Takeda), Len-Refractory (Takeda)]
	ISS stage at Study Entry	[I, II, III]
	Best Response	[>=CR, >=VGPR, >=PR, SD, PD]
	Creatinine Clearance (mL/min)	[Min<= - <50, 50<= - <=Max]
		[Min<= - <50, 50<= - <60, 60<= - <=Max]

	[Min<= - <60, 60<= - <=Max]
1 Prior Line with SCT	
High Risk	
ISS 3	
Prior IMiD	[Exposed, Naive]
Thalidomide	[Exposed, Naive]
Lenalidomide	[Exposed, Naive]
Maintenance Therapy	[Yes, No]
Time from SCT to First Dose (Months)	[0<= - <12, 12<= - <24, 24<= - <36, 36<= - <=Max]
Prior PI	[Exposed, Naive]
1 Prior Line with SCT	
Single vs. Double SCT	[Single SCT, Double SCT]
With Velcade + Thalidomide	[Yes, No]
With Velcade + Lenalidomide	[Yes, No]
Best Response on Prior SCT	[CR, PR, SD or PD]
ECOG	[0, 1]
Low Bone Marrow Cellularity	[Yes, No, Missing]
Cytogenetic Risk	[Not Available, 1 Line with SCT, Others]

Analytical Method(s): Frequency distributions for each analysis variable will be provided for each subgroup.

7.9 Pharmacokinetic/Pharmacodynamic Analysis

7.9.1 Pharmacokinetic Analysis

Not applicable.

7.9.2 Pharmacodynamic Analysis

Not applicable.

7.10 Other Outcomes

Not applicable.

7.11 Safety Analysis

7.11.1 Adverse Events

7.11.1.1 Overview of Treatment-Emergent Adverse Events

Analysis Set: Safety Analysis Set

Analysis Variable(s): TEAE

Analytical Method(s): The following summaries will be provided.

(1) Overview of Treatment-Emergent Adverse Events
   1) Any adverse event
   2) Grade 3 or higher adverse event
   3) Drug-related adverse event
   4) Drug-related grade 3 or higher adverse event
   5) Serious adverse event
   6) Drug-related serious adverse event
   7) Adverse events resulting in any study drug dose reduction
   8) Adverse events resulting in any study drug dose modification
   9) Adverse events resulting in any study drug discontinuation
   10) On-study deaths

For summary 8), dose modification will include dose reduction, dose increase, dose delay, and dose discontinuation.

TEAEs will be counted according to the rules below.

Number of subjects

- Summaries for 3), 4), and 6)
  A subject with occurrences of TEAE in both categories (i.e., Related and Not Related) will be counted once in the Related category.
- Summaries for 2) and 4)
  A subject with multiple occurrences of TEAE will be counted once for the TEAE with the maximum intensity.
- Summaries other than 2), 3), 4), and 6)
  A subject with multiple occurrences of TEAE will be counted only once.

7.11.1.2 Overview of Treatment-Emergent Adverse Events by Subgroups

Analysis Set:	Safety Analysis Set	
Analysis Variable(s) :	TEAE	
Subgroup(s):	Cycles	[1-6, 7-12, 13-18, >=19]
	Sex	[Male, Female]
	Creatinine Clearance (mL/min)	[Min<= - <30, 30<= - <60, 60<= - <90, 90<= - <=Max]
Analytical Method(s) :	The same overview summary as Section 7.11.1.1 will be provided for each subgroup category. (1) Overview of Treatment-Emergent Adverse Events by Cycle in Subjects with >= 12 Cycles Exposure (2) Overview of Treatment-Emergent Adverse Events by Sex (3) Overview of Treatment-Emergent Adverse Events by Creatinine Clearance The summary in (1) will be based on subjects who have completed 12 cycles or more of the study drug.	

7.11.1.3 Displays of Treatment-Emergent Adverse events

Analysis Set:	Safety Analysis Set	
Analysis Variable(s) :	TEAE	
Categories:	Intensity	[Grade 1, Grade 2, Grade 3, Grade 4, Grade 5]
	Time of Onset (Cycle)	[1 –3, 4 – 6, 7 – 9, 10 – 12, 13 – 15, 16 – 18, 19 – 21, 22 – 24]
Analytical Method(s) :	The following summaries will be provided using frequency distribution. TEAEs will be coded using the MedDRA and will be summarized using SOC, HLT, and PT. SOC, HLT, and PT will be sorted in decreasing frequency for tables provided by SOC, HLT, and PT. SOC will be sorted alphabetically and PT will be sorted in decreasing frequency for tables provided by SOC and PT. PT will be sorted in decreasing frequency for tables provided by PT only.	

(1) Treatment-Emergent Adverse Events by System Organ Class, High Level Term, and Preferred Term
(2) Treatment-Emergent Adverse Events by Preferred Term
(3) Treatment-Emergent Drug-Related Adverse Events by System Organ Class, High Level Term, and Preferred Term
(4) Treatment-Emergent Grade 3 or Higher Adverse Events by System Organ Class, High Level Term, and Preferred Term
(5) Treatment-Emergent Grade 3 or Higher Adverse Events by Preferred Term
(6) Treatment-Emergent Drug-Related Grade 3 or Higher Adverse Events by System Organ Class, High Level Term, and Preferred Term
(7) Treatment-Emergent Grade 4 Adverse Events by System Organ Class, High Level Term, and Preferred Term
(8) Intensity of Treatment-Emergent Adverse Events by System Organ Class, High Level Term, and Preferred Term
(9) Intensity of Treatment-Emergent Drug-Related Adverse Events by System Organ Class, High Level Term, and Preferred Term
(10) Treatment-Emergent Adverse Events Leading to Study Drug Discontinuation by System Organ Class, High Level Term, and Preferred Term
(11) Treatment-Emergent Serious Adverse Events by System Organ Class, High Level Term, and Preferred Term
(12) Treatment-Emergent Drug-Related Serious Adverse Events by System Organ Class, High Level Term, and Preferred Term
(13) Treatment-Emergent Adverse Events by System Organ Class, High Level Term, and Preferred Term Over Time
(14) Most Frequent Non Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
(15) Summary of Treatment-Emergent Adverse Events which Resulted in Dose Reduction by System Organ Class and Preferred Term
(16) Summary of Treatment-Emergent Adverse Events which Resulted in Dose Held by System Organ Class and Preferred Term
(17) Summary of Treatment-Emergent Adverse Events which Resulted in Dose Discontinuation by System Organ Class and Preferred Term

The frequency distribution will be provided according to the rules below.

Number of subjects

- Summary tables other than (4) to (9) and (13)
  A subject with multiple occurrences of TEAE within a SOC will be counted only once in that SOC. A subject with multiple occurrences of TEAE within an HLT will be counted only once in that HLT. A subject with multiple occurrences of TEAE within a PT will be counted only once in that PT. Percentages will be based on the number of subjects in the safety analysis set.
- Summary tables for (4) to (9)
  A subject with multiple occurrences of TEAE within a SOC, an HLT, or a PT will be counted only once for the TEAE with the maximum intensity. Percentages will be based on the number of subjects in the safety analysis set.
- Summary table for (13)
  A subject with a TEAE that occurs in more than one interval is counted in all the intervals that the TEAE occurs. For each time interval, a subject with multiple occurrences of TEAE within a SOC, an HLT, or a PT will be counted only once in that SOC, HLT, or PT.
  When calculating percentages for each time interval, the number of subjects at risk (i.e., subjects who either have an exposure or have an occurrence of TEAE, during or after the corresponding time interval) will be used as the denominator. The number of subjects whose onset of any one of the TEAEs is within the time interval will be used as the numerator.
- Summary table for (14)
  Most frequent non-serious TEAEs refer to PTs that are not serious whose percentages are at least 5%.
- Summary table for (15)
  TEAEs which resulted in dose reduction in Ixazomib, in Lenalidomide, and in Dexamethasone will each be displayed, as well as the TEAEs which resulted in dose reduction in any of Ixazomib, Lenalidomide, or Dexamethasone.
- Summary table for (16)
  TEAEs which resulted in dose held in Ixazomib, in Lenalidomide, and in Dexamethasone will each be displayed, as well as the TEAEs which resulted in dose held in any of Ixazomib, Lenalidomide, or Dexamethasone.
- Summary table for (17)

TEAEs which resulted in dose discontinuation in Ixazomib, in Lenalidomide, and in Dexamethasone will each be displayed, as well as the TEAEs which resulted in dose discontinuation in any of Ixazomib, Lenalidomide, or Dexamethasone.

7.11.1.4 Displays of Treatment-Emergent Adverse Events of Clinical Importance and Haemorrhage

Analysis Set: Safety Analysis Set

Analysis Variable(s): TEAE of clinical importance
Treatment-emergent haemorrhage adverse events

Categories: NCI CTCAE Grade [Grade 1, Grade 2, Grade 3, Grade 4, Grade 5]

Analytical Method(s): Adverse events of clinical importance will include diarrhea, rash, neutropenia, thrombocytopenia, nausea, peripheral neuropathy, vomiting, arrhythmias, renal, liver impairment, hypotension, heart failure, new primary malignancy, myocardial infarction, and encephalopathy. The following summaries will be provided using frequency distribution. For (2) and (3), descriptive statistics will be provided. For (3), time to resolution from the first onset of the AE will be summarized. If no date of resolution is recorded, then the last date of visit will be used as the date of resolution.
TEAEs will be coded using the MedDRA and will be summarized using PT for (1) to (6). For (1), PT will be sorted in decreasing frequency. For (4) to (6), AECI and PT will both be sorted alphabetically. A subject with multiple occurrences of TEAE within a PT will be counted only once for the TEAE with the maximum intensity. For (4), TEAEs of clinical importance which resulted in dose reduction in Ixazomib, in Lenalidomide, and in Dexamethasone will each be displayed, as well as TEAEs of clinical importance which resulted in dose reduction in any of Ixazomib, Lenalidomide, or Dexamethasone. For (5), TEAEs of clinical importance which resulted in dose held in Ixazomib, in Lenalidomide, and in Dexamethasone will each be displayed, as well as TEAEs of clinical importance which resulted in dose held in any of Ixazomib, Lenalidomide, or Dexamethasone. For (6), TEAEs of clinical importance which resulted in dose discontinuation in Ixazomib, in Lenalidomide, and in Dexamethasone

will each be displayed, as well as TEAEs of clinical importance which resulted in dose discontinuation in any of Ixazomib, Lenalidomide, or Dexamethasone. For (7), TEAEs will be summarized using SOC, HLT, and PT, where SOC, HLT, and PT will be sorted in decreasing frequency. TEAEs will be graded using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) (Version 4.03).

(1) Treatment-Emergent Adverse Events of Clinical Importance by Preferred Term and NCI CTCAE Grade
(2) Summary of Time to First Onset in Treatment-Emergent Adverse Events of Clinical Importance
(3) Summary of Time to Resolution in Treatment-Emergent Adverse Events of Clinical Importance
(4) Treatment-Emergent Adverse Events of Clinical Importance which Resulted in Dose Reduction by Preferred Term
(5) Treatment-Emergent Adverse Events of Clinical Importance which Resulted in Dose Held by Preferred Term
(6) Treatment-Emergent Adverse Events of Clinical Importance which Resulted in Dose Discontinuation by Preferred Term
(7) Treatment-Emergent Haemorrhage Adverse Events by System Organ Class, High Level Term, and Preferred Term

7.11.1.5 Summary of Treatment-Emergent Adverse Events Overall, and by Toxicity, Seriousness, Relatedness, Discontinuation, and Dose Modification

Analysis Set: Safety Analysis Set

Analysis Variable(s) : TEAE
TEAE of clinical importance

Analytical Method(s) : The following summaries will be provided using frequency distribution. The summaries will include the number and percentages of subjects who had any TEAEs, drug-related TEAEs, Grade 3 or higher TEAEs, Grade 3 or higher drug-related TEAEs, serious TEAEs, TEAEs resulting in death, TEAEs leading to study drug discontinuation, TEAEs which resulted in dose reduction, dose held, and dose delayed in any of Ixazomib, Lenalidomide, or Dexamethasone. TEAEs will be coded using the MedDRA and will be

summarized using SOC and PT. SOC and PT will be sorted in decreasing frequency.

(1) Summary of Treatment-Emergent Adverse Events Overall, and by Toxicity, Seriousness, Relatedness, Discontinuation, and Dose Modification

(2) Summary of Treatment-Emergent Adverse Events of Clinical Importance Overall, and by Toxicity, Seriousness, Relatedness, Discontinuation, and Dose Modification

7.11.2 Clinical Laboratory Evaluations

7.11.2.1 Hematology and Blood Chemistry

Analysis Set: Safety Analysis Set

Analysis Variable(s) :

Hematology		
Hemoglobin	Hematocrit	Platelet Count
WBC Count	Neutrophils	Lymphocytes
Serum Chemistry		
Blood Urea Nitrogen	Creatinine	Total Bilirubin
Uric Acid	Lactate dehydrogenase (LDH)	Alkaline Phosphatase
AST	ALT	Albumin
Glucose	Sodium	Potassium
Chloride	Carbon dioxide	Magnesium
Calcium	Phosphate	Thyroid Stimulating Hormone (TSH)

Categories: Intensity [Grade 0, Grade 1, Grade 2, Grade 3, Grade 4]

Visit: Hematology: Screening, Baseline, Cycle 1 Day 1, Cycle 1 Day 7, Cycle 1 Day 14, Cycle 1 Day 21, Cycle 2 Day 1, Cycle 2 Day 7, Cycle 2 Day 14, Cycle 2 Day 21, Cycle 3 Day 1, Cycle 3 Day 14, Cycle 4 Day 1, Cycle 5 Day 1, Cycle 6 Day 1, ... (up to the maximum cycle), End of Treatment, Last Assessment

Serum Chemistry: Screening, Baseline, Cycle 1 Day 1, Cycle 2 Day 1, Cycle 3 Day 1, Cycle 4 Day 1, Cycle 5 Day 1, Cycle 6 Day 1, ... (up to the maximum cycle), End of Treatment, Last Assessment

Analytical

Method(s) : For each variable, (1) will be provided.
For applicable variables, (2), (3), and (4) will be provided.
NCI CTCAE (Version 4.03) will be used for grading. Last Assessment is defined as the last measurement prior to or on the last visit conducted 30 days after the last dose of study drug regimen.
Laboratory test results from the central laboratory will be used when they are available. Laboratory test results from local laboratory will be used only when no central laboratory test result exists at the same scheduled sample collection time point.

(1) Summary of Laboratory Test Results and Change from Baseline by Visit
Descriptive statistics for observed values for each visit and changes from baseline will be provided.

(2) Case Plots
Plots over time for each subject will be presented for platelet count and neutrophils.

(3) Line Plot of Platelet Count Over Time
For the platelet count, the overall median over time will be presented.

(4) Maximum Grade Shift from Baseline of Laboratory Parameters
The maximum (worst) post-baseline grade will be determined for each subject. Shift tables showing the number of subjects in each grade category at baseline and post-baseline visit will be provided using evaluable data.

7.11.3 Vital Signs and Weight

Analysis Set: Safety Analysis Set
Analysis
Variable(s) : Systolic Blood Pressure (mmHg)
Diastolic Blood Pressure (mmHg)
Heart Rate (bpm)
Respiratory Rate (bpm)
Temperature (C)
Weight (kg)
Visit: Screening, Baseline, Cycle 1 Day 1, Cycle 2 Day 1, Cycle 3 Day 1, Cycle 4 Day 1, ... (up to the maximum cycle), End of Treatment, Last Assessment

Analytical
Method(s) : For each variable, the following summaries will be provided.
Last Assessment is defined as the last measurement prior to or on the last visit conducted 30 days after the last dose of study drug regimen.

(1) Summary of Vital Signs Parameters and Change from Baseline by Visit
Descriptive statistics for observed values for each visit and changes from baseline will be provided.

7.11.4 12-Lead ECGs

Not applicable.

7.11.5 Other Observations Related to Safety

7.11.5.1 ECOG Performance Status

Analysis Set: Safety Analysis Set
Analysis
Variable(s) : ECOG Performance Status
Categories: ECOG Score [0, 1, 2, 3, 4]
Visit: Screening, Baseline, Cycle 2 Day 1, Cycle 3 Day 1, ... (up to the maximum cycle), End of Treatment, Last Assessment
Analytical
Method(s) : For each variable, the following summaries will be provided.
Last Assessment is defined as the last measurement prior to or on the last visit conducted 30 days after the last dose of study drug regimen.

(1) ECOG Performance Status Data Measured Over Time
Descriptive statistics for observed values for each visit and changes from baseline will be provided.

(2) ECOG Performance Score Shift from Baseline to Post-Baseline Assessments Over Time
Shift tables showing the number of subjects in each ECOG score category at baseline and each post-baseline visit will be provided.

7.11.5.2 Subsequent Anti-Cancer Therapy

Analysis Set: Safety Analysis Set
Analysis
Variable(s) : Subsequent Anti-Cancer Therapy

Analytical
Method(s) : (1) Subsequent Anti-Cancer Therapy by Class of Agent and WHO Generic Term

Frequency distributions will be provided.

7.12 Interim Analysis

Analysis is planned to be performed twice during the study. The primary analysis is planned to be performed using the data obtained at approximately 12 months from the enrollment of the last patient. The final analysis is planned to be performed after the final database lock using the data obtained at approximately 24 months from the enrollment of the last patient. The timing of analysis may be changed or additional analysis may be added upon request of the regulatory authorities.

7.13 Changes in the Statistical Analysis Plan

The analyses in the statistical analysis plan do not differ from the analyses specified in the protocol.

8.0 REFERENCES

Not applicable.