



Title: A Phase 1 Study of MLN9708 in Japanese Patients with Relapsed and/or Refractory Multiple Myeloma

NCT Number: TBD

Statistical analysis plan Approve Date: 12-FEB-2014

Certain information within this statistical analysis plan has been redacted (ie, specific content is masked irreversibly from view with a black/blue bar) to protect either personally identifiable information or company confidential information.

This may include, but is not limited to, redaction of the following:

- Named persons or organizations associated with the study.
- Patient identifiers within the text, tables, or figures or in by-patient data listings.
- Proprietary information, such as scales or coding systems, which are considered confidential information under prior agreements with license holder.
- Other information as needed to protect confidentiality of Takeda or partners, personal information, or to otherwise protect the integrity of the clinical study.

If needed, certain appendices that contain a large volume of personally identifiable information or company confidential information may be removed in their entirety if it is considered that they do not add substantially to the interpretation of the data (eg, appendix of investigator's curriculum vitae).

STATISTICAL ANALYSIS PLAN APPROVAL SHEET

Product	MLN9708 (ixazomib citrate)
Protocol Number	TB-MC010034
Study Title	A Phase 1 Study of MLN9708 in Japanese Patients with Relapsed and/or Refractory Multiple Myeloma
Author	PPD [REDACTED]
Date Prepared	12 February 2014
Version	2.0

Approval signature

Signature	Date
PPD [REDACTED]	Development Operations
Signature	Date
PPD [REDACTED]	Biostatistics

STATISTICAL ANALYSIS PLAN

**A Phase 1 Study of MLN9708 in Japanese Patients with Relapsed and/or Refractory
Multiple Myeloma**

MLN9708 (ixazomib citrate)

Protocol Number: TB-MC010034

Version:	2.0
Date:	12 February 2014
Biostatistician:	PPD

1. LIST OF ABBREVIATIONS

Abbreviation or Term	Definition/Explanation
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
BSA	body surface area
BUN	blood urea nitrogen
CR	complete response
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DLT	dose limiting toxicity
DOR	duration of response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EOS	end of study
ESEC	Efficacy and Safety Evaluation Committee
HbA1c	hemoglobin A1c
LDH	lactate dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
ORR	objective response rate
PD	progressive disease
PK	pharmacokinetic
PR	partial response
PT	preferred term
QTc	corrected QT interval
QTcB	corrected QT interval by Bazetts formula
QTcF	corrected QT interval by Fridericias formula
RBC	red blood cell
Rd	lenalidomide and dexamethasone
sCR	stringent complete response
SD	stable disease
SOC	system organ class
TEAE	treatment-emergent adverse event
VGPR	very good partial response
WBC	white blood cell

2. TABLE OF CONTENTS

	Page
1. LIST OF ABBREVIATIONS	2
2. TABLE OF CONTENTS	3
3. INTRODUCTION	5
4. STUDY OBJECTIVES	5
4.1 Primary Objective	5
4.2 Secondary Objective	5
5. STUDY OVERVIEW	5
5.1 Summary of Study Design	5
5.2 Sample Size Considerations	7
6. STUDY ENDPOINTS	7
6.1 Primary Endpoint	7
6.2 Secondary Endpoints	7
7. ANALYSIS SETS	8
7.1 Safety Analysis Set	8
7.2 Dose Limiting Toxicity (DLT) Analysis Set	8
7.3 Response Evaluable Analysis Set	8
7.4 Pharmacokinetic (PK) Analysis Set	8
8. DATA HANDLING	8
8.1 Handling of Missing Data	8
8.2 Handling of Partial Date	8
8.3 Definition of Baseline Values	9
8.4 Windowing of Visits	9
9. STATISTICAL METHODS OF ANALYSIS	9
9.1 General Principles	9
9.2 Enrollment and Disposition of Subjects	10
9.2.1 Subject Disposition	10
9.2.2 Analysis Sets	10
9.2.3 Protocol Deviations and Treatment Compliance	10
9.3 Demographic and Other Baseline Characteristics	11
9.4 Safety Analyses	13
9.4.1 Extent of Exposure	13
9.4.2 Adverse Events	14

9.4.3	Clinical laboratory	15
9.4.4	12-Lead Electrocardiograms	16
9.4.5	Vital Signs	17
9.4.6	Eastern Cooperative Oncology Group (ECOG) Performance Status	17
9.5	Efficacy Analyses	18
9.5.1	Tumor Response	18
10.	LISTING	19
11.	APENDICES	20
12.	REFERENCES	20
13.	DOCUMENT HISTORY	21

3. INTRODUCTION

The purpose of this statistical analysis plan is to provide details of the statistical analyses that have been outlined within the protocol for MLN9708 study TB-MC010034. The scope of this plan includes the final analysis that is planned and will be performed by the Biostatistics department or designee.

4. STUDY OBJECTIVES

4.1 Primary Objective

To evaluate the tolerability, safety, and pharmacokinetics of MLN9708 alone or in combination with lenalidomide and dexamethasone (Rd) in patients with relapsed and/or refractory multiple myeloma.

4.2 Secondary Objective

To evaluate the antitumor activity of MLN9708 in patients with relapsed and/or refractory multiple myeloma.

5. STUDY OVERVIEW

5.1 Summary of Study Design

This is a phase 1, multicenter, single-arm, open-label, dose-escalation study to evaluate the tolerability, safety, and pharmacokinetics of MLN9708 administered alone or in combination with Rd in patients with relapsed and/or refractory multiple myeloma.

This study consists of the following 4 cohorts.

- Cohort 1: MLN9708 4.0 mg
- Cohort 2: MLN9708 4.0 mg + Rd
- Cohort 3: MLN9708 5.5 mg
- Cohort 4: MLN9708 5.5 mg + Rd

Three subjects will be enrolled sequentially from cohorts 1 (MLN9708 4.0 mg alone) to 4. If dose-limiting toxicity (DLT) occurs in 1 subject during DLT-assessment period, 3 additional subjects will be enrolled in the applicable cohort to evaluate the tolerability in a total of 6 subjects. If DLT occurs in 2 of the 3 subjects, the given dosage is considered intolerable. If DLT occurs in 2 of the 6 subjects, the sponsor will determine the tolerability to the given dosage after discussing with the Efficacy and Safety Evaluation Committee (ESEC).

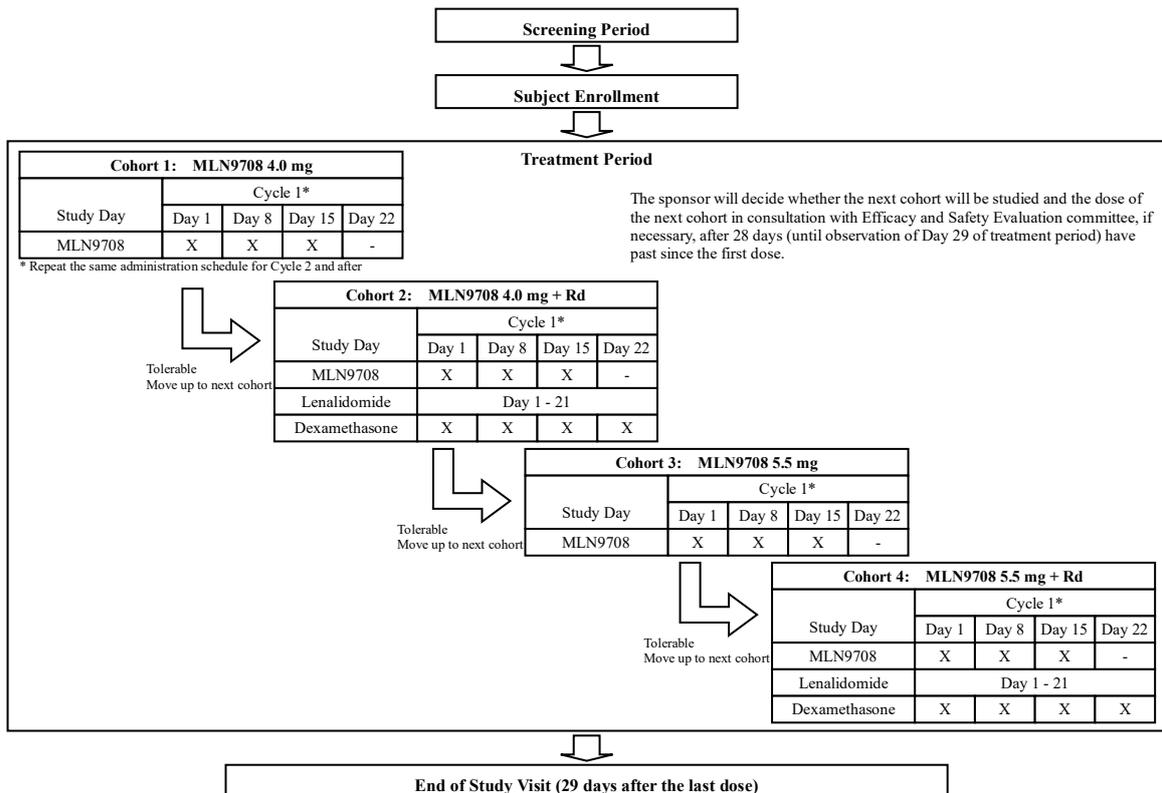
The sponsor will evaluate the tolerability of MLN9708 on the basis of the safety data including DLT incidences during the DLT-assessment period. The sponsor will decide whether the next cohort will be studied and the dose of the next cohort in consultation with the ESEC, if necessary. If the current cohort is considered tolerable, the next cohort will be in the order of cohorts 2 (MLN9708 4.0 mg + Rd), 3 (MLN9708 5.5 mg alone), and 4 (MLN9708 5.5 mg + Rd). Even if a dosage is considered tolerable and transition to the next cohort is considered feasible, the next cohort may not be studied based on the results of the overseas clinical studies and the current study.

The additional written informed consent for extended treatment will be obtained before the first dose of MLN9708 in Cycle 2 from the subjects who meet the criteria for beginning the next cycle of treatment and have no safety concern. Subjects who do not give the consent will undergo end of study (EOS) visit on 29 days after the last dose of MLN9708 in Cycle 1. The subjects giving the consent can continue the study treatment up to 12 cycles unless they meet the criteria of subject removal including evidence of progressive disease (PD) and intolerable toxicity. Subjects may remain on treatment after the 12 cycles if the investigator considers it beneficial for the subjects.

All subjects should undergo EOS visit on 29 days after the last dose of MLN9708.

The overall study design is described in Table 5-1. "Study Design and Treatment Schema".

Table 5-1. Study Design and Treatment Schema



5.2 Sample Size Considerations

The planned number of subjects in this study is 3 to 6 for each cohort (12 to 24 in total).

The sample size was selected with reference to the preceding overseas clinical studies and the “Anti-Malignant Tumor Drug Clinical Assessment Guidelines” (PFSB/ELD Notification No. 1101001, dated November 1, 2005). The sample size was not selected based on a statistical rationale.

6. STUDY ENDPOINTS

6.1 Primary Endpoint

- DLTs, adverse events, body weight, vital signs, 12-lead electrocardiograms (ECGs), laboratory tests.
- MLN2238 plasma concentration.

6.2 Secondary Endpoints

- Number of subjects achieving CR, VGPR, and PR.

7. ANALYSIS SETS

7.1 Safety Analysis Set

The safety analysis set will consist of all subjects who received at least one dose of study treatment. Subjects will be analyzed according to the treatment received. Safety analysis set will be used for all safety analyses unless otherwise specified.

7.2 Dose Limiting Toxicity (DLT) Analysis Set

The DLT analysis set will consist of all subjects who experienced at least one DLT during DLT-assessment period (i.e., from the first dose to start of dose in cycle 2), or who received 3 planned doses of MLN9708 and completed the DLT-assessment period. DLT analysis set will be used for DLT analyses.

7.3 Response Evaluable Analysis Set

The response evaluable analysis set will consist of all subjects who received at least one dose of study treatment, have measurable disease at baseline, and at least one post-baseline tumor assessment. Response evaluable analysis set will be the primary analysis set for the analyses of response.

7.4 Pharmacokinetic (PK) Analysis Set

The PK analysis set will consist of all subjects who had at least one evaluable concentration data and received at least one dose of study treatment. Unless otherwise specified, the PK analysis set will be used for all PK analyses.

8. DATA HANDLING

8.1 Handling of Missing Data

Missing values by drop-out or error will be removed from analysis and not be imputed. However, estimation of pharmacokinetic parameters will be performed as much as possible, even if there are missing values. PK data below the lower limit of quantitation will be treated as “zero”.

8.2 Handling of Partial Date

For initial diagnosis or each last prior event (antineoplastic therapy, radiation therapy, bone marrow transplant or stem cell transplant, and any surgical procedures) with the dates that are partially missing, the following rules will be applied:

- If only month and year are provided, the 1st of the month will be used if the year and the month are the same as those for the first dose of study treatment. Otherwise, the 15th will be used.
- If only year is provided and it is the same as the year of the first dose of study treatment, the 1st of January will be used. Otherwise, the 1st of July will be used.

The listing will be prepared based on original date (e.g., 2007/01/UN / 2007/UN/UN).

8.3 Definition of Baseline Values

Unless otherwise specified, the baseline value is defined as the value collected at the time closest to, but prior to, the first dose of any study treatment.

8.4 Windowing of Visits

If some multiple values are observed in the same time window, the value on the closer day to the target date will be adopted. If the difference between the observed dates and the target date is same, later value is adopted for safety evaluation. However, the actual dates of these values should be used in the listings and individual plots.

9. STATISTICAL METHODS OF ANALYSIS

9.1 General Principles

- Tables will be tabulated by the following groups unless otherwise specified;
 - monotherapy treatment group
 - combination treatment group
 - total of all subjects
- Listings and figures are provided by treatment group unless otherwise specified.
- Continuous variables will be summarized descriptively using summary statistics (n, mean, standard deviation, median, max, and min).
- Categorical variables will be summarized using frequencies and percentages.
- The analyses will not be performed for N=1.
- The National Cancer Institute-Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03 will be used for grading the adverse events and clinical laboratory abnormalities.
- International uniform response criteria for multiple myeloma (Durie et al, 2006) will be used for evaluating the tumor response.

9.2 Enrollment and Disposition of Subjects

9.2.1 Subject Disposition

9.2.1.1 Items

Items for subject enrollment

- Subjects screened
- Subjects enrolled

Items for subject disposition

- MLN9708 administration: [Received, Never received]
- Lenalidomide administration: [Received, Never received]
- Dexamethasone administration: [Received, Never received]
- Study treatment completion: [Ongoing, Discontinuation, #Reasons]
- Study status: [Ongoing, Completed Safety Follow-up, Discontinued Without Safety Follow-up]

9.2.1.2 Methods

The following tabulations will be prepared:

- Subject enrollment (Subjects screened)
- Subject disposition (Subjects enrolled)

9.2.2 Analysis Sets

9.2.2.1 Items

Every analysis set defined in Section 7 “ANALYSIS SETS”.

9.2.2.2 Methods

The number of subjects included in and excluded from each analysis set will be tabulated for all subjects enrolled.

9.2.3 Protocol Deviations and Treatment Compliance

9.2.3.1 Items

The following categories of important protocol deviations:

- EN : Entered study even though entry criteria was not satisfied
- XM : Received an excluded concomitant treatment
- NW : Developed withdrawal criteria but was not withdrawn
- TA : Received the wrong treatment or incorrect dose
- TC : Other Treatment Compliance

- OS : Off-schedule procedures (other than TA or TC)
- MD : Missing data (other than TA or TC)
- OT : Other Deviations

9.2.3.2 Methods

The number of subjects with any important protocol deviations and each important protocol deviation will be tabulated for all subjects enrolled.

9.3 Demographic and Other Baseline Characteristics

9.3.1.1 Items

Items for demographic and baseline characteristics

- Sex
- Age
- Age group: [< 65 , ≥ 65 years]
- Height
- Weight
- Body Surface Area (BSA)
BSA will be calculated using the following formula:
 - $BSA (m^2) = Height (cm)^{0.5} * Weight (kg)^{0.5} / 60$
- Eastern Cooperative Oncology Group (ECOG) performance status: [0, 1, 2]
- Medical and surgical history: [Yes, No]

Items for disease characteristics

- Disease type: [IgG (Kappa, Lambda), IgA (Kappa, Lambda), IgD (Kappa, Lambda), IgE (Kappa, Lambda), IgM (Kappa, Lambda), Other]
- Stage at initial diagnosis (Durie-Salmon Stage): [IA, IB, IIA, IIB, IIIA, IIIB, Unknown]
- Stage at initial diagnosis (International Staging System Stage): [I, II, III, Unknown]
- Duration from initial diagnosis to first dose
- Duration from last prior antineoplastic therapy to first dose
- Duration from last prior radiation therapy to first dose
- Duration from last prior bone marrow transplant or stem cell transplant to first dose
- Duration from last prior surgical procedures to first dose
Duration will be calculated using the following formula:
 - $Duration (months) = (Date of first dose - Date of initial diagnosis or each last prior event) * 12 / 365.25$
- Evidence of lytic bone disease at initial diagnosis: [Yes, No, Unknown]
- Evidence of extramedullary disease at initial diagnosis: [Yes, No, Unknown]
- Stage at study entry (Durie-Salmon Stage): [IA, IB, IIA, IIB, IIIA, IIIB, Unknown]

- Stage at study entry (International Staging System Stage): [I, II, III, Unknown]
- Serum creatinine (in summary statistics)
- Serum creatinine by category: [≤ 2 , > 2 mg/dL]
- Creatinine clearance by category: [< 30 ; $30 \leq$, < 60 ; ≥ 60 mL/min]
Creatinine clearance will be calculated using the Cockcroft-Gault formulas as follows:
 - For male subjects:
Creatinine clearance (mL/min) = $(140 - \text{Age [years]}) * \text{Weight (kg)} / (72 * \text{Serum creatinine [mg/dL]})$
 - For female subjects:
Creatinine clearance (mL/min) = $0.85 * (140 - \text{Age [years]}) * \text{Weight (kg)} / (72 * \text{Serum creatinine [mg/dL]})$
- Kappa/Lambda ratio by category: [< 1 , ≥ 1]
- Serum M-protein (total M-protein)
- 24 hour urine M-protein (urine total M-protein)
- Beta-2-microglobulin by category: [< 2.5 ; $2.5 \leq$, ≤ 5.5 ; > 5.5 mg/L]
- Albumin by category: [< 3.5 , ≥ 3.5 g/dL]
- Corrected calcium
Corrected calcium will be calculated using the following formulas:
 - Corrected calcium (mmol/L) = $0.25 * (\text{Serum calcium [mg/dL]} - 0.8 * (\text{Albumin [g/dL]} - 4))$, when Albumin (g/dL) is ≤ 4 .
 - Corrected calcium (mmol/L) = $0.25 * \text{Serum calcium (mg/dL)}$, when Albumin (g/dL) is > 4 .
- Subjects with bone marrow aspirate: [Available, Unable to detect, Not available]
- Bone marrow aspirate results (% Plasma cells)
- Skeletal survey results at screening: [Within Normal Limits, Abnormal not clinically significant, Abnormal clinically significant]
- Lytic bone lesions at screening: [Yes, No, Indeterminate]
- Chest X-Ray results at screening: [Not done, Done (Within Normal Limits, Abnormal not clinically significant, Abnormal clinically significant, Not evaluated/Inevaluable)]
- CT/MRI results at screening: [Within Normal Limits, Abnormal not clinically significant, Abnormal clinically significant]
- Plasmacytomas at screening: [Yes, No, Indeterminate]
- Prior antineoplastic therapy: [Yes, No]
- Prior radiation therapy: [Yes, No]
- Prior bone marrow transplant or stem cell transplant: [Yes, No]
- Prior surgical procedures: [Yes, No]

9.3.1.2 Methods

The following tabulations will be prepared:

- Demographic and other baseline characteristics (safety analysis set)

- Disease characteristics (safety analysis set)

9.4 Safety Analyses

9.4.1 Extent of Exposure

9.4.1.1 Items

Items for summary of exposure

- Number of treated cycles (in summary statistics)
- Number of treated cycles: [≥ 1 , ≥ 2 , ≥ 3 , ... ≥ 13]
- Total amount of dose taken
- Number of doses taken
- Dose intensity
Dose intensity will be calculated using the following formula:
 - $\text{Dose Intensity (mg/cycle)} = \text{Total amount of dose taken (mg)} / \text{Number of treated cycles}$
- Relative dose intensity
Relative dose intensity will be calculated using the following formula:
 - $\text{Relative Dose Intensity (\%)} = (\text{Total amount of dose taken [mg]} / \text{Total amount of dose expected per initial dose [mg]}) * 100$
- Dosing compliance
Dosing compliance will be calculated using the following formula:
 - $\text{Dosing compliance (\%)} = (\text{Total amount of dose taken [mg]} / \text{Total amount of dose expected [mg]}) * 100$The dose expected is defined as the scheduled dose level for a dosing day when the action on drug is not "held" or "discontinued".

Items for change in exposure

- Subjects with any dose reduced prescribed: [#Reasons]
- Subjects with any dose reduced non-prescribed: [#Reasons]
- Subjects with any dose held: [#Reasons]
- Subjects with any dose missed: [#Reasons]
- Subjects with any dose delayed: [#Reasons]
- Subjects with any dose discontinued permanently: [#Reasons]

9.4.1.2 Methods

The following tabulations will be prepared:

- Summary of exposure to MLN9708 (Safety analysis set)
- Summary of exposure to Lenalidomide (Safety analysis set)
- Summary of exposure to Dexamethasone (Safety analysis set)

- Change in exposure to MLN9708 (Safety analysis set)
- Change in exposure to Lenalidomide (Safety analysis set)
- Change in exposure to Dexamethasone (Safety analysis set)

9.4.2 Adverse Events

9.4.2.1 Items

- Treatment-emergent adverse events (TEAEs)
- Treatment-related adverse events
- Serious treatment-emergent adverse events
- Serious treatment-related adverse events
- Treatment-emergent adverse events leading to permanent discontinuation of study treatment
- Treatment-related adverse events leading to permanent discontinuation of study treatment
- Dose limiting toxicities (DLTs)

9.4.2.2 Methods

TEAEs are defined as adverse events or events resulting from exacerbation of complications that have occurred after the first dose of MLN9708.

Treatment-related adverse events are defined as TEAEs that relationship to study treatment is assessed as “Yes”.

The Medical Dictionary for Regulatory Activities (MedDRA) version 16.0 will be used to code all adverse events to a system organ class (SOC) and a preferred term (PT).

The following tabulations will be prepared:

- Summary of treatment-emergent adverse events (Safety analysis set)
- Summary of treatment-related adverse events (Safety analysis set)
- Subject incidence of treatment-emergent adverse events by system organ class and preferred term by grade (Safety analysis set)
- Subject incidence of treatment-related adverse events by system organ class and preferred term by grade (Safety analysis set)
- Subject incidence of serious treatment-emergent adverse events by system organ class and preferred term by grade (Safety analysis set)
- Subject incidence of serious treatment-related adverse events by system organ class and preferred term by grade (Safety analysis set)
- Subject incidence of treatment-emergent adverse events leading to permanent discontinuation of study treatment by system organ class and preferred term by grade (Safety analysis set)

- Subject incidence of treatment-related adverse events leading to permanent discontinuation of study treatment by system organ class and preferred term by grade (Safety analysis set)
- Subject incidence of treatment-emergent adverse events by preferred term in descending order of frequency (Any vs. grade 3 or higher events) (Safety analysis set)
- Subject incidence of treatment-related adverse events by preferred term in descending order of frequency (Any vs. grade 3 or higher events) (Safety analysis set)
- Subject incidence of serious treatment-emergent adverse events by preferred term in descending order of frequency (Safety analysis set)
- Subject incidence of serious treatment-related adverse events by preferred term in descending order of frequency (Safety analysis set)
- Subject incidence of treatment-emergent adverse events leading to permanent discontinuation of study treatment by preferred term in descending order of frequency (Safety analysis set)
- Subject incidence of treatment-related adverse events leading to permanent discontinuation of study treatment by preferred term in descending order of frequency (Safety analysis set)
- Subject incidence of dose limiting toxicities by preferred term in descending order of frequency by safety evaluation committee in cycle 1 (DLT analysis set)

A subject counts once for each SOC and PT for its worst grade.

All “by SOC and PT” and “by PT” tabulations are prepared by descending order of frequency for total of treatment groups and by alphabetical order.

Serious adverse event that occurred prior to first dose of MLN9708 will be presented in the listing.

9.4.3 Clinical laboratory

9.4.3.1 Items

- Hematology
- Chemistry (including corrected calcium)
- Urinalysis

9.4.3.2 Methods

For the purposes of summarization in the tables, listings and figures, all laboratory values will be converted to standardized units.

The textbook range (Pagana KD and Pagana TJ, 2011) will be used for the grading of differential.

The following tables will be prepared for all evaluable clinical laboratory abnormalities:

- Subject incidence of hematology abnormalities at post-baseline by grade (Safety analysis set)
- Subject incidence of chemistry abnormalities at post-baseline by grade (Safety analysis set)
- Subject incidence of urinalysis abnormalities at post-baseline by grade (Safety analysis set)
- Maximum grade shift from baseline for hematology (Safety analysis set)
- Maximum grade shift from baseline for chemistry (Safety analysis set)
- Maximum grade shift from baseline for urinalysis (Safety analysis set)

The following table will be prepared for all categorical values:

- Worst category shift from baseline for urinalysis (Safety Analysis Set)

The following tables and figures will be prepared for all continuous values:

- Summary of maximum/minimum post-baseline values for hematology (Safety analysis set)
- Summary of maximum/minimum post-baseline values for chemistry (Safety analysis set)
- Summary of maximum/minimum post-baseline values for urinalysis (Safety analysis set)
- Line plot of hematology by subject (Safety analysis set)
- Line plot of chemistry by subject (Safety analysis set)
- Line plot of urinalysis by subject (Safety analysis set)

9.4.4 12-Lead Electrocardiograms

9.4.4.1 Items

ECG interpretation, heart rate, PR, QRS, QT, QTcB, and QTcF.

(QTcB and QTcF which are calculated at site will not be used for analyses and will be presented on the listing only.)

QTcB and QTcF will be calculated using the following formulas:

- $QTcB = QT / (RR^{0.5})$
 - $QTcF = QT / (RR^{0.33})$
- where $RR = 60 / \text{heart rate (bpm)}$

9.4.4.2 Methods

The following table will be prepared for ECG interpretation:

- Shift table of ECG interpretation by visit (Safety analysis set)

The following tables and figures will be prepared for heart rate, PR, QRS, QT, QTcB, and QTcF:

- Summary of maximum/minimum post-baseline values for 12-lead ECGs (Safety analysis set)
- Line plot of 12-lead ECGs by subject (Safety analysis set)

The following tables will be prepared for QT, QTcB, and QTcF:

- Category of QT, QTcB, and QTcF by visit (Safety analysis set)
- Category of change from baseline of QT, QTcB, and QTcF by visit (Safety analysis set)

The categories of QT, QTcB, and QTcF are as follows:

- ≤ 450 msec; $450 < , \leq 480$ msec; $480 < , \leq 500$ msec; > 500 msec

The categories of change from baseline of QT, QTcB, and QTcF are as follows:

- ≤ 30 msec; $30 < , \leq 60$ msec; > 60 msec

9.4.5 Vital Signs

9.4.5.1 Items

Temperature, pulse, systolic blood pressure, diastolic blood pressure, SpO₂, and weight.

9.4.5.2 Methods

The following tables and figures will be prepared for each item:

- Summary of maximum/minimum post-baseline values for vital signs (Safety analysis set)
- Summary of maximum/minimum post-baseline values for weight (Safety analysis set)
- Line plot of vital signs by subject (Safety analysis set)
- Line plot of weight by subject (Safety analysis set)

9.4.6 Eastern Cooperative Oncology Group (ECOG) Performance Status

9.4.6.1 Items

ECOG performance status.

9.4.6.2 Methods

The following table will be prepared:

- Eastern Cooperative Oncology Group performance status by visit (Safety analysis set)

9.5 Efficacy Analyses

9.5.1 Tumor Response

Tumor response will be assessed using the International uniform response criteria for multiple myeloma (Durie et al, 2006).

9.5.1.1 Items

- Best response: [CR (including sCR), PR (including VGPR), SD, PD, Not Evaluable]
Best response for a subject is the best observed post-baseline tumor response. All response categories require two consecutive assessments made at anytime before the institution of any new therapy.

- Objective response rate (ORR)

ORR is defined as the rate of subjects with sCR, CR, VGPR, or PR in response evaluable analysis set.

- Duration of response (DOR)

DOR is defined as the time from the date of first documentation of objective tumor response (sCR, CR, VGPR, or PR) to the date of first subsequent documentation of PD or death due to disease progression, whichever comes first in subjects who have the documentation of objective tumor response. Subjects who are alive at the data cutoff date without the documentation of PD will be censored at the date of the last tumor assessment.

DOR will be calculated using the following formulas:

$$\text{DOR} = \text{Date of first documentation of PD or death} - \text{Date of first subsequent documentation of objective tumor response} + 1$$

- Time to response

Time to response is defined as the time from the date of first dose of study treatment to the date of first documentation of objective tumor response (sCR, CR, VGPR, or PR) in subjects who responded.

Time to response will be calculated using the following formulas:

$$\text{Time to response} = \text{Date of first documentation of objective tumor response} - \text{Date of first dose of study treatment}$$

- Time to progression (TTP)

TTP is defined as the time from the date of first dose of study treatment to the date of first documentation of PD or death caused by progression, whichever comes first. Subjects who are alive at the data cutoff date without the documentation of PD will be censored at the date of the last tumor assessment, but if the subjects have not had the last tumor assessment, then will be censored at the following day of first dose of study treatment.

TTP will be calculated using the following formulas:

$$\text{TTP} = \text{Date of first documentation of PD or death} - \text{Date of first dose of study treatment} + 1$$

- Maximum M-protein change: [-100%; -100% < , ≤ -90%; -90% < , ≤ -75%; -75% < , ≤ -50%; -50% < , ≤ -25%; -25% < , ≤ 25%; 25% <]

Maximum M-protein change is the largest percent change from baseline among all post-baseline measures of the Total M-protein. For subjects with measurable serum M-protein at baseline, it is the percent change from baseline to the best (lowest) post-baseline value in serum M-protein. For subjects with non-measurable serum M-protein but measurable urine M-protein at baseline, it is the percent change from baseline to the best (lowest) post-baseline value in urine M-protein.

9.5.1.2 Methods

For all items, the following table will be prepared using Response Evaluable Analysis Set:

- Summary of Tumor Response (Response Evaluable Analysis Set).

For ORR, frequencies and percentages with 2-sided 95% exact confidence interval using the F distribution method given in Collett (2002) will be presented.

DOR, time to response, and TTP will be summarized descriptively. For DOR and TTP, Kaplan-Meier method will be used.

For best response and maximum M-protein change, frequencies and percentages will be presented by category.

10. LISTING

- Deaths on study
- Treatment-emergent adverse events
- Treatment-related adverse events
- Serious adverse events
- Adverse events leading to permanent discontinuation of study treatment
- Dose limiting toxicities by safety evaluation committee in cycle 1
- Dose limiting toxicities by investigator
- Hematology
- Chemistry (including corrected calcium)
- Urinalysis
- Beta-2-microglobulin
- Serum free light chain
- Serum M-protein
- Serum immunofixation
- Quantitative immunoglobulins
- Spot urine M-protein
- 24-hour urine M-protein
- Urine immunofixation
- Bone marrow evaluations: Aspiration

- Chest X-ray
- Skeletal survey
- CT/MRI
- Plasmacytoma evaluation
- Vital signs
- Pregnancy test
- 12-lead ECGs
- Eastern Cooperative Oncology Group performance status
- Subject disposition (including informed consent for extended administration)
- Screen failures
- Important protocol deviations
- Analysis sets
- Demographics
- Medical and surgical history
- Disease characteristics
- Prior therapy
- Prior radiation therapy
- Prior transplant procedure
- Prior surgery
- Tumor response (Investigator response assessment)
- Overall efficacy
- Summary of exposure to MLN9708
- Summary of exposure to Lenalidomide
- Summary of exposure to Dexamethasone
- Exposure to MLN9708 by visit
- Exposure to Lenalidomide by visit
- Exposure to Dexamethasone by visit
- Concomitant medications
- Concomitant procedures
- Grade 3 or higher clinical laboratory abnormalities

11. APENDICES

- Appendix A: Pharmacokinetics Analysis Plan

12. REFERENCES

- Collett D. Modelling Binary Data, Second Edition. Chapman & Hall. 2002:408p.
- Durie BG, Harousseau JL, Miguel JS, Blade J, Barlogie B, Anderson K, et al. International uniform response criteria for multiple myeloma. *Leukemia* 2006;20(9):1467-73.

- National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03. NIH Publication. 2010:78p
- Pagana KD. and Pagana TJ. Mosbys Diagnostic and Laboratory Test Reference Tenth Edition. Mosby Elsevier. 2011:1152p.

13. DOCUMENT HISTORY

Version	Date	Author	Remarks
1.0	11 April 2012	PPD	Original version
2.0	12 February 2014	PPD	<p>"BSA" and "EOS" have been added to the list in section 1.</p> <p>Description of the study design has been corrected in section 5.1.</p> <p>Some descriptions have been corrected in section 7, 8, and 9.</p> <p>"8.2 Handling of Partial Date" has been added in section 8.</p> <p>"total of monotherapy treatment groups" and "total of combination treatment groups" have been deleted in section 9.1.</p> <p>To use "International uniform response criteria for multiple myeloma (Durie et al, 2006)" for evaluating the tumor response has been added in section 9.1.</p> <p>"MLN9708 completion", "Lenalidomide completion", "Dexamethasone completion", and "Study completion" have been deleted from items for subject disposition in section 9.2.1.1.</p> <p>"Study treatment completion" has been added to items for subject disposition in section 9.2.1.1.</p> <p>"Study status" has been added to items for subject disposition in section 9.2.1.1.</p> <p>Methods have been changed in section 9.2.1.2.</p> <p>"BSA" and formula for calculating it have been added to items for demographic and baseline characteristics in section 9.3.1.1.</p> <p>"Duration from last prior antineoplastic therapy to first dose", "Duration from last prior radiation therapy to first dose", "Duration from last prior bone marrow transplant or stem cell transplant to first dose", "Duration from last prior any surgical procedures to first dose", and formula for calculating them have been added to items for disease characteristics in section 9.3.1.1.</p> <p>"Evidence of lytic bone disease" has been changed to "Evidence of lytic bone disease at initial diagnosis" in section 9.3.1.1.</p> <p>"Evidence of extramedullary disease" has been changed to "Evidence of extramedullary disease at initial diagnosis" in section 9.3.1.1.</p> <p>"Serum creatinine and by category" has been deleted</p>

			<p>in section 9.3.1.1.</p> <p>"Serum creatinine (in summary statistics)" and "Serum creatinine by category" have been added in section 9.3.1.1.</p> <p>The Cockcroft-Gault formulas for calculating creatinine clearance have been added in section 9.3.1.1.</p> <p>"Detection of M-protein" has been deleted from items for disease characteristics in section 9.3.1.1.</p> <p>"Kappa/Lambda ratio" has been changed to "Kappa/Lambda ratio by category" in section 9.3.1.1.</p> <p>"Serum M-protein" has been changed to "Serum M-protein (total M-protein)" in section 9.3.1.1.</p> <p>"Urine M-protein" has been changed to "24 hour urine M-protein (urine total M-protein)" in section 9.3.1.1.</p> <p>"β₂-microglobulin by category" has been changed to "Beta-2-microglobulin by category" in section 9.3.1.1.</p> <p>"Serum albumin by category" has been changed to "Albumin by category" in section 9.3.1.1.</p> <p>Formulas for calculating corrected calcium have been added in section 9.3.1.1.</p> <p>"Number of subjects with bone marrow aspirate" has been changed to "Subjects with bone marrow aspirate" in section 9.3.1.1.</p> <p>"Bone marrow aspirate results" has been changed to "Bone marrow aspirate results (% Plasma cells)" in section 9.3.1.1.</p> <p>"Skeletal survey results" has been changed to "Skeletal survey results at screening" in section 9.3.1.1.</p> <p>"Lytic bone lesions at screening" has been added in section 9.3.1.1.</p> <p>"Chest X-Ray results" has been changed to "Chest X-Ray results at screening" in section 9.3.1.1.</p> <p>"MRI/CT results" has been changed to "CT/MRI results at screening" in section 9.3.1.1.</p> <p>"Plasmacytomas at screening" has been added in section 9.3.1.1.</p> <p>"Number of prior antineoplastic therapy" has been deleted in section 9.3.1.1.</p> <p>"Prior antineoplastic therapy" has been added in section 9.3.1.1.</p> <p>Items for concomitant medications have been deleted in section 9.3.1.1.</p> <p>Methods have been changed in section 9.3.1.2.</p> <p>"Number of doses taken" has been added in section 9.4.1.1.</p> <p>Formulas for calculating dose intensity, relative dose intensity, and dosing compliance have been added in</p>
--	--	--	--

		<p>section 9.4.1.1.</p> <p>Definition for dose expected has been added in section 9.4.1.1.</p> <p>The MedDRA version 15.0 for coding all adverse events to a SOC and a PT has been changed to version 16.0 in section 9.4.2.2.</p> <p>To use "The textbook range (Pagana KD and Pagana TJ, 2011)" for grading of differential has been added in section 9.4.3.2.</p> <p>"Subject incidence of hematology abnormalities by grade (Safety analysis set)" has been changed to "Subject incidence of hematology abnormalities at post-baseline by grade (Safety analysis set)" in section 9.4.3.2.</p> <p>"Subject incidence of chemistry abnormalities by grade (Safety analysis set)" has been changed to "Subject incidence of chemistry abnormalities at post-baseline by grade (Safety analysis set)" in section 9.4.3.2.</p> <p>"Subject incidence of urinalysis abnormalities by grade (Safety analysis set)" has been changed to "Subject incidence of urinalysis abnormalities at post-baseline by grade (Safety analysis set)" in section 9.4.3.2.</p> <p>"Shift table of urinalysis (Safety Analysis Set)" has been changed to "Shift table of urinalysis by visit (Safety Analysis Set)" in section 9.4.3.2.</p> <p>"RR" has been deleted from items in section 9.4.4.1.</p> <p>Formulas for calculating QTcB and QTcF have been added in section 9.4.4.1.</p> <p>Definitions for "ORR", "DOR", "time to response", "TTP", "Best response", and "Maximum M-protein change" have been changed in section 9.5.1.1.</p> <p>Methods for "ORR", "DOR", "time to response", "TTP", "Best response", and "Maximum M-protein change" have been changed in section 9.5.1.2.</p> <p>"Adverse events" has been deleted in section 10.</p> <p>"Treatment-emergent adverse events" has been added in section 10.</p> <p>"Adverse events leading to permanent discontinuation of investigational product" has been changed to "Adverse events leading to permanent discontinuation of study treatment" in section 10.</p> <p>"Dose limiting toxicities" has been deleted in section 10.</p> <p>"Dose limiting toxicities by safety evaluation committee in cycle 1" and "Dose limiting toxicities by investigator" have been added in section 10.</p> <p>"Chemistry" has been changed to "Chemistry (including corrected calcium)" in section 10.</p> <p>"Urine M-protein" has been deleted in section 10.</p> <p>"Spot urine M-protein" and "24-hour urine M-</p>
--	--	--

			<p>protein" have been added in section 10.</p> <p>"Pregnancy test" has been added in section 10.</p> <p>"Subject disposition" has been changed to "Subject disposition (including informed consent for extended administration)" in section 10.</p> <p>"Prior radiation" has been changed to "Prior radiation therapy" in section 10.</p> <p>"Investigator response assessment (IMWG)" has been changed to "Tumor response (Investigator response assessment)" in section 10.</p> <p>"Overall efficacy" has been added in section 10.</p> <p>"Concomitant medications" has been added in section 10.</p> <p>"Concomitant procedures" has been added in section 10.</p> <p>"Summary of tumor response" has been deleted in section 10.</p> <p>"MLN9708 dosing" has been changed to "Exposure to MLN9708 by visit" in section 10.</p> <p>"Lenalidomide dosing" has been changed to "Exposure to Lenalidomide by visit" in section 10.</p> <p>"Dexamethasone dosing" has been changed to "Exposure to Dexamethasone by visit" in section 10.</p> <p>"Bone marrow evaluations" has been changed to "Bone marrow evaluations: Aspiration" in section 10.</p> <p>"β2-microglobulin" has been changed to "Beta-2-microglobulin" in section 10.</p> <p>"12-Lead Electrocardiograms" has been changed to "12-lead ECGs" in section 10.</p> <p>"ECOG performance status" has been changed to "Eastern Cooperative Oncology Group performance status" in section 10.</p> <p>"Grade 3 or higher clinical laboratory abnormalities" has been added in section 10.</p> <p>The section "12 REFERENCES" has been added.</p>
--	--	--	--