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

NCT Number: TBD

Protocol Approve Date: 22-NOV-2016

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

MLN9708 (ixazomib citrate)

Protocol Number: TB-MC010034

Clinical Study Sponsor:	Takeda Pharmaceutical Company Limited
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Version/Date:	Version 3.3 22 November 2016

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Document History

Version 1: 12 January 2012

Version 2: 7 February 2012

Version 2.1: 7 March 2012

Version 2.2: 11 September 2012

Version 3: 4 December 2013

Version 3.1: 4 December 2014

Version 3.2: 18 November 2015

PROTOCOL SUMMARY

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

Study Phase: 1

Indication: Patients with relapsed and/or refractory multiple myeloma

Study Objectives:

Primary:

- 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.

Secondary:

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

Overview of Study Design:

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 cohort 1 (MLN9708 4.0 mg alone). If dose-limiting toxicity (DLT) occurs in one subject during DLT-assessment period, 3 additional subjects will be enrolled in the same 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 dosage 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 plus Rd), 3 (MLN9708 5.5 mg alone), and 4 (MLN9708 5.5 mg plus 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 in "6.4 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 in "8.1 Removal of Subjects" 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 end of study visit on 29 days after the last dose of MLN9708.

The overall study design is described in "Study Design and Treatment Schema".

Primary and Secondary Endpoints:

Primary:

- DLT, adverse events, body weight, vital sign, 12-lead ECGs, and laboratory tests
- Plasma MLN2238 (active boronic acid form of MLN9708) concentration

Secondary:

- Number of subjects with complete response (CR), very good partial response (VGPR), or partial response (PR)

Number of Subjects: 12 to 24 (3 to 6 subjects in each cohort)

Number of Study Center(s): 5 centers

Summary of Subject Eligibility Criteria:

Inclusion Criteria:

Patients must give written consent to the participation and meet ALL of the following inclusion criteria to be eligible for the study.

Disease related

1) Japanese patients with multiple myeloma according to diagnostic criteria shown in Appendix E
2) Previously treated with 2 or more regimens including all the following drugs:
   - bortezomib
   - thalidomide or lenalidomide
   - corticosteroids
3) Patients who have relapsed following the previous therapy or failed to continue the treatment due to their intolerability to the last treatment regimen for multiple myeloma
4) Measurable disease defined by at least one of the following 3 measurements
   - Serum M-protein: ≥ 1 g/dL (≥ 10 g/L)
   - Urine M-protein: ≥ 200 mg/24 hours
   - Serum free light chain (FLC) assay: involved FLC level ≥ 10 mg/dL (≥ 100 mg/L), provided that the serum FLC ratio is abnormal.
5) Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2

Demographic

6) Patients 20 years or older at giving their informed consent
7) Patients must be able to stay in the hospital for Cycle 1 treatment

Laboratory values

Patients must meet the following laboratory criteria at screening. Patients must not receive granulocyte colony stimulating factor (G-CSF) or blood transfusion within 7 days before the test of neutrophil and platelet counts:

8) Absolute neutrophil count (ANC): ≥ 1,000/mm^3
9) Platelet count: ≥ 75,000/mm^3

10) Total bilirubin: ≤1.5 × the upper limit of normal range (ULN)
11) Alanine aminotransferase (ALT) and aspartate aminotransferase (AST): ≤ 3 × ULN
12) Creatinine clearance: calculated by using Cockcroft-Gault formula (Appendix F)
    MLN9708 monotherapy cohort: ≥ 30 mL/min
    MLN9708 with Rd cohort: ≥ 60 mL/min

General

13) Patients recovered (≤ Grade 1) from the toxicities of the prior treatments.
    ANC ≥ 1,000/mm^3.
14) Life expectancy of at least 3 months, in the judgment of the investigator
15) Patients conforming to proper management guidelines of lenalidomide (MLN9708 with Rd cohort only)

Exclusion Criteria:

Patients meeting ANY of the following exclusion criteria cannot be enrolled in the study.

Disease related

1) Patients with plasmacytoma only
2) Patients with plasma cell leukemia
3) Patients with central nervous system invasion

Medications

4) Radiotherapy within 14 days before enrollment.
5) Other anti-tumor drug administration within 21 days before enrollment.
6) Other investigational products administration within 21 days before enrollment (60 days from the last dose for carfilzomib).
7) Antibody treatment within 42 days before enrollment.
8) Systemic treatment with potent CYP1A2 inhibitors (fluvoxamine, enoxacin), potent CYP3A inhibitors (clarithromycin, telithromycin, itraconazole, voriconazole, ketoconazole), or potent CYP3A inducers (rifampin, rifabutin, carbamazepine, phenytoin, phenobarbital), or use of foods containing Ginkgo biloba extract, St. John's Wort, or grapefruit within 14 days before enrollment.
9) Treatment with corticosteroids greater than 10 mg of prednisolone per day. Inhaled and topical steroids are permitted.

Other medical conditions

10) Peripheral neuropathy ≥ Grade 2.
11) Diarrhea ≥ Grade 2.
12) Major surgery requiring general anesthesia within 14 days before enrollment.
13) Infection requiring systemic antibiotic treatment or other serious infections within 14 days before enrollment.
14) Evidence of concurrent uncontrolled cardiovascular conditions including hypertension, cardiac arrhythmias, New York Heart Association (NYHA) Class III or worse congestive heart failure, angina, myocardial infarction, or cerebral infarction within 6 months before enrollment.

15) Corrected QT interval (QTc) > 470 milliseconds on a 12-lead ECG obtained during the screening period.
16) Tested positive for human immunodeficiency virus (HIV) antibody, hepatitis B virus surface antigen (HBs antigen), or hepatitis C virus (HCV) antibody during the screening period.
17) Hypersensitivity to MLN9708 (including excipients), boron, or boron-containing drugs.
18) Hypersensitivity to lenalidomide, or dexamethasone, or excipients contained in the formulation of each drug (MLN9708 with Rd cohort only).
19) Known gastrointestinal diseases (difficulty swallowing, inflamed gastroenteritis, and Crohn disease), or gastrointestinal procedure (endoscopic procedure is permitted), that could interfere with the oral absorption or tolerance of the study treatment.
20) Uncontrolled diabetes mellitus.
21) A history of interstitial lung disease or lung fibrosis, or a current complication of interstitial lung disease or lung fibrosis diagnosed by diagnostic chest imaging.
22) Prior or current complications of deep vein thrombosis or pulmonary embolism (MLN9708 with Rd cohort only).
23) Diagnosed or treated for another malignancy within 2 years before the first dose or previously diagnosed with another malignancy and have any evidence of residual disease. Patients with nonmelanoma skin cancer or carcinoma in situ of any type are not excluded if they have complete resection.

General

24) Patients who do not consent to use adequate contraceptive precautions (e.g. condoms and oral contraceptives) during the following term:
    - For women with childbearing potential*, from when giving their consent through 3 months after the last dose of MLN9708, dexamethasone, or lenalidomide
    - For men having their partners with childbearing potential, from giving their consent through 4 months after last dose of MLN9708, dexamethasone, or lenalidomide

    * Women with child-bearing potential are those who are premenopausal (menopause is defined as the time when there has been no menstrual periods for at least 1 year), or who have not had a bilateral tube ligation, bilateral oophorectomy, or hysterectomy. The menstruation is possibly interrupted by chemotherapy not defined as menopause.)
25) Pregnant (e.g. positive for pregnancy test) or lactating. Lactation is prohibited from the first dose through 6 months after the last dose of MLN9708, dexamethasone, and lenalidomide.
26) Use of an investigational medical device within 28 days before enrollment.
27) Any inabilities that could potentially interfere with the consent or completion of treatment according to this protocol.
28) Having difficulties in participation to this study by the investigator's judgment

Investigational Product Dosage and Administration:

One capsule of MLN9708 will be orally administered once weekly for 3 weeks (Days 1, 8, and 15, and skip Day 22) in a 28-day cycle for up to 12 cycles.

- Cohort 1: 4.0 mg of MLN9708

• Cohort 2: 4.0 mg of MLN9708 plus Rd • Cohort 3: 5.5 mg of MLN9708 • Cohort 4: 5.5 mg of MLN9708 plus Rd One capsule contains 4.0 or 5.5 mg of active boronic acid form of MLN9708 (MLN2238)
Statistical Considerations: Demographic data and all endpoints data will be analyzed. Summary statistics (number of subjects, mean, median, standard deviation, maximum, and minimum) will be calculated for the continuous data. Frequency and percentage will be calculated for the categorical data. The incidence and percentage of treatment-emergent adverse events will be summarized by system organ class (SOC) and preferred term (PT) of the ICH Medical Dictionary for Regulatory Activities (MedDRA) and by grade. In addition, the following adverse events will be summarized with the same method. • Serious adverse events • Adverse events leading to permanent discontinuation of study treatment • Treatment-related adverse events • Treatment-related serious adverse events • Treatment-related adverse events leading to permanent discontinuation of study treatment DLT will be summarized in DLT analysis set.
Sponsor: Takeda Pharmaceutical Company Limited

Study Design and Treatment Schema

Screening Period

Subject Enrollment

Treatment Period

The sponsor will decide whether the next cohort will be studied and the dose of the next cohort in consultation with Efficacy and Safety Evaluation committee, if necessary, after 28 days (until observation of Day 29 of treatment period) have past since the first dose.

Cohort 1: MLN9708 4.0 mg				
Study Day	Cycle 1*			
	Day 1	Day 8	Day 15	Day 22
MLN9708	X	X	X	-

* Repeat the same administration schedule for Cycle 2 and after

Tolerable
Move up to next cohort

Cohort 2: MLN9708 4.0 mg + Rd				
Study Day	Cycle 1*			
	Day 1	Day 8	Day 15	Day 22
MLN9708	X	X	X	-
Lenalidomide	Day 1 - 21			
Dexamethasone	X	X	X	X

Tolerable
Move up to next cohort

Cohort 3: MLN9708 5.5 mg				
Study Day	Cycle 1*			
	Day 1	Day 8	Day 15	Day 22
MLN9708	X	X	X	-

Tolerable
Move up to next cohort

Cohort 4: MLN9708 5.5 mg + Rd				
Study Day	Cycle 1*			
	Day 1	Day 8	Day 15	Day 22
MLN9708	X	X	X	-
Lenalidomide	Day 1 - 21			
Dexamethasone	X	X	X	X

End of Study Visit (29 days after the last dose)

Study Glossary

Abbreviation	Definition/Explanation
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AUC	area under the concentration versus time curve
BCRP	breast cancer resistance protein
CL_b	blood clearance
CL_p	plasma clearance
C_{max}	maximum plasma concentration
CR	complete response
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DLT	dose-limiting toxicity
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EOS	end of study
ESEC	the Efficacy and Safety Evaluation Committee
FLC	free light chain
GCP	Good Clinical Practice
G-CSF	granulocyte colony stimulating factor
GLP	Good Laboratory Practice
HbA1c	hemoglobin A1c
HBV	hepatitis B virus
HCV	hepatitis C virus
hERG	human ether à-go-go-related gene
HIV	human immunodeficiency virus
IC_{50}	half-maximal inhibitory concentration
ICH	International Conference on Harmonisation
IRB	institutional review board
IV	intravenous(ly)
J-GCP	Ministerial Ordinance Concerning the Standards for the Conduct of Clinical Trials of Medicinal Products including the relevant notifications
LDH	lactate dehydrogenase

1/3

Abbreviation	Definition/Explanation
MedDRA	Medical Dictionary for Regulatory Activities
MHLW	Ministry of Health, Labour and Welfare
MPI	Millennium Pharmaceuticals, Inc
MRI	magnetic resonance imaging
MRP2	multidrug resistance protein 2
MTD	maximum tolerated dose
NCCN	National Comprehensive Cancer Network
NYHA	New York Heart Association
PD	progressive disease
P-gp	para-glycoprotein
PO	by mouth, orally
PR	partial response
PT	preferred term
QTc	corrected QT interval
RBC	red blood cell
Rd	lenalidomide and dexamethasone
RevMate®	the lenalidomide proper management procedures
sCR	stringent complete response
SD	stable disease
SCID	severe combined immunodeficient
SOC	system organ class
SpO2	transcutaneous oxygen saturation
$t_{1/2}$	elimination half-life
T_{max}	time to first maximum plasma concentration
ULN	upper limit of normal range
VGPR	very good partial response
VRd	bortezomib, lenalidomide and low-dose dexamethasone
V_{ss}	volume of distribution at steady-state
$V_{ss,b}$	blood volume of distribution at steady-state
$V_{ss,p}$	plasma volume of distribution at steady-state

2/3

Term	Definition/Explanation
For overall study	
Study Initiation	The start of the study for the first subject
End of Study	The end of the study for the last subject
For each subject	
Study Initiation	The start of screening
End of study	The date of the last safety follow-up visit, or withdrawal of consent, or death
Start of Screening	The date a subject signs the informed consent
Study Day 1	The first day of the study-specific treatment
Enrollment	The date on Enrollment Confirmation Form
Screening failure	Subjects not enrolled into the study after signing of the informed consent
Baseline values	Values obtained on Study Day 1 prior to the first study-specified treatment. When no variables/evaluations are scheduled on Study Day 1, the values obtained during screening period immediately before Study Day 1 are used as baseline values.
MLN2238	Active boronic acid form of MLN9708

3/3

Table of Contents

Page

PROTOCOL SUMMARY 3

Study Design and Treatment Schema 8

Study Glossary 9

1. BACKGROUND AND RATIONALE 16
   - 1.1 Multiple myeloma 16
   - 1.2 MLN9708 17
   - 1.3 Nonclinical Studies 17
     - 1.3.1 Pharmacology 18
     - 1.3.2 Pharmacokinetics 18
     - 1.3.3 Safety Pharmacology 20
     - 1.3.4 Toxicology Study 21
   - 1.4 Clinical Experience 21
     - 1.4.1 Clinical Studies in Relapsed or Refractory Multiple Myeloma 22
     - 1.4.2 Clinical Studies in Patients With Newly Diagnosed Multiple Myeloma 25
     - 1.4.3 Clinical Trials in Other Tumor Types 26
     - 1.4.4 Nonclinical Pharmacology Studies 27
   - 1.5 Known and Anticipated Risks and Benefits of MLN9708 27
     - 1.5.1 Known and Anticipated Risks 27
     - 1.5.2 Anticipated benefits 30
   - 1.6 Concomitant medications 30
     - 1.6.1 Lenalidomide 31
     - 1.6.2 Dexamethasone 31
   - 1.7 Study plan rationale 31
     - 1.7.1 Rationale for starting to plan this study 31
     - 1.7.2 Rationale for using a fixed dose 32
     - 1.7.3 Rationale for including an MLN9708 + Rd cohort 33
     - 1.7.4 Rationale for the initial doses and cohorts 33
     - 1.7.5 Rationale for once-weekly dosing 34

2. OBJECTIVES 35
   - 2.1 Primary Objective 35
   - 2.2 Secondary Objective(s) 35

3. EXPERIMENTAL PLAN 36
3.1 Study Design 36
3.2 Study Centers 37
3.3 Number of Subjects 37
3.4 Estimated Study Duration 37
3.4.1 Study Duration for Participants 37
3.5 Study Committees 38
3.5.1 ESEC 38

4. SUBJECT ELIGIBILITY 39
4.1 Inclusion Criteria 39
4.2 Exclusion Criteria 40

5. SUBJECT ENROLLMENT 43
5.1 Enrollment Procedures 44
5.2 RevMate® Registration 44

6. TREATMENT PROCEDURES 46
6.1 MLN9708 46
6.2 Concomitant medications 46
6.2.1 Lenalidomide (CCI [redacted] 5 mg) 46
6.2.2 Dexamethasone (CCI [redacted] 4 mg) 47
6.3 Dosage, administration method, dosing schedule 47
6.3.1 MLN9708 administration 47
6.3.2 Lenalidomide Administration (Rd Concomitant Cohort Only) 47
6.3.3 Dexamethasone Administration (Rd Concomitant Cohort Only) 48
6.4 Criteria for Beginning the Next Cycle of Treatment 48
6.4.1 MLN9708 Monotherapy 48
6.4.2 MLN9708 in Combination With Rd 49
6.4.3 Criteria for Dose Delays 49
6.5 Dose Modification 50
6.5.1 MLN9708 Monotherapy 50
6.5.2 MLN9708 in combination with Rd 51
6.6 Cohort Transition and Early Stopping Guidelines 58
6.6.1 Cohort Transition 58
6.6.2 Early Stopping Guidelines 60
6.7 DLT 60
6.7.1 DLT Assessment Period 60
6.7.2 DLT-Evaluable Subjects 60

6.7.3 Definitions of DLT 60
6.8 Permitted Concomitant Medications and Procedures 61
6.9 Excluded Concomitant Medications and Procedures 61

7. STUDY PROCEDURES 63
7.1 Subject Screening 63
7.2 Examinations, observations, and evaluations 63
7.2.1 Screening period 63
7.2.2 Treatment period 65
7.2.3 End of study 68
7.2.4 Laboratory tests 70
7.2.5 Volume of blood collected 71
7.2.6 Pharmacokinetic sample collection time points 71
7.2.7 Assessment of antitumor activity 72

8. REMOVAL AND REPLACEMENT OF SUBJECTS 73
8.1 Removal of Subjects 73
8.2 Replacement of Subjects 74

9. SAFETY DATA COLLECTION, RECORDING, AND REPORTING 75
9.1 Definitions 75
9.1.1 Adverse Events 75
9.1.2 Serious Adverse Events 75
9.2 All Adverse Events Reporting Procedures 76
9.3 Serious Adverse Event Reporting Procedures 77

10. STATISTICAL CONSIDERATIONS 79
10.1 Endpoints and Analysis Set 79
10.1.1 Primary Endpoint 79
10.1.2 Secondary Endpoints 79
10.1.3 Analysis Set 79
10.2 Sample Size Considerations 79
10.3 Interim Analysis and Early Stopping Guidelines 80
10.4 Statistical Methods of Analysis 80
10.4.1 Safety endpoints 80
10.4.2 Efficacy endpoints 81
10.4.3 Pharmacokinetic analysis 81

11. REGULATORY OBLIGATIONS 82
11.1 Quality Control of Data and Quality Assurance 82
11.2 Informed Consent 82
11.3 Institutional Review Board 83

11.4 Subject Confidentiality 83
11.5 Dissemination of New Information 84

12. ADMINISTRATIVE AND LEGAL OBLIGATIONS 85
12.1 Protocol Amendments and Study Termination 85
12.2 Source Data and Essential Documents 85
12.3 Data Handling and Retention of Records 86
12.3.1 Data Handling 86
12.3.2 Retention of Records 86
12.4 Language 87
12.5 Publication Policy 87
12.6 Compensation 88
12.7 Financing 88

13. REFERENCES 89

CCI [redacted] 91

CCI [redacted] 92
CCI [redacted] 95
CCI [redacted] 96
CCI [redacted] 97
CCI [redacted] 98
CCI [redacted] 99
CCI [redacted] 100
CCI [redacted] CCI [redacted] 102

1. BACKGROUND AND RATIONALE

1.1 Multiple myeloma

Multiple myeloma is a disease in which the plasma cells proliferate monoclonally in the bone marrow and become malignant (myeloma cells). Multiple myeloma gets its name because the myeloma cells infiltrate the bone marrow and form tumors in multiple locations. Humoral factors such as cytokines that are produced by the interaction of the bone marrow interstitial cells with the myeloma cells and monoclonal immunoglobulin (M-protein), which is produced by the myeloma cells, result in complications such as bone marrow failure, bone destruction, hypercalcemia, and renal failure. Multiple myeloma frequently occurs in the elderly. In the US, it is the second-leading hematologic malignancy: approximately 5 to 7 new cases of multiple myeloma are diagnosed per 100,000 people each year (this works out to approximately 20,000 people total), and 11,000 people die of malignant myeloma each year (accounting for about 2% of all cancer deaths). The situation is similar in Europe (Jemal et al, 2005; NCCN Guidelines, Version 1, 2012). In Japan, approximately 2 to 3 new cases of multiple myeloma are diagnosed per 100,000 people each year, and the total number of patients with multiple myeloma is estimated to be 13,000 (MHLW 2008 Patient Survey). In 2009, the number of deaths due to multiple myeloma was 4,084 in all (2,089 males and 1,995 females), meaning that multiple myeloma accounted for 1.2% of all cancer deaths (National Cancer Center, Center for Cancer Control and Information Services, Cancer Statistics in Japan 2010). In Japan, multiple myeloma is treated in virtually the same way as in the US and Europe. In the US and Europe, diagnosis and treatment guidelines have been promulgated by the NCCN, the British Committee for Standards in Haematology, and the UK Myeloma Forum. The NCCN Guidelines (Version 1, 2012) recommend a treatment regimen that includes bortezomib or an immunomodulator (thalidomide or lenalidomide) in the frontline setting. Patients deemed eligible for autologous stem cell transplants (ASCT) subsequently receive ASCT with high-dose chemotherapy. Bortezomib, thalidomide, lenalidomide, and other antitumor agent combination therapies are listed as salvage therapies. In Japan, the Japanese Society of Myeloma Guidelines (Version 2) issued in 2008, and these guidelines recommend almost the same treatments as those recommended in the US and Europe.

Although treatments involving thalidomide, bortezomib, lenalidomide, and ASCT with high-dose chemotherapy have yielded better results – the 5-year survival was 25% in 1975, but rose to 34% in the period from 1999 to 2005 (NCCN Guidelines, Version 1, 2012). However, most patients, both in Japan and in other countries, experience re-exacerbation during treatment. Salvage therapies are only effective in the short term; in the end, the patients stop responding to treatment. New and better drugs are therefore needed.

1.2 MLN9708

MLN9708 is an inhibitor of the 20S proteasome currently under development by Millennium Pharmaceuticals, Inc (MPI) in the United States. Inhibition of the 20S proteasome has been validated as a therapeutic target for the treatment of malignancies by the efficacy of the first-in-class proteasome inhibitor, bortezomib (Velcade®) in multiple myeloma and other hematologic malignancies. MPI has been developing MLN9708 for the better efficacy, safety, and convenience of bortezomib.

MLN9708 is the citrate ester of the biologically active dipeptide boronic acid, MLN2238. In aqueous solution or in blood, MLN9708 rapidly hydrolyzes to MLN2238, the active form that selectively and reversibly inhibits the proteasome. Similar to bortezomib, MLN2238 binds the β5 subunit of the 20S proteasome; however, it has a shorter dissociation half-life than bortezomib which contributes to wide distribution to tissues, and expected to demonstrate stronger antitumor activity. Nonclinical study showed greater antitumor activity against various xenograft models compared to bortezomib.

MLN9708 has been formulated for both intravenous (IV) and oral (PO) administration, and oral formulation is used for development for multiple myeloma.

1.3 Nonclinical Studies

MLN9708 is primarily examined as MLN2238 in the nonclinical studies since MLN9708 rapidly hydrolyzes to the active form, MLN2238 after dosing.

1.3.1 Pharmacology

There are several features of MLN2238, such as sustained pharmacodynamics effects and activity in bortezomib-refractory lymphoma xenograft models, that suggest it may have activity that extends beyond that seen with bortezomib.

1.3.1.1 In Vitro Pharmacology

MLN2238 inhibits β5 site 20S proteasome activity in vitro, with a concentration producing 50% inhibition (IC_{50}) of 3.4 nmol/L Potency is reduced roughly 10-fold versus β1 (IC_{50}= 31 nmol/L) and 1,000-fold versus β2 (IC_{50} = 3,500 nmol/L). MLN2238 was also tested for inhibition against a panel of 103 kinases, 18 receptors (neurotransmitter, ion channel, brain and gut receptors), and 9 serine proteases. In all cases, the IC_{50} values were ≥ 10 μmol/L. Furthermore, MLN2238 demonstrated potent cell growth inhibition activity against MDA-MB-231 human breast cancer cells.

1.3.1.2 In Vivo Pharmacology

To determine the activity of MLN2238 in vivo, pharmacodynamics studies were performed in immunocompromised mice bearing either CWR22 human prostate or WSU-DLCL2 (human diffuse large B-cell lymphoma) tumors. In CRW22 xenografts, there was a clear dose response seen in both tumor 20S proteasome inhibition and in changes in the protein markers of proteasome inhibition (GADD34 and ATF-3). In WSU-DLCL2 xenografts, increased expression of protein markers of proteasome inhibition was resulted with MLN2238, and observed greater tumor proteasome inhibition compared to bortezomib. MLN2238 demonstrated stronger antitumor activity in 3 human lymphoma xenograft models including WSU-DLCL (as compared to bortezomib). In the case of the CWR22 xenograft model, significant antitumor activity was seen with both IV and PO dosing.

1.3.2 Pharmacokinetics

The pharmacokinetic properties of MLN2238, the active form of MLN9708, were studied in severe combined immunodeficient (SCID) mice bearing human CWR22 tumor xenografts, Sprague-Dawley rats, beagle dogs, and cynomolgus monkeys. Because of the

extensive red blood cell (RBC) partitioning of MLN2238, both blood and plasma pharmacokinetic parameters were determined in these studies. MLN2238 had a very low blood clearance (CL_b) and a moderate blood volume of distribution at steady-state ($V_{ss,b}$) after IV administration. The concentration-versus-time curve of MLN2238 displayed a distinct biexponential profile with a steep initial distribution phase and a long terminal elimination half-life ($t_{1/2}$) (>24 hours) in all species tested. MLN2238 had higher plasma clearance (CL_p) and a larger plasma V_{ss} ($V_{ss,p}$) than in CL_b and $V_{ss,b}$, largely because of the extensive RBC partitioning.

The pharmacokinetic properties of MLN2238 after oral administration were studied in rats and dogs. The plasma oral bioavailability was 41% in rats and nearly 100% in dogs. A clinical prototype formulation of the MLN9708 capsule demonstrated that MLN2238 had excellent oral bioavailability and an excellent absorption profile in dogs. In addition, interindividual variability (coefficient of variation) in maximum plasma concentration (C_{max}) and area under the concentration versus time curve from 0 to 24 hours ($AUC_{0\text{-}24hr}$) after PO administration was low to moderate, similar to that after IV administration. The terminal $t_{1/2}$ after oral administration was also similar to that after IV administration.

Metabolism appears to be a major route of elimination for MLN2238 and urinary excretion of the parent drug was negligible (< 5% of dose). In vitro study demonstrated that MLN2238 was metabolized by multiple cytochrome P450 (CYP) isozymes and non-CYP enzymes and proteins. The rank order of relative biotransformation activity of each of the 5 major human CYP isozymes was 3A4 (34.2%) >1A2 (30.7%) >2D6 (14.7%) >2C9 (12.1%) >2C19 (negligible). All metabolites found in human liver microsome studies were also found in rat and dog liver microsomal studies, supporting the use of rats and dogs as appropriate species for toxicology studies. MLN2238 is neither an inhibitor of CYP isozymes 1A2, 2C9, 2C19, 2D6, and 3A4 (IC_{50} >30 µM, with an estimated inhibition dissociation constant [K_i] >15 µmol/L), nor a time-dependent inhibitor of CYP3A4/5 (up to 30 µmol/L). The potential for MLN9708 treatment to produce DDIs via CYP inhibition is inferred to be low. However, there may be a potential for DDIs with a concomitant strong CYP3A4 or CYP1A2 inhibitor or a strong CYP3A4 inducer because of the possible contribution of CYP3A4- and CYP1A2-mediated metabolism to the elimination of MLN9708 in humans.

MLN2238 may be a low-affinity substrate of para-glycoprotein (P-gp), breast cancer resistance protein (BCRP), and multidrug resistance protein 2 (MRP2). MLN2238 however is not an inhibitor of P-gp, BCRP, and MRP2 transporters (IC_{50} > 100 µmol/L). Consequently, the potential for MLN2238 to cause DDIs with substrates or inhibitors of P-gp, BCRP, and MRP2 is low.

1.3.3 Safety Pharmacology

In exploratory safety pharmacology studies, MLN2238 was a weak inhibitor of the cloned cardiac potassium (K^+) human ether à-go-go-related gene (hERG) channel, with an IC_{50} of 59.6 µM, which exceeds, by approximately 200-fold, the plasma C_{max} (111 ng/mL [0.3 µM]) predicted to occur in humans at the optimally efficacious dose after IV administration.

In the Good Laboratory Practice (GLP) compliant, 1-cycle, repeat-dose, PO toxicology study in beagle dogs, an increase in corrected QT interval (QTc) was seen in male dogs at nontolerated doses, and a potential increase in QTc was seen in male dogs at tolerated doses. However, increased QTc was not seen in female dogs at any dose, despite the fact that female dogs had plasma C_{max} values similar to those of male dogs. Additionally, in a GLP-compliant, 2-cycle, repeat-dose, IV toxicology study in beagle dogs, no increase in QTc was seen in either male or female dogs at any dose, even though dogs in the IV study had higher plasma MLN2238 concentration values than did the male dogs in the PO study. These data suggest that MLN2238 has a low potential for prolonging the QT interval in vivo. In the GLP-compliant, repeat-dose toxicology studies in beagle dogs, no effects on clinical signs or physical examination findings indicative of impaired respiratory or CNS function were noted at tolerated doses (≤ 0.14 mg/kg) after IV or PO administration. Detailed neurologic examinations MLN2238-related changes in neurologic parameters, primarily observed as changes in mental status (very low arousal) and changes in gait (ataxia) were observed at nontolerated doses (≥ 0.18 mg/kg). Similar findings were not observed at tolerated doses with any consistency.

1.3.4 Toxicology Study

1.3.4.1 In Vitro Toxicology

MLN2238 was not mutagenic in a GLP-compliant bacterial reverse mutation assay (Ames assay).

1.3.4.2 In Vivo Toxicology

After repeated IV and PO administration of MLN2238, the exposures that were tolerated in rats were similar to those tolerated in dogs, indicating similar species sensitivity. The target tissues for dogs and rats were similar and consisted of the bone marrow, peripheral ganglia, and intestines. Higher exposures were achieved in the IV study compared to the PO study, and it is likely that the differences seen in peripheral white blood cell counts and bone marrow hypocellularity between the 2 studies reflected differences in exposure and not differences in toxicologic response after PO versus IV administration. Similarly, the lower exposures achieved after PO versus IV administration likely account for the lack of peripheral nervous system effects seen in the PO study. The toxicologic effects seen in rats (bone marrow hypocellularity with corresponding thrombocytopenia and neutropenia, degeneration of peripheral ganglia with secondary degeneration of peripheral nerves and spinal cord dorsal column, intestinal mucosal hyperplasia, and hepatocellular hypertrophy and vacuolization) are qualitatively similar to what was observed previously in rodents treated with bortezomib.

See MLN9708 Investigator's Brochure for more detail.

1.4 Clinical Experience

No clinical studies evaluating MLN9708 have been conducted in Japan to date. Safety, tolerability, pharmacokinetics, and disease response are assessed in 7 phase 1 or phase 1/2 studies (Table 1-1). IV and PO administration are being evaluated with a weekly and a twice-weekly dosing schedule. MLN9708 is given on Days 1, 8, and 15 of a 28-day cycle in the once weekly dosing schedule, and the drug is given on Days 1, 4, 8, and 11 of a 21-day cycle in the twice-weekly dosing schedule. As of 12 October 2011, preliminary data have been obtained from 247 subjects enrolled across 7 ongoing studies.

Table 1-1. Summary of Overseas Studies

Phase 1 Study	
Study C16001	IV, single agent, twice weekly, solid tumors
Study C16002	IV, single agent, weekly, lymphoma
Study C16003	PO, single agent, twice weekly, relapsed or refractory multiple myeloma
Study C16004	PO, single agent, weekly, relapsed or refractory multiple myeloma
Study C16007	PO, single agent, weekly, relapsed or refractory light-chain amyloidosis
Phase 1/2 Study	
Study C16005	PO, combination with Rd[a], weekly, newly diagnosed multiple myeloma
Study C16006	PO, combination with melphalan and prednisolone, weekly and twice weekly, newly diagnosed multiple myeloma

[a] Lenalidomide, 25 mg once daily for 21 consecutive days; dexamethasone, 40 mg once weekly

In addition to these ongoing studies, phase 1/2 study (Study C16008) in newly diagnosed multiple myeloma patients and global phase 3 study (Study C16010) in relapsed or refractory multiple myeloma patients are currently planned.

Table 1-2. Summary of Planned Overseas Clinical Studies

Phase 1/2 Study	
Study C16008	PO, combination with Rd, twice weekly, newly diagnosed multiple myeloma
Phase 3 Study	
Study C16010	PO, combination with Rd, weekly, relapsed or refractory multiple myeloma

1.4.1 Clinical Studies in Relapsed or Refractory Multiple Myeloma

Two ongoing clinical trials, Studies C16003 and C16004, investigate single-agent MLN9708 in patients with relapsed or refractory multiple myeloma.

In Study C16003 (0.24, 0.48, 0.80, 1.20, 1.68, 2.23 mg/m^2; twice-weekly), 56 patients were enrolled as of 12 October 2011 and received treatment for 1 to 28 cycles (median, 3.5 cycles). One patient achieved complete response, 5 patients achieved a partial response, and 29 patients achieved minor response.

In Study C16003, 1 of 3 patients experienced a protocol-defined DLT (Grade 3 rash) at a dose of 2.23 mg/m^2, and an additional patient at this dose experienced Grade 4 thrombocytopenia at DLT. The intermediate dose of 2.0 mg/m^2 was set as a new dose

group approximately half way between the 2 existing dose levels of 2.23 mg/m^2 and 1.68 mg/m^2. Given that none of the 6 patients treated at the 2.0 mg/m^2 group experienced a DLT, the maximum tolerated dose (MTD) of MLN9708 administered twice weekly was determined to be 2.0 mg/m^2.

Overall, 98% of patients experienced a treatment-emergent adverse event. Peripheral neuropathy was limited to Grade 1 or 2 in 10% of patients; with all of these patients reporting baseline Grade 1 peripheral neuropathy at study entry. The most common (≥ 20%) treatment-emergent adverse events are shown in Table 1-3.

Table 1-3. Most Common (≥ 20%) Treatment-Emergent Adverse Events (Study C16003, N=56)

	Treatment-Emergent Adverse Events
Most Common (≥ 20%) Any Grade	Fatigue (57%) Skin rash (all terms) (50%) Thrombocytopenia (41%) Diarrhea (36%) Nausea (34%) Vomiting and fever (30% each) Cough (25%) Anorexia (23%) Neutropenia (21%)
Drug-Related Grade ≥3 in ≥ 2 Patients	Thrombocytopenia (n = 19) Neutropenia (n = 8) Fatigue (n = 5) Rash (all terms) (n = 5)

Data cutoff 12 October 2011

Fifteen patients have experienced drug-related serious adverse events involving thrombocytopenia, anemia, neutropenia, febrile neutropenia, nausea, vomiting, abdominal pain, chest pain (noncardiac), orthostatic hypotension, hypotension, hypophosphatemia, hyperuricemia, fever, chills, rash, pneumonia, hypoxia, pulmonary hypertension, fall, headache, fatigue, or dehydration. Five patients discontinued therapy due to a treatment-emergent adverse event; 3 patients due to events considered at least possibly related to MLN9708 (thrombocytopenia, pulmonary hypertension, and pruritic rash) and remaining 2 patients due to events related to disease progression (spinal cord

compression and bone pain). There have been 2 on study deaths reported as not related to MLN9708.

In Study C16004 (0.24, 0.48, 0.80, 1.20, 1.68, 2.23, 2.97, and 3.95 mg/m^2, weekly), 32 patients were enrolled as of 12 October 2011 and received treatment for 1 to 11 cycles (median, 2 cycles). One patient achieved a VGPR and one patient achieved a PR.

In Study C16004, 2 of 3 patients experienced protocol-defined DLT (Grade 3 rash, Grade 3 nausea, vomiting, and diarrhea) at a dose of 3.95 mg/m^2. Additional patients were enrolled and treated at 2.97 mg/m^2. One of 6 patients treated at 2.97 mg/m^2 experienced a DLT (Grade 3 nausea, vomiting, and diarrhea). The MTD of MLN9708 administered weekly was determined to be 2.97 mg/m^2.

Overall, 97% of patients experienced a treatment-emergent adverse event. Peripheral neuropathy was limited to Grade 1 or 2 in 3 patients; with all patients reporting baseline Grade 1 peripheral neuropathy at study entry. The most common (≥20%) treatment-emergent adverse events are shown in Table 1-4.

Table 1-4. Most Common (≥ 20%) Treatment-Emergent Adverse Events (Study C16004, N=32)

	Treatment-Emergent Adverse Events
Most Common (≥ 20%) Any Grade	Fatigue (50%) Thrombocytopenia (34%) Nausea (38%) Diarrhea (31%) Vomiting (28%)
Drug-Related Grade ≥ 3 in ≥ 2 Patients	Thrombocytopenia (n = 4; 1 Grade 4 and 3 Grade 3) Neutropenia and diarrhea (n = 3 each)

Data cutoff 12 October 2011

There have been 2 drug-related serious adverse events (diarrhea, dehydration, and dizziness). Six patients discontinued MLN9708 due to a treatment-emergent adverse event considered at least possibly related to MLN9708 (thrombocytopenia, rash, neutropenia, diarrhea, nausea, vomiting, and abdominal pain). There has been one on study death reported which was considered related to disease progression.

1.4.2 Clinical Studies in Patients With Newly Diagnosed Multiple Myeloma

Two ongoing clinical trials of Studies C16005 and C16006 in patients with newly diagnosed multiple myeloma are currently ongoing.

In Study C16005 where MLN9708 is administered weekly (1.68, 2.23, 2.97, and 3.95 mg/m^2) in combination with lenalidomide and dexamethasone (Rd), 15 patients have been enrolled as of 12 October 2011 and completed 1 to 9 treatment cycles (median, 5 cycles). No DLTs were seen at doses up to 2.23 mg/m^2. Three of 3 patients treated at the 3.95 mg/m^2 dose cohort experienced Grade 3 nausea and vomiting despite adequate antiemetic therapy; one of which additionally experienced Grade 2 syncope and in another patient the dose of lenalidomide was compromised such that they received < 80% of the planned doses. Subsequent patients were treated at one dose level below (2.97 mg/m^2) where one of 6 patients experienced a DLT (Grade 3 rash). The MTD of weekly MLN9708 in combination with Rd was established at 2.97mg/m^2. However with this dose, 3 of 6 patients experienced Grade 2 and 3 rash and had to discontinue lenalidomide. Therefore, the recommended dose was determined to be 2.23 mg/m^2 plus Rd in the phase 2 portion of the combination trial and phase 3 Rd combination trial.

To date, all 15 response-evaluable patients have achieved ≥ PR to therapy including 4 CRs, 4 VGPRs, and 7 PRs; 14 out of 15 patients achieved ≥ PR after Cycle 1, and all 15 achieved ≥ PR after Cycle 2.

Overall, all 15 patients experienced a treatment-emergent adverse event. Peripheral neuropathy was limited to Grade 1 or 2 in 3 patients. The most common (≥ 20%) treatment-emergent adverse events are shown in Table 1-5.

Table 1-5. Most Common (≥ 20%) Treatment-Emergent Adverse Events (Study C16005, N=15)

	Treatment-Emergent Adverse Events
Most Common (≥ 20%) Any Grade	Fatigue (60%) Vomiting (53%) Anemia (40%) Diarrhea and nausea (33% each) Insomnia, peripheral edema, and thrombocytopenia (27% each)
Drug-Related Grade ≥ 3 in ≥ 2 Patients	Rash and vomiting (n = 2 each)

Data cutoff 12 October 2011

No death has been reported in Study C16005. One patient discontinued MLN9708 due to an unrelated treatment-emergent adverse event. Four patients have experienced drug-related serious adverse event involving nausea, vomiting, dehydration, dizziness, fainting, orthostatic hypotension, hypotension, deep vein thrombosis, atrial fibrillation, and muscle weakness.

In Study C16006, MLN9708 is administered in weekly and twice-weekly schedules in combination with melphalan and prednisone, and 6 patients have been enrolled as of 12 October 2011. There has not been any serious adverse event, drug discontinuation due to treatment-emergent adverse event, or death reported to date.

1.4.3 Clinical Trials in Other Tumor Types

In Study C16001 conducted in patients with solid tumors, MLN9708 (IV, twice-weekly) is administered, and a total of 111 patients have been treated as of 12 October 2011. One partial response in a patient with head and neck cancer has been reported. MTD in Study C16001 was determined to be 1.76 mg/m^2. In Study C16002 conducted in patients with lymphoma, MLN9708 (IV, twice-weekly) is administered, and a total of 21 patients have been treated as of 12 October 2011. Three patients have achieved PR.

In Study C16007 conducted in patients with amyloidosis, MLN9708 (PO, weekly) is administered, and a total of 6 patients have been treated as of 12 October 2011. As of the data cut, 2 patients achieved VGPR and one patient achieved PR. Treatment-emergent adverse events occurring in at least 2 patients include diarrhea and peripheral edema

(3 patients each), anemia, fatigue, nausea, and thrombocytopenia (2 patients each). As of 12 October 2011, no subjects died or discontinued study treatment due to adverse events.

1.4.4 Nonclinical Pharmacology Studies

Pharmacokinetics of MLN2238 after IV weekly or twice-weekly MLN9708 dosing is multi-exponential with the rapid initial phase largely over by 4 hours followed by much slower disposition phases. The plasma MLN2238 concentration decreases by almost 90% in the initial phase of 4 hours. The mean $t_{1/2}$ after multiple IV dosing of MLN9708 ranges from 4 to 8 days. Plasma MLN2238 exposures appear to increase proportionally with increasing dose over the MLN9708 IV dose range of 0.5 to 2.34 mg/m^2. Oral MLN9708 is bioavailable and MLN2238 is rapidly absorbed with a T_{max} of 0.5 to 8 hours. The mean terminal half-life after multiple dosing of oral MLN9708 ranges from 4 to 7 days. MLN2238 exposures appear to increase proportionally with increasing dose over the oral MLN9708 dose range of 0.8 to 2.23 mg/m^2. Blood 20S proteasome inhibition is dose dependent and immediate confirming target inhibition by MLN9708. Maximal 20S inhibition is approximately 60% to 62% for 1.76 mg/m^2 twice-weekly IV dose and 60% to 72% for 2.23 mg/m^2 twice-weekly oral dose.

1.5 Known and Anticipated Risks and Benefits of MLN9708

1.5.1 Known and Anticipated Risks

Hematological Toxicities

Reversible thrombocytopenia, neutropenia, and anemia have been reported to date primarily at the higher doses tested. In addition to monitoring for recovery of blood counts, anemia, neutropenia, and thrombocytopenia induced by administration of MLN9708 should be managed in a similar manner to that used for myelosuppression resulting from standard cytotoxic chemotherapeutic agents. Administration of MLN9708 should be modified as noted in each specific protocol with reinitiation of therapy at a reduced level from where thrombocytopenia, neutropenia, or anemia was noted has been instituted in the clinical studies.

Gastrointestinal Toxicities

Reversible diarrhea, nausea, vomiting, anorexia, constipation, and abdominal pain have been reported. Patients should be monitored for gastrointestinal toxicity and should be given appropriate supportive care that includes fluids for volume depletion and antibiotics for any associated infection. Other supportive measures such as loperamide or other antidiarrheal agents may be considered for diarrhea only if it is established that there is no active infection or anti-emetics including 5-HT_3 antagonists are recommended.

Peripheral Neuropathy

Mild and reversible peripheral neuropathy has been reported. Therefore, patients on MLN9708 should be monitored for symptoms of neuropathy, such as a burning sensation, hyperesthesia, hypoesthesia, paresthesia, discomfort, neuropathic pain, or weakness. In cases of new or worsening sensory peripheral neuropathy, with or without pain, administration of MLN9708 should be modified as noted in each specific protocol. Reinitiation of therapy at a reduced level from where symptoms were noted may be considered.

Lymphopenia

Reversible lymphopenia has been reported primarily at the higher doses tested. Infrequent incidences of herpes zoster have been reported.

If lymphopenia is noted, patients may be at an increased risk of infection. In particular, lymphopenia can be associated with reactivation of herpes zoster and herpes simplex viruses. Initiation of antiviral therapy should be considered if infection occurs and prophylaxis therapy should then be initiated following the course of therapy for the infection and through the following courses of treatment with MLN9708.

Acute Phase Response

Acute phase response, characterized by increases in total WBC, neutrophils, monocytes, and fibrinogen, was observed in nonclinical studies. These can be monitored in the clinic by clinical chemistry and vital sign evaluations. Therefore, patients should be observed for fever and metabolic changes.

Fever

Cases of fever without neutropenia have been reported in the clinical studies; however, the relationship of onset of fever to MLN9708 is not yet completely established in humans. Patients may receive supportive care agents in response to fever that are associated with MLN9708.

Tumor Lysis Syndrome

Because MLN9708 is a cytotoxic agent and can rapidly kill malignant cells, patients with a high tumor burden prior to treatment should be monitored for the complications of tumor lysis syndrome with appropriate laboratory studies and supportive care.

Elevated Creatinine

Modest transient increases in creatinine and reversible renal failure have been reported. In some situations this has been severe, requiring temporary dialysis. Appropriate supportive care that includes IV fluids to prevent volume depletion according to standard medical practice is recommended. Non-steroidal anti-inflammatory drugs are not recommended given they may in and of themselves have an association to renal dysfunction.

Erythematous Rash With or Without Pruritis

Rash with or without pruritus has been reported with MLN9708 primarily at the higher doses tested. The rash has been transient and has resolved with standard symptomatic measures such as oral, topical, or IV anti-histamines or corticosteroids.

Cough, Dyspnea, Peripheral Edema, Pneumonia/Pneumonitis, and Headache

Cases of cough, dyspnea, peripheral edema, pneumonia/pneumonitis, and headache have been reported in the clinical studies; however, the relationship of onset to MLN9708 is not yet completely established in humans. Standard supportive care and additional monitoring should be performed as clinically indicated.

Fatigue

Cases of profound fatigue have been reported in the clinical trials. Standard supportive care are recommended.

For more detailed information regarding the risks associated with MLN9708, refer to the MLN9708 Investigator's Brochure.

MLN9708, like Velcade®, is a modified dipeptidyl boronic acid derived from leucine and phenylalanine. MLN9708 is in the early stages of investigation in humans; therefore, its safety profile in humans is not yet fully known. For more detailed information regarding the risks associated with Velcade®, refer to the Velcade® 3 mg (bortezomib) for Injection Package Insert.

1.5.2 Anticipated benefits

MLN9708 is a 20S proteasome inhibitor that has a mechanism of action similar to that of bortezomib, the clinical efficacy of which has been verified both in Japan and overseas. MLN9708 demonstrates antitumor activity superior to that of bortezomib in some tumor models, and has exhibited antitumor activity even in bortezomib-resistant models. It is therefore hoped that MLN9708 will be effective in previously treated patients. In overseas clinical studies of MLN9708, patients have achieved partial response on MLN9708 monotherapy. In addition, since patients have achieved complete response (CR), very good partial response (VGPR), and partial response (PR) in clinical studies of MLN9708 with Rd in patients with newly diagnosed multiple myeloma, MLN9708 is expected to exhibit antitumor activity in patients with newly diagnosed multiple myeloma as well. Furthermore, although most existing therapeutic medications for multiple myeloma are injectable formulations, oral formulation of MLN9708 may improve patient convenience.

1.6 Concomitant medications

In Japan, lenalidomide (CCI [redacted] 5 mg) has been approved for the treatment of relapsed or refractory multiple myeloma, and dexamethasone CCI [redacted] 4 mg) has been approved for the treatment of multiple myeloma. The Rd combination therapy is one treatment option for relapsed or refractory multiple myeloma.

1.6.1 Lenalidomide

Lenalidomide is an immunomodulator that was discovered by PPD in the US. It is a derivative of thalidomide, which is known to be teratogenic in man. Lenalidomide is known to manifest its antitumor activity through, for example, a cytokine production modulating action and an angiogenic tumor cell proliferation inhibiting action. Since the results of toxicity studies suggest that lenalidomide might be teratogenic, the lenalidomide proper management procedures (CCI [redacted]) for preventing fetuses from being exposed to lenalidomide should be observed.

In this study, subjects will be registered in accordance with the lenalidomide proper management procedures when supplying lenalidomide to subjects receiving MLN9708 plus Rd. The registration system for this study is described in "5.2 CCI [redacted] Registration"

1.6.2 Dexamethasone

Dexamethasone is a corticosteroid that, in addition to exhibiting anti-inflammatory and anti-allergy effects, also possesses various pharmacological effects, including inhibition of immune response and the metabolism of, for example, fats and sugars. Dexamethasone also acts to inhibit the proliferation of multiple myeloma cells by inducing apoptosis, and it is known that dexamethasone can increase the effects of immunomodulators or chemotherapy agents that kill myeloma cells.

1.7 Study plan rationale

1.7.1 Rationale for starting to plan this study

As described in "1.1 Multiple myeloma," the current treatments for relapsed or refractory multiple myeloma are all unsatisfactory. All are only effective in the short term, and ultimately result in treatment non-responsiveness. New, superior medications are therefore needed. In addition, most existing therapies are based on injectable formulations that require hospital visit and are therefore relatively inconvenient for patients. MLN9708 is a 20S proteasome inhibitor that possesses a mechanism of action similar to that of bortezomib, an existing therapeutic medication for multiple myeloma,

and that can be taken orally. In nonclinical studies, MLN9708 exhibited antitumor activity superior to that of bortezomib in some tumor models, and exhibited antitumor activity in bortezomib resistant models as well, and it is therefore hoped that MLN9708 will be effective in patients who have not responded to previous treatments. MLN9708 was well-tolerated in an overseas phase 1 study in patients with relapsed or refractory multiple myeloma. Responders, including complete responders, were found, and the results of this study therefore suggest that MLN9708 will be useful. Based on the results that have been obtained in overseas clinical studies, including this phase 1 study, a global phase 3 study of the concomitant use of MLN9708 with Rd in relapsed or refractory multiple myeloma (Study C16010) has been planned, and Japan is expected to participate in this study as well. Therefore, a phase 1 study has been planned as the first clinical study of MLN9708 in Japan to confirm the tolerability and safety of MLN9708 alone and MLN9708 in combination with Rd in relapsed or refractory multiple myeloma.

1.7.2 Rationale for using a fixed dose

The results of a population pharmacokinetic analysis in 137 subjects who received MLN9708 in overseas studies suggest that neither body surface area nor body weight appreciably affect MLN9708 clearance or distribution volume. It was concluded that body surface area does not affect the C_{max} or AUC, so changing to a fixed dose would be appropriate. In addition, since it has been decided that fixed doses will be used in future overseas clinical studies, we concluded that it would be appropriate to use a fixed dose in this Japanese phase 1 study as well. When converting the dose from a body surface area dose to a fixed dose, we used 1.86 m^2, which was the mean body surface area of the subjects who participated in overseas clinical studies of bortezomib in multiple myeloma that were conducted by MPI. Converting 2.97 mg/m^2, which was the MTD both in MLN9708 monotherapy and in the combined use of MLN9708 with Rd, was converted into a fixed dose, yielded a fixed dose of 5.5 mg, and converting 2.23 mg/m^2, which is the recommended dose of MLN9708 when used in combination with Rd, yielded a fixed dose of 4.0 mg.

1.7.3 Rationale for including an MLN9708 + Rd cohort

Since this study will be the first clinical study of MLN9708 in Japan, we decided to first investigate the tolerability, safety and pharmacokinetics of MLN9708 in monotherapy. However, in the treatment of relapsed or refractory multiple myeloma, proteasome inhibitors, immunomodulators and steroid combination therapies are commonly used. The combined use of bortezomib, lenalidomide and low-dose dexamethasone (VRd) therapy in multiple myeloma has been confirmed to be safe and effective (Anderson et al, 2010; Kumar et al, 2010; Richardson et al, 2010a; Richardson et al, 2010b). MLN9708, a new proteasome inhibitor, is expected to possess pharmacological efficacy and safety superior to that of bortezomib. In study C16005, a study of the combined use of MLN9708 with Rd, not only did 15 of 15 subjects achieve PR or better response, but good safety results were obtained in all subjects as well. Given this result, a global phase 3 study of the combined use of MLN9708 with Rd (study C16010) is currently being planned. Consequently, in this study, in addition to investigating MLN9708 monotherapy, we decided to also investigate MLN9708 when used in combination with Rd. For the dosages of Rd, we used the dosages used in overseas clinical studies in which the efficacy and safety of VRd therapy were confirmed. Comparison of the efficacy and safety of dexamethasone in 445 newly diagnosed multiple melanoma patients overseas between a group of 223 patients who received high-dose dexamethasone (40 mg/day on Days 1-4, 9-12, and 17-20) and a group of 222 patients who received low-dose dexamethasone (40 mg/day on Days 1, 8, 15, and 22) revealed that low-dose dexamethasone afforded a level of efficacy similar to that obtained with high-dose dexamethasone (Rajkumar et al, 2010). Weekly low-dose dexamethasone was therefore selected.

1.7.4 Rationale for the initial doses and cohorts

In study C16004, Grade 3 adverse events were reported in 2 of 6 subjects at the MTD of 2.97 mg/m^2 (equivalent to 5.5 mg), but Grade 3 or higher adverse events were not reported at the next lowest dose of 2.23 mg/m^2 (equivalent to 4.0 mg). Therefore, in this study, we decided to use 4.0 mg at the initial dose (cohort 1). For the MLN9708 + Rd cohort (cohort 2), we selected a dose of 4.0 mg + Rd, which was the recommended dose in the MLN9708 + Rd phase 3 study and the phase 2 part of study C16005, and was the next dose level below the MTD of 2.97 mg/m^2 (equivalent to 5.5 mg) in study C16005.

Furthermore, we have also established a monotherapy cohort that will receive 5.5 mg (cohort 3) and a MLN9708 + Rd cohort that will receive 5.5 mg + Rd (cohort 4) in order to confirm the tolerability in Japanese at the dose equivalent to the MTD overseas once the tolerability of 4.0 mg and 4.0 mg + Rd have been confirmed.

1.7.5 Rationale for once-weekly dosing

Based on the nonclinical and clinical study results, we selected a 28-day MLN9708 dosing cycle with weekly oral dosing on Days 1, 8, and 15 and no dose given on Day 22. In a mouse model, peak antitumor activity was obtained with weekly dosing, and the results of multiple-dose toxicity studies also support the case for weekly dosing. MLN9708 weekly dosing was confirmed to be tolerable in study C16004 in relapsed or refractory multiple myeloma.

Since the global phase 3 study that is currently being planned (study C16010) will also employ a similar dosing method, we have decided to confirm the tolerability of such a dosing method in this study.

2. OBJECTIVES

2.1 Primary Objective

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

2.2 Secondary Objective(s)

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

3. EXPERIMENTAL PLAN

3.1 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 a DLT occurs in one 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 in "6.4 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 in "8.1 Removal of Subjects" 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 "Study Design and Treatment Schema" (page 8).

3.2 Study Centers

The study is planned at 5 study centers.

3.3 Number of Subjects

Approximately 12 to 24 subjects (3 to 6 subjects in each cohort) will be enrolled in the study.

If any significant protocol deviation that affects DLT assessment is observed or a subject could not complete the protocol-specified MLN9708 treatment during the DLT-assessment period for reasons other than DLTs, the subject will be excluded from the DLT assessment, and additional subject(s) may be enrolled. Moreover, if there seems to be needs for additional data for safety or pharmacokinetics evaluation, the sponsor may decide to enroll additional subjects. See "10.2 Sample Size Considerations for the sample size justification.

3.4 Estimated Study Duration

The study will be conducted between March 2012 and March 2019.

3.4.1 Study Duration for Participants

Study duration for patients will last for up to approximately 14 months, including maximum of 4 weeks screening period, maximum 12 cycles of treatment period (approximately 12 months), and 4 weeks follow-up after the last dose. Subjects may remain on treatment after the 12 cycles if the investigator and the sponsor determine that the subjects would derive benefit from continued therapy beyond 12 months.

3.5 Study Committees

3.5.1 ESEC

An ESEC will be formed before starting the study and will be composed of 3 medical experts/oncologists who are not the investigators or the sponsor staff of this study.

The ESEC may evaluate the safety of MLN9708 and the appropriateness to continue this study upon the sponsor's request. Further details will be provided in the ESEC charter.

4. SUBJECT ELIGIBILITY

Investigators must ensure that subjects meet all the eligibility criteria (inclusion criteria/exclusion criteria).

4.1 Inclusion Criteria

Patients must give written consent to the participation and meet ALL of the following inclusion criteria to be eligible for the study.

[Disease Related]

1) Japanese patients with multiple myeloma according to diagnostic criteria shown in Appendix E[1]
2) Previously treated with 2 or more regimens including all the following drugs[1]
   - bortezomib
   - thalidomide or lenalidomide
   - corticosteroids
3) Patients who have relapsed following the previous therapy or failed to continue the treatment due to their intolerability to the last treatment regimen for myeloma[1]
4) Measurable disease defined by at least one of the following 3 measurements[1]
   - Serum M-protein: ≥ 1 g/dL (≥ 10 g/L)
   - Urine M-protein: ≥ 200 mg/24 hours
   - Serum free light chain (FLC) assay: involved FLC level ≥ 10 mg/dL (≥ 100 mg/L), provided that the serum FLC ratio is abnormal.
5) Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2[1,2]

[Demographic]

6) Patients 20 years or older at giving their informed consent[1]
7) Patients must be able to stay in the hospital for Cycle 1 treatment[2]

[Laboratory Values]

Patients must meet the following laboratory criteria at screening. Patients must not receive granulocyte colony stimulating factor (G-CSF) or blood transfusion within 7 days before the test of neutrophil and platelet counts:

8) Absolute neutrophil count (ANC): $\geq$ 1,000/mm^3[(2)]
9) Platelet count: $\geq$ 75,000/mm^3[(2)]
10) Total bilirubin: $\leq$ 1.5 × the upper limit of normal range (ULN)[(2)]
11) Alanine aminotransferase (ALT) and aspartate aminotransferase (AST): $\leq$ 3 × ULN[(2)]
12) Creatinine clearance: calculated by using Cockcroft-Gault formula (Appendix F)
    MLN9708 monotherapy cohort: $\geq$ 30 mL/min[(2)]
    MLN9708 with Rd cohort: $\geq$ 60 mL/min[(2)]

[General]

13) Patients recovered (Grade 1) from the toxicities of the prior treatments.[(2)] ANC $\geq$1,000/mm^3.
14) Life expectancy of at least 3 months, in the judgment of the investigator[(2)]
15) Patients conforming to proper management guidelines of lenalidomide[(2)] (MLN9708 with Rd cohort only).

<Basis for setting the criteria>

(1) To enroll subjects who represent the intended indication population.

(2) To minimize risks and ensure safety of subjects.

4.2 Exclusion Criteria

Patients meeting ANY of the following exclusion criteria cannot be enrolled in the study.

[Disease related]

1) Patients with plasmacytoma only[(2)]
2) Patients with plasma cell leukemia[(2)]
3) Patients with central nervous system invasion[(2)]

[Medications]

4) Radiotherapy within 14 days before enrollment[(2)]
5) Other anti-tumor drug administration within 21 days before enrollment[(2)]
6) Other investigational products administration within 21 days before enrollment (60 days from the last dose for carfilzomib)[(2)]
7) Antibody treatment within 42 days before enrollment[(2)]

8) Systemic treatment with potent CYP1A2 inhibitors (fluvoxamine, enoxacin), potent CYP3A inhibitors (clarithromycin, telithromycin, itraconazole, voriconazole, ketoconazole), or potent CYP3A inducers (rifampin, rifabutin, carbamazepine, phenytoin, phenobarbital), or use of foods containing Ginkgo biloba extract, St. John's Wort, or grapefruit within 14 days before enrollment(2)
9) Treatment with corticosteroids greater than 10 mg of prednisolone per day. Inhaled and topical steroids are permitted(2)

[Other Medical Conditions]

10) Peripheral neuropathy ≥ Grade 2(1)
11) Diarrhea ≥ Grade 2(1)
12) Major surgery requiring general anesthesia within 14 days before enrollment(1)
13) Infection requiring systemic antibiotic treatment or other serious infections within 14 days before enrollment(1)
14) Evidence of concurrent uncontrolled cardiovascular conditions including hypertension, cardiac arrhythmias, New York Heart Association (NYHA) Class III or worse congestive heart failure, angina, myocardial infarction, or cerebral infarction within 6 months before enrollment(1)
15) QTc > 470 milliseconds on a 12-lead ECG obtained during the screening period(1)
16) Tested positive for human immunodeficiency virus (HIV) antibody, hepatitis B virus surface antigen (HBs antigen), or hepatitis C virus (HCV) antibody during the screening period(1)
17) Hypersensitivity to MLN9708 (including excipients), boron, or boron-containing drugs (1)
18) Hypersensitivity to lenalidomide, or dexamethasone, or excipients contained in the formulation of each drug(1)(MLN9708 with Rd cohort only)
19) Known gastrointestinal diseases (difficulty swallowing, inflamed gastroenteritis, and Crohn disease), or gastrointestinal procedure (endoscopic procedure is permitted), that could interfere with the oral absorption or tolerance of the study treatment(2)
20) Uncontrolled diabetes mellitus(1)
21) A history of interstitial lung disease or lung fibrosis, or a current complication of interstitial lung disease or lung fibrosis diagnosed by chest imaging.(1)
22) Prior or current complications of deep vein thrombosis or pulmonary embolism(1) (MLN9708 with Rd cohort only)
23) Diagnosed or treated for another malignancy within 2 years before the first dose of MLN9708 or previously diagnosed with another malignancy and have any evidence of residual disease. Patients with nonmelanoma skin cancer or carcinoma in situ of any type are not excluded if they have complete resection(1)

[General]

24) Patients who do not consent to use adequate contraceptive precautions (e.g. condoms and oral contraceptives) during the following term:(3)
    - For women with childbearing potential*, from when giving their consent through 3 months after the last dose of MLN9708, dexamethasone, or lenalidomide
    - For men having their partners with childbearing potential, from when giving their consent through 4 months after the last dose of MLN9708, dexamethasone, or lenalidomide

    * Women with child-bearing potential are those who are premenopausal (menopause is defined as the time when there has been no menstrual periods for at least 1 year), or who have not had a bilateral tubal ligation, bilateral oophorectomy, or hysterectomy. The menstruation possibly interrupted by chemotherapy is not defined as menopause.
25) Pregnant (e.g. positive for pregnancy test) or lactating. Lactation is prohibited from the first dose through 6 weeks after the last dose of MLN9708, dexamethasone, and lenalidomide(3)
26) Use of an investigational medical device within 28 days before enrollment(2)
27) Any inabilities that could potentially interfere with the consent or completion of treatment according to this protocol(2)
28) Having difficulties in participation to this study by the investigator's judgment(2)

<Basis for setting the criteria>

(1) To minimize risks and ensure safety of subjects.

(2) To eliminate any impact on evaluation of MLN9708.

(3) For unclear potential of reproductive and developmental toxicity associated with MLN9708 and teratogenicity evident by lenalidomide in the Rd cohort.

5. SUBJECT ENROLLMENT

The investigators must obtain written informed consent from all subjects before any study specific procedures are performed.

All subjects who enter into the screening period for the study (defined as the point at which the subject signs the informed consent) will receive a unique, 8-digits subject identification number (e.g. 34XXXYYY). The first 2 digits (i.e. 34) represent the protocol number, next 3 digits (XXX) represent the study center number, and the last 3 digits (YYY) represent the subject number which is assigned in each study center.

This number will be used to identify the subject throughout the study and must be used on all study documentation related to that subject. The subject identification number must remain the same throughout the entire clinical study; it must not be changed at the time of re-screening or re-enrollment. The number is assigned in sequential order of the subject's consent at the site, in principle (e.g. 001, 002, 003).

Subjects must be registered within 28 days of the consent.

Subjects not meeting the eligibility criteria during the screening period cannot be enrolled. However, subjects can be re-screened with the investigator's discretion as long as they are not registered as a screen failure. When subjects are re-screened, the investigators must obtain additional written informed consent before the re-screening to reconfirm the subject's consent for study participation. A subject cannot be re-screened more than once, and will be defined as a screen failure if subject is not qualified to undergo re-screening or is determined as a screen failure after the re-screening.

A subject will be defined as a screen failure, if the subject signs the informed consent but fails to enroll into the study. The investigators must document all screen failures and the reasons for the failure on the electronic case report form (eCRF).

For addition or replacement of subjects, refer to "8.2 Replacement of Subjects".

5.1 Enrollment Procedures

After the completion of subject screening for each subject, the investigator enrolls the subject according to the following procedures:

The investigator ensures that a subject meets all the eligibility criteria and faxes a "subject registration sheet" to the Registration Center after confirming the necessary information is completed. The "subject registration sheet" may be the source data of the investigator's judgment for the each eligibility criteria.

The Registration Center confirms that a subject meets the all inclusion criteria and does not meet any of the exclusion criteria, and then the Registration Center identifies the subject as an enrolled subject and faxes a "registration confirmation sheet" to the investigator. If a subject is considered ineligible by the Registration Center, the center will not identify the subject as an enrolled subject. A "registration confirmation sheet" describing the "reason for ineligibility" will be faxed to the investigator.

The investigator must retain a "subject registration sheet", a "registration confirmation sheet", and the "reason for ineligibility" as the source documents appropriately in the study centers.

The Registration Center will report above subject registration progress promptly to the sponsor.

MLN9708 (TB-MC010034) Subject Registration Center
Takeda Pharmaceutical Company Limited
Marunouchi Eiraku Building, 1-4-1 Marunouchi, Chiyoda-ku, Tokyo, Japan
PPD
PPD
PPD

5.2 CCI [redacted] Registration

The CCI [redacted] procedures must be followed when providing lenalidomide to the subjects in the MLN9708 with Rd cohort in the study.

Before a patient is enrolled in this study, the patient must be registered in accordance with the CCI [redacted], and it must be confirmed that the patient is eligible to receive lenalidomide.

If the patient is already registered in CCI [redacted], then no re-registration is necessary.

6. TREATMENT PROCEDURES

6.1 MLN9708

MLN9708 is manufactured (including packaging and labeling) by MPI and supplied by Takeda Pharmaceutical Company.

Specifications and storage conditions for MLN9708 are presented below.

Table 6-1. Specifications for MLN9708

Investigational Product	MLN9708
Formulation and strength	capsules One capsule contains 2.3, 3.0, 4.0, or 5.5 mg of active boronic acid form of MLN9708 (MLN2238)
Packaging	foil-foil blisters
Packaging Unit	Three capsules per foil-foil blister, which is contained by 1 unit carton.
Storage	to be refrigerated at 2ºC to 8ºC
Manufacturer	Millennium Pharmaceuticals, Inc. (the United States)

See the Directions for Use located in the Pharmacy Manual for details on the labeling and storage of MLN9708. There is very limited experience with clinically significant overdose of MLN9708 and no specific antidotes exist for the treatment of MLN9708 overdose. General supportive care is recommended.

The maximum dose of MLN9708 previously used in monotherapy was 3.95 mg/m^2 weekly.

6.2 Concomitant medications

The concomitant medications (MLN9708 + Rd cohort only) are described below. The concomitant medications will be dispensed at the study center.

6.2.1 Lenalidomide (CCI [redacted] 5 mg)

Lenalidomide (CCI [redacted] 5 mg) is an anti-angiogenic malignant tumor agent that is indicated for relapsed and/or refractory multiple myeloma and myelodysplastic

syndromes with 5q- syndrome. For detailed information about lenalidomide, refer to the latest version of the package insert for CCI [redacted] 5 mg.

6.2.2 Dexamethasone (CCI [redacted] 4 mg)

Dexamethasone (CCI [redacted] 4 mg) is a corticosteroid that is indicated for multiple myeloma. For detailed information on dexamethasone, refer to the latest version of the package insert for CCI [redacted] 4 mg.

6.3 Dosage, administration method, dosing schedule

6.3.1 MLN9708 administration

In this study, MLN9708 will be administered orally once weekly for 3 weeks (on Days 1, 8, and 15 and skip Day 22) in a 28-day cycle for up to 12 cycles.

MLN9708 will be taken on an empty stomach at least 1 hour before or no sooner than 2 hours after a meal.

In Cycle 1, MLN9708 will be given according to the dosage and administration specified in this study protocol; no interruption, delays, or reduction will be permitted.

Missed doses of MLN9708 in Cycle 2 and subsequent cycles can be taken as soon as the patient remembers provided that at least 3 days elapses between doses (until Day 4). If a patient vomits after taking MLN9708, the patient should not repeat the dose, but resume dosing at the time of the next schedule.

Once a dose is reduced, no re-escalation will be permitted.

6.3.2 Lenalidomide Administration (Rd Concomitant Cohort Only)

Lenalidomide will be administered as a single, daily oral dose of 25 mg/day on Days 1 to 21 for 21 consecutive days followed by one week rest period in a 28-day cycle. This cycle will be repeated.

Lenalidomide should be taken at approximately the same time each day. Patients should be instructed to swallow lenalidomide capsules whole with water and not to break, chew, or open the capsules.

Lenalidomide and MLN9708 should be taken simultaneously. Lenalidomide should be used according to the package insert of CCI [redacted] 5 mg.

A missed dose of lenalidomide can be taken as soon as the patient remembers provided that it is within 12 hours from the regular dosing schedule. A double dose should not be taken to make up for a missed dose. If enough time has elapsed that the missed dose is not taken within the same day, the missed dose should be skipped. If the patient vomits after taking a dose, the patient should not repeat the dose but should resume dosing at the time of the next schedule.

6.3.3 Dexamethasone Administration (Rd Concomitant Cohort Only)

Dexamethasone will be administered as a single, oral dose of 40 mg/day weekly on Days 1, 8, 15, and 22 of a 28-day cycle.

Dexamethasone will be taken at approximately the same time each day, approximately 1 hour after MLN9708 and lenalidomide. Each dose of dexamethasone should be taken with food or milk. Dexamethasone should be used according to the package insert of CCI [redacted] 4 mg.

Missed doses of dexamethasone can be taken as soon as the patient remembers provided that at least 3 days elapses between doses (until Day 4). If the patient vomits after taking a dose, the patient should not repeat the dose but resume dosing at the time of the next schedule.

6.4 Criteria for Beginning the Next Cycle of Treatment

6.4.1 MLN9708 Monotherapy

Treatment with MLN9708 will be repeated every 28 days as 1 cycle. For a new treatment cycle to begin, the patient must satisfy the following criteria:

- ANC must be ≥ 1,000 mm^3
- Platelet count must be ≥ 50,000 mm^3
- All other toxicity (except for alopecia) considered related to MLN9708 must be resolved to ≤ Grade 1 or to the patient's baseline values

6.4.2 MLN9708 in Combination With Rd

Treatment of MLN9708 with Rd will be repeated every 28 days as 1 cycle. For a new treatment cycle to begin, the patient must satisfy the following criteria:

- ANC must be ≥ 1,000 mm^3
- Platelet count must be ≥ 75,000 mm^3
- All other nonhematological toxicities (except for alopecia) considered related to MLN9708 or Rd must be resolved to ≤ Grade 1 or to the patient's baseline values

6.4.3 Criteria for Dose Delays

If a subject fails to meet the criteria for beginning the next cycle of treatment, initiation of the next cycle should be delayed for one week for re-evaluation. If the subject still fails to meet the criteria, the subject should be re-evaluated weekly. The next cycle treatment can be initiated if the subject meets the criteria for initiating the next cycle within 3 weeks of the scheduled initiation of the next cycle. The MLN9708 and lenalidomide starting doses for the next cycle are presented below.

- Reinitiate with one dose level reduction
  - If MLN9708 or lenalidomide treatment was interrupted during the preceding cycle in accordance with "6.5 Dose Modification" and treatment could not be resumed within the same cycle
- Reinitiate with the same dose level as the preceding cycle
  - If there was no need for dose adjustment in the preceding cycle
  - If MLN9708 or lenalidomide treatment was interrupted during the preceding cycle in accordance with "6.5 Dose Modification" and treatment could be resumed during the cycle

Should the start of the next cycle need to be delayed for more than 3 weeks because of incomplete recovery from treatment-related toxicity, the patient undergoes the EOS exams, and treatment should be discontinued.

6.5 Dose Modification

6.5.1 MLN9708 Monotherapy

6.5.1.1 Criteria for Dose Modification

Dose modifications of MLN9708 are not permitted in Cycle 1.

If dose modification is required in Cycle 2 or subsequent cycles, MLN9708 dose will be reduced by one level according to Table 6-2. If multiple toxicities are noted, the dose should be interrupted or reduced according to the most severe toxicity guidelines (Table 6-3 and Table 6-4). Toxicity will be assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

Table 6-2. Dose Reduction Levels of MLN9708

Initial dose	Level 1	Level 2	Level 3	Level 4
4.0 mg	3.0 mg	2.3 mg	Discontinue	-
5.5 mg	4.0 mg	3.0 mg	2.3 mg	Discontinue

6.5.1.1.1 Dose Modification for Hematological Toxicity

If platelet count is less than 30,000/mm^3 or ANC is less than 750/mm^3 in Cycle 2 or subsequent cycles, MLN9708 dose should be interrupted. If the platelet count is recovered to at least 30,000/mm^3 and ANC is recovered to at least 750/mm^3 within the same cycle, MLN9708 may be reinitiated with one dose level reduction. If the subject meets the criteria for retreatment by delaying the initiation of the subsequent cycle, the subjects may be retreated with MLN9708 with one dose level reduction (See "6.4 Criteria for Beginning the Next Cycle of Treatment").

Table 6-3. Dose Modification of MLN9708 for Hematological Toxicities

Criteria	Action
Within-cycle Dose Modifications (Days 8 and 15)	
If platelet count < 30,000/mm^3 or ANC < 750/mm^3	Interrupt MLN9708, follow CBC weekly. Upon recovery, MLN9708 may be reinitiated with one dose level reduction.

ANC = absolute neutrophil count, CBC = complete blood count

6.5.1.1.2 Dose Modification for Non-hematological Toxicity

If non-hematological toxicities shown in Table 6-4 occur in Cycle 2 and subsequent cycles, MLN9708 should be interrupted. Upon recovery, MLN9708 may be reinitiated with one dose level reduction. For Grade 4 non-hematological toxicities, MLN9708 should be discontinued permanently.

Table 6-4. Dose Modification of MLN9708 for Non-hematological Toxicities

Criteria	Action
Peripheral Neuropathy: Grade 2 peripheral neuropathy with pain	MLN9708 therapy should be interrupted until toxicities have resolved to ≤ Grade 1 or baseline. Upon recovery, MLN9708 may be reinitiated with one dose level reduction.
Grade 3 non-hematological toxicities	MLN9708 therapy should be interrupted until toxicities have resolved to ≤ Grade 1 or baseline. Upon recovery, MLN9708 may be reinitiated with one dose level reduction.
Grade 4 non-hematological toxicities	Discontinue MLN9708. With agreement by the sponsor, investigators may consider restarting the therapy for patients continue to clinically benefit from the therapy.

6.5.2 MLN9708 in combination with Rd

6.5.2.1 Criteria for Dose Modification

Dose modifications of MLN9708 are not permitted in Cycle 1. Dose modifications of Rd should be avoided as much as possible. If a subject experiences an adverse event(s) considered strongly related to lenalidomide or dexamethasone and the investigator considers it difficult to continue the treatment with Rd, the investigator and the sponsor will discuss the alternative dose modification.

If dose modification is required in Cycle 2 or subsequent cycles, MLN9708, lenalidomide, or dexamethasone dose will be modified levels according to Table 6-5. If multiple toxicities are noted, the dose should be modified or delayed according to the most severe toxicity guidelines (Table 6-6 through Table 6-11). Once a dose is reduced, no re-escalation will be permitted.

Each adverse event should be attributed to a specific drug, if possible, so that the dose can be modified accordingly. Reduction of one agent and not the other is appropriate if toxicity is related primarily to one of the agents. Toxicity will be assessed according to the CTCAE version 4.03.

Table 6-5. Dose Reduction Levels for MLN9708, lenalidomide and dexamethasone

Drug	Initial dose	Level 1	Level 2	Level 3	Level 4
MLN9708	4.0 mg	3.0 mg	2.3 mg	Discontinue	-
	5.5 mg	4.0 mg	3.0 mg	2.3 mg	Discontinue
lenalidomide	25 mg	15 mg	10 mg	5 mg	Discontinue
dexamethasone	40 mg	20 mg	8 mg	Discontinue	-

6.5.2.2 Dose Modification for Hematological Toxicity

6.5.2.2.1 Dose Modification for Thrombocytopenia

If platelet count is less than 30,000/mm^3 in Cycle 2 or subsequent cycles, lenalidomide dose should be interrupted. If the platelet count is recovered to at least 30,000/mm^3 within the same cycle, lenalidomide may be reinitiated with one dose level reduction. MLN9708 dose can be kept as is. If the subject meets the criteria for retreatment with delaying the initiation of the subsequent cycle, the subjects may be retreated with lenalidomide with one dose level reduction (See "6.4 Criteria for Beginning the Next Cycle of Treatment").

If thrombocytopenia occurs more than once, MLN9708 or lenalidomide dose will be modified at each occurrence according to Table 6-6 to continue the treatment. In some severe situations, both MLN9708 and lenalidomide may be interrupted or reduced if needed based on discussion between the investigator and the sponsor.

Table 6-6. MLN9708 and Lenalidomide Dose Modification for Thrombocytopenia

Platelets	Action
First fall to < 30,000/mm^3	Interrupt lenalidomide treatment, follow CBC weekly
Return to ≥ 30,000/mm^3 within the same cycle	Resume lenalidomide at 15 mg
Second fall: Subsequent drop below 30,000/mm^3	Interrupt MLN9708, follow CBC weekly
Return to ≥ 30,000/mm^3 within the same cycle	Resume MLN9708 at reduced dose by 1 level (Level 1)
Third fall: Subsequent drop below 30,000/mm^3	Interrupt lenalidomide treatment, follow CBC weekly
Return to ≥ 30,000/mm^3 within the same cycle	Resume lenalidomide at 10 mg
Fourth fall: Subsequent drop below 30,000/mm^3	Interrupt MLN9708, follow CBC weekly
Return to ≥ 30,000/mm^3 within the same cycle	Resume MLN9708 at reduced dose by 1 level (Level 2)
	Do not dose MLN9708 below 2.3 mg
Fifth fall: Subsequent drop below 30,000/mm^3	Interrupt lenalidomide, follow CBC weekly
Return to ≥ 30,000/mm^3 within the same cycle	Resume lenalidomide at 5 mg
	Do not dose lenalidomide below 5 mg

CBC = complete blood count

6.5.2.2.2 Dose Modification for Neutropenia

If ANC count is less than 1,000/mm^3 in Cycle 2 or subsequent cycles, lenalidomide dose should be interrupted. If the ANC is recovered to at least 1,000/mm^3 within the same cycle, lenalidomide may be reinitiated with one dose level reduction. MLN9708 dose can be kept as is. If the subject meets the criteria for retreatment by delaying the initiation of the subsequent cycle, the subjects may be retreated with lenalidomide with one dose level reduction (See section "6.4 Criteria for Beginning the Next Cycle of Treatment").

If neutropenia occurs more than once, MLN9708 or lenalidomide dose will be modified according to Table 6-7 to continue the treatment. G-CSF is not permitted in Cycle 1 unless Grade 4 neutropenia occurs (See section 6.9 Excluded Concomitant Medications and Procedures). In some severe situations, both lenalidomide and MLN9708 may be interrupted or reduced if needed based on discussion between the investigator and the sponsor.

Table 6-7. MLN9708 and Lenalidomide Dose Modification for Neutropenia

Absolute Neutrophil Count	Action
First fall to < 1,000/mm^3	Interrupt lenalidomide treatment, follow CBC weekly
Returns to ≥ 1,000/mm^3 within the same cycle	Resume lenalidomide at 15 mg
Second fall: Subsequent drop below 1,000/mm^3	Interrupt MLN9708, follow CBC weekly
Returns to ≥ 1,000/mm^3 within the same cycle	Resume MLN9708 at reduced dose by 1 level (Level 1)
Third fall: Subsequent drop below 1,000/mm^3	Interrupt lenalidomide treatment, follow CBC weekly
Returns to ≥ 1,000/mm^3 within the same cycle	Resume lenalidomide at 10 mg
Fourth fall: Subsequent drop below 1,000/mm^3	Interrupt MLN9708, follow CBC weekly
Returns to ≥ 1,000/mm^3 within the same cycle	Resume MLN9708 at reduced dose by 1 level (Level 2)
	Do not dose MLN9708 below 2.3 mg
Fifth fall: Subsequent drop below 1,000/mm^3	Interrupt lenalidomide, follow CBC weekly
Returns to ≥ 1,000/mm^3 within the same cycle	Resume lenalidomide at 5 mg
	Do not dose lenalidomide below 5 mg

CBC = complete blood count

6.5.2.3 Dose Modification for Non-hematological Toxicity

6.5.2.3.1 Dose Modification for Rash

If Grade 2 or 3 rash occurs in Cycle 2 or subsequent cycles, lenalidomide dose should be interrupted. If the rash is recovered to Grade 1 or lower within 2 weeks, lenalidomide may be reinitiated with one dose level reduction. MLN9708 dose can be kept as is. If rash occurs more than once, MLN9708 or lenalidomide dose will be reduced according to Table 6-8 to continue the treatment. In some severe situations, both lenalidomide and MLN9708 may be interrupted or reduced if needed based on discussion between the investigator and the sponsor.

Table 6-8. MLN9708 and Lenalidomide Dose Modification for Rash

Rash	Action
Grade 2 or 3	Interrupt lenalidomide treatment
Recovers to < Grade 2 within 2 weeks	Resume lenalidomide at 15 mg
If does not recover to < Grade 2 in 2 weeks	Interrupt MLN9708
OR for subsequent occurrence of Grade 2 or 3 rash	
Recovers to < Grade 2 within 2 weeks	Resume MLN9708 at reduced dose by 1 level (Level 1)
If does not recover to < Grade 2 in 2 weeks	Interrupt lenalidomide treatment
OR for subsequent occurrence of Grade 2 or 3 rash	
Recovers to < Grade 2 within 2 weeks	Resume lenalidomide at 10 mg
If does not recover to < Grade 2 in 2 weeks	Interrupt MLN9708
OR for subsequent occurrence of Grade 2 or 3 rash	
Recovers to < Grade 2 within 2 weeks	Resume MLN9708 at reduced dose by 1 level (Level 2)
	Do not dose MLN9708 below 2.3 mg
If does not recover to < Grade 2 in 2 weeks	Interrupt lenalidomide treatment
OR for subsequent occurrence of Grade 2 or 3 rash	
Recover to < Grade 2 within 2 weeks	Resume lenalidomide at 5 mg
	Do not dose lenalidomide below 5 mg

6.5.2.3.2 MLN9708 Treatment Modification

MLN9708 dose adjustments are allowed based on clinical and laboratory findings. Dose reduction levels of MLN9708 for toxicity are indicated in Table 6-5. Treatment modifications due to MLN9708-related non-hematological toxicities are outlined in Table 6-9.

Table 6-9. MLN9708 Treatment Modification Due to Non-hematological Toxicities

Adverse Event (Severity)	Action on MLN9708	Further Considerations
Grade 2 peripheral neuropathy with pain	• Hold MLN9708 until resolution to Grade ≤ 1 or baseline • MLN9708 may be reinitiated with one dose level reduction.	
Grade 3 non-hematological toxicity	• Hold MLN9708 until resolution to Grade ≤ 1 or baseline • MLN9708 may be reinitiated with one dose level reduction	
Grade 4 non-hematological toxicities	• Consider permanently discontinuing MLN9708	With agreement by the sponsor, investigators may consider restarting the therapy for patients continue to benefit from the therapy

6.5.2.3.3 Lenalidomide Treatment Modification

Lenalidomide dose adjustments are allowed based on clinical and laboratory findings. Dose reduction levels of lenalidomide for toxicity are indicated in Table 6-5. Treatment modifications due to lenalidomide-related adverse events are outlined in Table 6-10.

Table 6-10. Lenalidomide Treatment Modification Guidelines Due to Non-hematological Toxicities

Adverse Event (Severity)	Action on Lenalidomide	Further Considerations
Grade 3/4 toxicities judged to be related to lenalidomide (other than the toxicities listed below)	• Hold lenalidomide treatment, and restart at the next lower dose level when toxicity has resolved to ≤ Grade 2	Do not dose below 5 mg
Renal dysfunction	• Dose reduction, interruption, or discontinuation per lenalidomide package insert	Care should be taken in dose selection/modification in the elderly as they are more likely to have decreased renal function Monitor renal function regularly
≥Grade 2 thrombosis/embolism	• Hold lenalidomide and start anticoagulation therapy; restart at investigator's discretion after adequate anticoagulation; maintain dose level (No dose modification)	For patients treated with Rd, thromboprophylaxis such as aspirin according to the institutional standard of care is recommended
Angioedema, Stevens-Johnson Syndrome (SJS), and Toxic Epidermal Necrolysis (TEN)		
Grade 2/3 skin rash	• Hold or discontinue lenalidomide	
Grade 4 exfoliative or bullous rash or if SJS or TEN suspected	• Permanently discontinue lenalidomide	
Any grade angioedema	• Permanently discontinue lenalidomide	
Any grade tumor Lysis syndrome	• Hold lenalidomide in the same cycle. Upon recovery, lenalidomide can be restarted at the same dose used before interruption.	Monitor closely and take appropriate medical precautions.

6.5.2.3.4 Dexamethasone Treatment Modification

Dexamethasone dose adjustments are outlined in Table 6-5. Treatment modifications due to dexamethasone-related adverse events are outlined in Table 6-11.

Table 6-11. Dexamethasone Treatment Modification Guidelines Due to Non-hematological Toxicities

Adverse Event (Severity)		Action on Dexamethasone
Gastrointestinal	Dyspepsia, gastric, or duodenal ulcer, gastritis Grade 1-2 (requiring medical management)	If symptoms persist, reduce dexamethasone by 1 dose level as needed.
	> Grade 2	Hold dexamethasone until symptoms adequately controlled. Restart and reduce 1 dose level of current dose.
Cardiovascular	Edema > Grade 2 (limiting function and unresponsive to therapy or anasarca)	Diuretics as needed and reduce dexamethasone by 1 dose level. If edema persists despite these measures, reduce dose another level. Discontinue dexamethasone and do not resume if symptoms persist despite second reduction.
Neurological	Confusion or mood alteration > Grade 2	Hold dexamethasone until symptoms resolve. Restart with 1 dose level reduction. If symptoms persist despite these measures, discontinue dexamethasone and do not resume.
Musculoskeletal	Muscle weakness > Grade 2	Reduce dexamethasone dose by 1 dose level. If weakness persists despite these measures, reduce dose by 1 dose level. Discontinue dexamethasone and do not resume if symptoms persist.
Metabolic	Hyperglycemia > Grade 2	Treatment with insulin or oral hypoglycemics as needed. If uncontrolled despite these measures, decrease dose by 1 dose level until levels are satisfactory.
Acute pancreatitis		Discontinue dexamethasone.

6.6 Cohort Transition and Early Stopping Guidelines

6.6.1 Cohort Transition

Three subjects will be initially enrolled into each dose level in order starting with cohort 1. The sponsor will evaluate the tolerability of MLN9708 dosage in each cohort on the basis of the DLT incidences in consultation with the ESEC, if necessary.

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.

1. Cohort Transition From Cohort 1 to Cohort 2

If no DLT occurs during the DLT assessment period for cohort 1 (the initial dose through before Cycle 2), the dosage will be considered tolerable. If a DLT occurs in one subject during the DLT assessment period, 3 additional subjects will be enrolled into a given dose level to evaluate tolerability in a total of 6 subjects. If DLTs occur in no more than 1 of the 6 subjects, then this dosage will be considered tolerable. If DLTs occur in 2 of 3 subjects, then this dosage will be considered intolerable. If DLTs occur in 2 of 6 subjects, the sponsor will determine the tolerability of this dosage in consultation with the ESEC. Even if a dosage is considered tolerable, the appropriateness of transition to cohort 2 will be determined by the sponsor in consultation with the ESEC as necessary.

2. Cohort Transition From Cohort 2 to Cohort 3

If no DLT occurs during the DLT assessment period for cohort 2, the dosage will be tolerable. If a DLT occurs in one subject during the DLT assessment period, 3 additional subjects will be enrolled into a given dose level to evaluate tolerability in a total of 6 subjects. If DLTs occur in no more than 1 of the 6 subjects, then this dosage will be considered tolerable. If DLTs occur in 2 of 3 subjects, then this dosage will be considered intolerable. If DLTs occur in 2 of 6 subjects, then the sponsor will determine the tolerability of this dosage in consultation with the ESEC. Even if a dosage is considered tolerable, the appropriateness of transition to cohort 3 will be determined by the sponsor in consultation with the ESEC as necessary. If the cohort 2 dosage is found to be intolerable, the sponsor will determine the appropriateness of transition to cohort 3 based on the data obtained from cohort 1 and cohort 2 in consultation with the ESEC.

3. Cohort Transition From Cohort 3 to Cohort 4

If no DLTs occur during the DLT assessment period for cohort 3, the dosage will be tolerable. If a DLT occurs in one subject during the DLT assessment period, 3 additional subjects will be enrolled into a given dosage level to evaluate tolerability in a total of 6 subjects. If DLTs occur in no more than 1 of the 6 subjects, then this dosage will be considered tolerable. If DLTs occur in 2 of 3 subjects, then this dosage will be considered intolerable. If DLTs occur in 2 of 6 subjects, then the sponsor will determine the tolerability of this dosage in consultation with the ESEC. Even if a dosage is considered

tolerable, the appropriateness of transition to cohort 4 will be determined by the sponsor based on the data obtained from cohort 2, in consultation with the ESEC as necessary.

6.6.2 Early Stopping Guidelines

Should the start of the next cycle need to be delayed for more than 3 weeks because of incomplete recovery from treatment-related toxicity (6.4.3 Criteria for Dose Delays), the patient undergoes the EOS exams, and treatment should be discontinued.

6.7 DLT

6.7.1 DLT Assessment Period

DLTs will be assessed from the first dose until Cycle 2 Day 1 of MLN9708 treatment.

6.7.2 DLT-Evaluable Subjects

DLT-evaluable subjects are defined as follows:

- DLTs ≥ 1 during DLT-assessment period.

OR

- Received 3 doses of MLN9708 specified for the applicable cohort and completed the DLT-assessment period.

Subjects whose treatment with MLN9708 was interrupted or reduced in Cycle 1 for reasons other than DLTs are not eligible for DLT assessment in principle.

6.7.3 Definitions of DLT

DLT will be defined as any of the following AEs that are considered possibly related to MLN9708. Toxicity will be accessed according to the CTCAE version 4.03.

1. Grade 4 neutropenia (ANC < 500/mm^3) lasting more than 7 consecutive days.
2. Grade 3 or greater neutropenia (ANC < 1,000/mm^3) with fever and/or infection, where fever is defined as axillary temperature ≥ 38.0ºC.
3. Grade 4 thrombocytopenia (platelets < 25,000/mm^3) lasting more than 7 consecutive days.
4. Grade 3 or greater thrombocytopenia (< 50,000/mm^3) with clinically significant bleeding, or which requires blood transfusion.

5. A platelet count < 10,000/mm^3.
6. Grade 2 peripheral neuropathy with pain or Grade 3 or greater peripheral neuropathy.
7. Any other Grade 3 or greater nonhematologic toxicities with the following exceptions:
   - Grade 3 or greater arthralgia/myalgia.
   - Grade 3 or greater fatigue lasting less than 7 days.
   - Grade 3 nausea and/or emesis which can be controlled with anti-emetic therapies including anti-emetic prophylaxis. Anti-emetic prophylaxis is defined as an anti-emetic regimen that employs a 5-HT3 antagonist given in standard doses and according to standard schedules. Dexamethasone should not be administered as an anti-emetic.
   - Diarrhea that is controlled with appropriate supportive care
8. A delay of more than 14 days in the initiation of Cycle 2 treatment because of a lack of adequate recovery of MLN9708 related hematological or nonhematologic toxicities.
9. Other Grade 2 or greater MLN9708 related nonhematologic toxicities that, in the opinion of the investigator, require permanent discontinuation of MLN9708.
10. Inability to give at least 80% of the planned lenalidomide doses (Rd combination cohort only) due to the adverse events related to MLN9708.

When a subject experiences any of the above DLTs, MLN9708 therapy should be interrupted within the same cycle after DLT. With agreement by the sponsor, investigators may consider restarting the MLN9708 therapy from next cycle for subjects continue to clinically benefit from the therapy. MLN9708 should be reinitiated in accordance with "6.4.3 Criteria for Dose Delays".

The sponsor will consult with the ESEC for the final decision if determination of DLT or subjects' eligibility for DLT-assessment is difficult.

6.8 Permitted Concomitant Medications and Procedures

Throughout the study, investigators may prescribe any concomitant medications or perform procedures deemed necessary to provide adequate supportive care except for those listed in "6.9 Excluded Concomitant Medications and Procedures

6.9 Excluded Concomitant Medications and Procedures

The following medications and procedures are prohibited during the study.

- Systemic treatment with strong inhibitors of CYP3A inducers (rifampicin, rifabutin, carbamazepine, phenytoin, phenobarbital), or use/ intake of foods containing St. John's Wort during the study.
- Any antineoplastic treatment other than Rd administered concomitantly with MLN9708 in the Rd combination cohort. Treatment with corticosteroids 10 mg of prednisolone per day or less is permitted.
- Radiotherapy (note that, in general, the requirement for local radiation therapy indicates disease progression).
- Myeloid growth factors (e.g., G-CSF, granulocyte macrophage-colony stimulating factor [GM-CSF] is not permitted in Cycle 1 unless Grade 4 neutropenia occurs. Their use should follow published guidelines and/or institutional practice, however, alternative usage may be reviewed with the Millennium clinician or study clinician designee.
- Platelet transfusions to help patients meet eligibility criteria of ANC and platelet counts are not allowed prior to MLN9708 dosing on Cycle 1 Day 1 (within 7 days before the test).

7. STUDY PROCEDURES

MLN9708 treatment must be initiated within 7 days after the enrollment. Refer to Appendix A for an outline of procedures required at each visit.

7.1 Subject Screening

Before any protocol-specified procedure, all subjects must sign and date the informed consent form.

The investigator will be expected to create and maintain a screening log for all potential study candidates that includes information about the potential candidate (sex, date of birth), date, and outcome of the screening process (e.g., enrollment into study, reason for ineligibility or refused to participate).

All existing test results (e.g., HIV, hepatitis B virus [HBV], HCV), diagnostic imaging results (e.g., X-ray, CT, MRI) and bone marrow test results, for example, obtained prior to the date of consent acquisition may be used as data at the time of screening, provided the subject's consent is obtained.

7.2 Examinations, observations, and evaluations

The investigator will conduct examinations, observations, and evaluations of the subject according to the following procedures from the informed consent until the end of treatment visit. The subject assessments/observations will all be performed by the same investigator, in principle.

7.2.1 Screening period

All of the following exams, observations, and evaluations will be performed within 28 days before first dose, unless otherwise specified. Subjects meeting all of the eligibility criteria specified in "4 SUBJECT ELIGIBILITY" prior to subject enrollment will be enrolled to this study in accordance with Section 5 “SUBJECT ENROLLMENT."

- Informed consent
- Assessment of eligibility, according to the inclusion/exclusion criteria

- Subject background (including medical history, concomitant disease, details of multiple myeloma diagnosis [date of diagnosis, histological type, current clinical stage] (see Appendix H), history of prior-treatment for multiple myeloma [chemotherapy, radiotherapy, transplantation, surgery])
  - For past medical history, the following clinically significant diseases and procedures that have resolved or ended before the initial dose.
    1. Diseases listed in the exclusion criteria (all such diseases that have resolved or ended prior to enrollment)
    2. Diseases or procedures experienced by the patient in the last 3 months other than those described in #1, except for transient diseases (e.g., upper respiratory tract inflammation, cold, headache)
    3. Other diseases that could affect the MLN9708 evaluation
  - "Concomitant disease" refers to any symptoms or diseases being experienced by the subject at the time of the first study treatment, and includes all clinically significant laboratory tests, 12-lead ECGs, and physical examination finding abnormalities. Concurrent illnesses will be investigated in detail (and diagnosis terms obtained wherever possible).
- ECOG performance status (see Appendix B)
- Vital signs (sitting blood pressure, pulse rate and axillary temperature, and transcutaneous oxygen saturation [SpO2]
- Height, weight
- 12-lead ECG (QRS, QT, QTc, PR and heart rate)
  - The 12-lead ECG is performed with the subject at rest in a supine position.
- Laboratory tests: See Table 7-1 for the test parameters.
  - Hematology tests
  - Chemistry tests
  - Urinalysis
  - Virus tests (HIV antibody, HBs antigen, HCV antibody. The test results will not be recorded in the eCRF.)
  - β2-microglobulin
  - Immunoglobulin quantitation (IgG, IgM, IgA, IgD)
  - FLC
- Serum M-protein (protein fraction test by electrophoresis; immunofixation)
- Urine M-protein by 24-hour urine collection (protein fraction test by electrophoresis; immunofixation)
- Pregnancy test (serum or urine; only if the subject is of childbearing potential)
- Serious adverse events (see "9.1.1 Adverse Events" through "9.3 Serious Adverse Event Reporting Procedures")

- X-rays
  - Chest
  - Bone (head, cervical vertebrae, thoracic vertebrae, lumbar vertebrae, pelvis, both upper arms, both forearms, both femurs, both lower legs); in two directions for each, except for the pelvis
  - If bone X-ray is performed within 8 weeks before the first dose, the X-ray results may be used as screening data.
- CT/MRI (chest, abdomen)
  - Unless a patient shows hypersensitivity to contrast or concern for potential aggravation of renal dysfunction, all CT/MRI should be performed with contrast.
  - When CT/MRI scan is performed within 8 weeks before the first dose of MLN9708, it may be used as screening data.
- Bone marrow aspirate: Percentage of plasma cells in bone marrow (Note: When collecting the sample, anatomical locations that are irradiated in the past should be avoided.)

7.2.2 Treatment period

Study treatment must be initiated within 7 days after enrollment. If study treatment cannot be initiated within 7 days, the patient may be rescreened after obtaining additional informed consent. For details, see "5 SUBJECT ENROLLMENT." Hospitalization is generally required from the first dose of MLN9708 through the start of Cycle 2. However, if a subject wishes to return home temporarily and the investigator confirms that the subject's symptoms are stable based on the available data collected in the study to that point, then the subject may return home temporarily, provided this does not interfere with the study observations/tests.

See "6.3 Dosage, administration method, dosing schedule" for more details on the administration of MLN9708 and Rd. Unless otherwise specified, the following procedures must be followed before administering MLN9708 in each cycle. See Appendix A for the acceptable test, observation, and examination time windows.

- Obtaining informed consent to extended treatment
  - Written consent to the extended administration of MLN9708 will be obtained prior to Cycle 2 treatment from subjects who meet the criteria specified in "6.4 Criteria for Beginning the Next Cycle of Treatment" and who have experienced no safety concerns.

- Medical interview (including confirmation of treatment compliance): Day 1 of each Cycle
- ECOG performance status: See Appendix B
  - Cycle 1: Days 1, 8, and 15
  - Cycles 2 and subsequent cycles: Day 1
- Vital signs (sitting blood pressure, pulse rate and axillary temperature, SpO2)
  - Cycle 1: Days 1, 8 and 15
  - Cycles 2 to 12: Days 1 and 15
  - Cycle 13 and subsequent cycles: Day 1
- Body weight
  - Cycle 1: Before MLN9708 dosing on Day 1. If a patient's body weight at screening is measured within 3 days before the first dose, then this measurement may be used for the Cycle 1 Day 1 data.
  - Cycle 2 and subsequent cycles: Day 1 of each cycle. Measurements taken within 3 days before dosing will be accepted.
- 12-lead ECG (QRS, QT, QTc, PR and heart rate)
  - Day 1 of Cycle 1: Before dosing
  - Day 15 of Cycle 1: Before dosing, 30 minutes (± 10 min) after dosing, 1 hour (± 15 min) after dosing, and 4 hours (± 45 min) after dosing
  - Day 16 of Cycle 1: 24 hours (± 1 hr) after dosing on Day 15
- Laboratory tests: See Table 7-1 for the test parameters.
  - Hematology tests
    - Cycle 1: Days 1, 8, 15 and 22
    - Cycles 2 and 3: Days 1, 8 and 15
    - Cycles 4 to 12: Days 1 and 15
    - Cycle 13 and subsequent cycles: Day 1

      If a screening test is performed within 3 days before the first dose, the results may be used as the Cycle 1 Day 1 data.
  - Chemistry tests
    - Cycle 1: Days 1, 8, 15 and 22
    - Cycles 2 and 3: Days 1, 8 and 15
    - Cycles 4 to 12: Days 1 and 15
    - Cycle 13 and subsequent cycles: Day 1

      If a screening test is performed within 3 days before the first dose, the result may be used as the data as Cycle 1 Day 1 data. Hemoglobin A1c (HbA1c) will be measured only on Day 1 of each cycle.

  - Urinalysis: Day 1 of each cycle
  - Immunoglobulin quantitation (IgG, IgM, IgA, IgD): Day 1 of each cycle
  - FLC: FLC will be measured as appropriate if a response assessment requires confirmation or disease progression is suspected (see Appendix G).
- Serum M-protein (electrophoresis protein fraction test): Performed on Day 1 of each cycle. If a screening test is performed within 7 days before the first dose, the results may be used as the Cycle 1 Day 1 data.
- Urine M-protein (electrophoresis protein fraction test):

  Subjects whose urine M-protein is detected only in urine at screening

  - Measurement by 24-hour urine collection
    - Urine samples will be collected prior to MLN9708 dosing on Cycle 1 Day 1. If a screening test is performed within 7 days before the first dose, the results may be used as the Cycle 1 Day 1 data.
    - Samples will be collected every 2 cycles prior to MLN9708 dosing on Day 1 of Cycles 3 and subsequent cycles (Cycles 3, 5, 7, 9, 11 and on [odd-numbered cycles]). It will be acceptable to collect samples between Days 23 and 28 of the preceding cycle.
  - Measurement by casual urine
    - Samples will be collected every 2 cycles prior to MLN9708 dosing on Day 1 of Cycles 2 and subsequent cycles (Cycles 2, 4, 6, 8, 10, 12 and on [even-numbered cycles]).

  Subjects whose urine M-protein is detected in serum and urine at screening

  - Measurement by 24-hour urine collection.
    - Urine samples will be collected prior to MLN9708 dosing on Cycle 1 Day 1. If a screening test is performed within 7 days before the first dose, the results may be used as the Cycle 1 Day 1 data.
    - If a response assessment requires confirmation or disease progression is suspected (see Appendix G), a urine M-protein measurement will be collected as appropriate using 24-hour urine collection.
- Immunofixation
  - Immunofixation will be performed only if it is necessary to confirm response (see Appendix G).
- Pregnancy test (serum or urine, only for women of childbearing potential): Day 1 of each cycle
- Concomitant drugs/therapies
  - All drugs or medical procedures used from the first dose of MLN9708 to the tests performed at EOS visit. At subject visits after the subject has become an outpatient, subjects will be asked about drugs or medical procedures he/she has received (other than Rd in the MLN9708 + Rd cohort).

- Adverse events: See "9.1.1 Adverse Events" to "9.3 Serious Adverse Event Reporting Procedures."
- Pharmacokinetics: See "7.2.6 Pharmacokinetic sample collection time points."
- X-rays
  - Bone (head, cervical vertebrae, thoracic vertebrae, lumbar vertebrae, pelvis, both upper arms, both forearms, both femurs, both lower legs); in two directions for each, except for the pelvis
  - X-rays will be performed as appropriate if osteolytic lesions are found at screening and there are concerns about bone lesions increasing or new bone lesions developing during the study.
- CT/MRI (head, abdomen):
  - If soft tissue plasmacytoma is found at screening, a CT/MRI scan will be performed every 2 cycles before MLN9708 dosing on Day 1 of Cycle 3 and subsequent cycles (Cycles 3, 5, 7, 9, 11 and on [odd-numbered cycles]). It will be acceptable to perform the scan between Days 23 and 28 of the preceding cycle. A scan may be performed as appropriate if disease progression is suspected or a response assessment requires confirmation if necessary outside a specified cycle (see Appendix G).
  - All diagnostic imaging scans will be performed using contrast media, except for subjects who are hypersensitive to contrast media or shows concern for potential aggravation of renal dysfunction.
- Bone marrow aspiration: Percentage of plasma cells in bone marrow (Note: When collecting the sample, anatomical locations that are irradiated in the past should be avoided.)

  Bone marrow puncture will be performed as appropriate if a response assessment requires confirmation or when disease progression is suspected (see Appendix G).

7.2.3 End of study

The following assessments will be performed on Day 29 after the last dose (acceptable time window + 21days) for subjects who have received MLN9708. These assessments will be performed before any poststudy therapy is provided. If tests, observations, or examinations are not going to be performed due to some unavoidable circumstance, such as complete withdrawal of subject consent or because follow-up is not possible or the patient has died or is in poor condition, the reason for this will be recorded in the source documents and the study completed. In such cases, the missing tests, observations, or examinations that is to be conducted on Day 29 after the last dose will not be considered protocol deviations.

- ECOG performance status: See Appendix B
- Vital signs (sitting blood pressure, pulse rate and axillary temperature, SpO2)
- Body weight
- 12-lead ECG (QRS, QT, QTc, PR and heart rate)
  - The 12-lead ECG will be performed with the patient at rest in a supine position.
- Laboratory tests: See Table 7-1 for the test parameters.
  - Hematology tests
  - Chemistry tests
  - Urinalysis
  - Immunoglobulin quantitation (IgG, IgM, IgA, IgD)
  - FLC
- Serum M-protein (protein fraction test by electrophoresis)
- Urine M-protein by 24-hour urine collection (protein fraction test by electrophoresis): Performed only for subjects whose urine M-protein is detected at screening.
- Immunofixation
  - Performed when response confirmation is necessary.
- Pregnancy test (serum or urine; only if the patient is of childbearing potential)
- Adverse events: See "9.1.1 Adverse Events" to "9.3 Serious Adverse Event Reporting Procedures")
- X-rays
  - Bone (head, cervical vertebrae, thoracic vertebrae, lumbar vertebrae, pelvis, both upper arms, both forearms, both femurs, both lower legs); in two directions for each, except for the pelvis
  - X-rays will be performed as appropriate if osteolytic lesions are found at screening.
- CT/MRI (chest, abdomen)
  - If soft tissue plasmacytoma is found at screening, a CT/MRI scan will be performed.
  - All diagnostic imaging scans will be performed using contrast media, except for subjects who are hypersensitive to contrast media or shows concern for potential aggravation of renal dysfunction.

7.2.4 Laboratory tests

The laboratory tests listed in "Table 7-1. Study Test Parameters" will be performed at the study center. The investigator will retain the laboratory test criteria, including the history.

Table 7-1. Study Test Parameters

Hematology	Chemistry	Urinalysis	Others
RBC count	Sodium	PH	β_2-microglobulin[i]
Hemoglobin	Potassium	Occult blood	IgG
Hematocrit	Chlorine	Sugar	IgM
Platelet count	Total protein	Specific gravity	IgA
WBC count	Albumin	Ketone bodies	IgD[g]
WBC differentials	Calcium	Urobilinogen	FLC
• Neutrophils	Inorganic phosphorus	Bilirubin	MLN2238 plasma concentration
• Eosinophils	Magnesium	Urinary sediment	Serum M-protein (protein fractionation by electrophoresis, immunofixation)
• Basophils	Glucose[a]	Nitrite	
• Lymphocytes	HbA1c	Qualitative urinary protein	Urine M-protein (protein fractionation by electrophoresis, immunofixation)
• Monocytes	Urea nitrogen	Quantitative urinary protein[h]	
	Creatinine		Pregnancy test[b] (serum or urine)
	Uric acid		
	Total bilirubin		
	ALP[c]		
	LDH[d]		
	AST (SGOT[e])		
	ALT (SGPT[f])		

[a] At screening and for Cycle 1, the samples will be collected at fasting (at least 4 hours after food)
[b] Only for women of childbearing potential
[c] Alkali phosphatase
[d] Lactate dehydrogenase
[e] Serum glutamate oxaloacetate transaminase
[f] Serum glutamate pyruvate transaminase
[g] Performed only for subjects suspected of having IgD-type multiple myeloma
[h] The amount of protein will be measured by 24-hour urine collection at screening and study completion. The amount of protein will be measured by 24-hour urine collection or casual urine at the specified time points (see 7.2.2) for subjects whose urine M-protein was detected at screening.
[i] β_2-microglobulin performed only at screening

7.2.5 Volume of blood collected

The volume of blood collected each time for the following parameters is shown below.

- Pharmacokinetics
  - Plasma MLN2238 concentration: 3 mL in total

7.2.6 Pharmacokinetic sample collection time points

The blood samples used for the pharmacokinetic assessments will be collected in accordance with "Table 7-2. Pharmacokinetic Sample Collection Time Points." Information on sample collection, processing, storage conditions, and shipping methods is shown in the sampling handling manuals.

The pharmacokinetic blood samples at predose will be collected before MLN9708, Rd dosing in the MLN9708 + Rd cohort as well.

Table 7-2. Pharmacokinetic Sample Collection Time Points

Cycle	Test Day	Time	Allowable Time Window
Cycle 1	Day 1	Predose	-1 hour
		15 minutes postdose	±3 minutes
		30 minutes postdose	±5 minutes
		60 minutes postdose	±15 minutes
		90 minutes postdose	±15 minutes
		2 hours postdose	±15 minutes
		4 hours postdose	±45 minutes
		8 hours postdose	±1 hour
	Day 2	24 hours postdose	±1 hour
	Day 3	48 hours postdose	±2 hours
	Day 5	96 hours postdose	±4 hours
	Day 8	168 hours postdose (before dosing on Day 8)	-4 hours
	Day 15	Predose	-1 hour
		15 minutes postdose	±3 minutes
		30 minutes postdose	±5 minutes
		60 minutes postdose	±15 minutes
		90 minutes postdose	±15 minutes
		2 hours postdose	±15 minutes
		4 hours postdose	±45 minutes
		8 hours postdose	±1 hour
	Day 16	24 hours postdose	±1 hour
	Day 17	48 hours postdose	±2 hours
	Day 19	96 hours postdose	±4 hours
	Day 22	168 hours postdose	±4 hours
Cycle 2	Day 1	Predose (336 hours postdose)	-1 hour

7.2.7 Assessment of antitumor activity

Antitumor activity will be evaluated at Cycles 3, 5, 7, 9 and 11 and whenever possible at EOS visit, in accordance with Appendix G, based on the Uniform Response Criteria for Multiple Myeloma of the International Myeloma Working Group, using the results obtained from serum and urine M-protein measurements, FLC measurements, percentage of plasma cells in bone marrow, and X-ray and CT/MRI measurements performed at the time points specified in the study protocol.

8. REMOVAL AND REPLACEMENT OF SUBJECTS

8.1 Removal of Subjects

Subjects have the right to withdraw fully or partially from the study at any time and for any reason.

Withdrawal of full consent for a study means that the subject does not wish to receive further study treatment and does not wish to or is unable to continue further study participation. Any subject may withdraw full consent to participate in the study at any time during the study. The investigator will discuss with the subject the most appropriate way to withdraw to ensure the subject's health.

Withdrawal of partial consent means that the subject does not wish to take investigational product any longer but is still willing to collaborate in providing further data by continuing on study (e.g. participate in all subsequent study visits or procedures). Subjects may withdraw partial consent to continue receiving investigational product at any time during the study. These subjects should continue the schedule of study observations.

Subjects who discontinue the investigational product by investigator's discretion or reasons other than the subject's withdrawal of consent also must continue the schedule of study observations.

All the procedures should be completed for the subject who discontinued the study by any reasons except the withdrawal of full-consent, lost to follow-up or death. If study observations cannot be performed due to unavoidable circumstances, such as the worsening of the subject's condition, the reasons must be documented on the source documents and no further follow-up is necessary. In this case, the missing of protocol-specified tests or assessments between the day of the last dose of the investigational product and the 29th day after the last dose will not be considered as any protocol deviations.

Reasons for removal from investigational product or observation might include:

- withdrawal of full consent
- withdrawal of partial consent
- no consent for extended treatment
- administrative decision by the investigator or the sponsor
- pregnancy (refer to Appendix D)
- ineligibility
- important protocol deviation
- patient noncompliance
- adverse event
- disease progression
- death
- lost to follow-up.

8.2 Replacement of Subjects

Subjects in this study who have not received study treatment may be replaced.

If any major protocol deviation that potentially affects DLT assessment for reasons other than safety concerns as DLT occurs during DLT assessment period, the subject will be excluded from the DLT assessment and additional subjects may be enrolled in this cohort. Additional patients may also be enrolled throughout the study if there seems to be a need for additional data for safety or pharmacokinetics evaluation.

9. SAFETY DATA COLLECTION, RECORDING, AND REPORTING

9.1 Definitions

9.1.1 Adverse Events

An adverse event is any untoward medical occurrence or unintended signs, symptoms, or disease (including abnormal laboratory findings) appears in a subject which does not necessarily have a causal relationship to the study treatment. Adverse events may include the onset of new illness and worsening of pre-existing conditions.

The worsening of pre-existing medical condition indicates that the condition becomes worse in severity, frequency, or duration, or has an association with a significantly worse outcome. A pre-existing condition that has not worsened during the study, and a non-emergent medical procedure such as elective cosmetic surgery is not considered an adverse event.

Disease progression itself is not considered as an adverse event; however, signs and symptoms of disease progression will be recorded as adverse events. If a new primary malignancy appears, it will be regarded as an adverse event.

The investigator is responsible for reviewing laboratory test results and determining whether an abnormal value in an individual study subject represents a change from values before the study. In general, abnormal laboratory findings without clinical significance (based on the investigator's judgment) should not be recorded as adverse events; however, laboratory value changes requiring therapy or adjustment in prior therapy are regarded as adverse events.

9.1.2 Serious Adverse Events

A serious adverse event is defined as an adverse event that

- is fatal
- is life threatening (places the subject at immediate risk of death)
- requires in-patient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity

- is a congenital anomaly/birth defect
- is other significant medical hazard

A hospitalization meeting the regulatory definition for "serious" is any inpatient hospital admission that includes a minimum of an overnight stay in a health care facility. Any adverse event that does not meet the definitions of serious (e.g., emergency room visit, outpatient surgery, or requires urgent investigation) may be considered by the investigator to meet the "other significant medical hazard" criterion for classification as a serious adverse event.

9.2 All Adverse Events Reporting Procedures

The investigator is responsible for ensuring that all adverse events (as defined in "Section 9.1 Definitions" and as further specified below) observed by the investigator or reported by subjects are collected and recorded in the subjects' medical records, in the eCRF, and, for serious adverse events, on the serious adverse event report form. These adverse events will include the following:

- All non-serious adverse events (as defined in "Section 9.1.1 Adverse Events") that occur after initiation of investigational product to an end-of-study.
- All serious adverse events (as defined in "Section 9.1.2 Serious Adverse Events") that occur after the subject has signed the informed consent form to an end-of-study, and treatment-related serious adverse events that occur after the end-of-study.

The following adverse event attributes must be assigned by the investigator. The sponsor may ask the investigator to provide follow-up information, extracts from medical record, or eCRFs.

- Adverse event diagnosis or syndrome(s) (signs or symptoms if not known)
- Event description (with detail appropriate to the event)
- Dates of onset and resolution
- Severity
- Assessment of relatedness to the study treatment
- Action taken
- Outcome

If applicable, the relationship of the adverse event to the study treatment will be assessed by Yes or No.

CTCAE version 4.03 will be used for grading adverse events.

Adverse events requiring follow-up as determined by the investigator will be followed until resolved or considered stable. If the investigator judged that further follow-up is not necessary or follow-up is not possible before the adverse event is resolved or stable, follow-up may be terminated.

It will be left to the investigator's clinical judgment to determine whether an adverse event is related and of sufficient severity to require the subject's removal from treatment or from the study. A subject may also voluntarily withdraw from treatment due to what he or she perceives as an intolerable adverse event. If either of these situations arises, the subject should be strongly encouraged to undergo an end-of-study assessment and be under medical supervision until symptoms cease or the condition becomes stable.

9.3 Serious Adverse Event Reporting Procedures

All serious adverse events that occur after the subject has signed the informed consent form must be reported to the sponsor within 24 hours of discovery or notification of the event. Initial serious adverse event information and all amendments or additions must be recorded on a serious adverse event report form and submitted to the sponsor. Copies of relevant medical records should be submitted to the sponsor as soon as they become available; autopsy reports should be provided for deaths if available.

Serious adverse events occurring after the end of the study and thought to be possibly related to the study treatment will be collected and reported within 24 hours of discovery or notification of the event.

If a subject is permanently withdrawn from the treatment or from the study because of a serious adverse event, this information must be included in the initial or follow-up serious adverse event report form as well as the eCRF.

As a principle, initial information of a serious adverse event must be recorded on a predefined serious adverse event report form [initial report] and faxed by the investigator to the sponsor. The original initial report must be submitted to the study monitor.

The principal investigator should submit detailed information without delay after notification of initial information. As a principle, detailed report(s) must be recorded on a predefined serious adverse event report form and faxed to the sponsor. The original detailed report(s) must be submitted to the study monitor. If amendment is needed, the amendment should be reported according to the same procedure.

An operator of the Emergency Center for Safety Information is also available for contact 24 hours 365 days.

Emergency center for safety information (available 24 hours 365 days)

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The principal investigator should inform the head of the medical institution of all serious adverse events occurring at the center in accordance with procedures required at the center and notify the sponsor according to this protocol.

Determination of expectedness will be based on the contents in the latest investigator's brochure (including information on the adverse events that have already been reported to the medical institution).

10. STATISTICAL CONSIDERATIONS

10.1 Endpoints and Analysis Set

10.1.1 Primary Endpoint

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

10.1.2 Secondary Endpoints

- Numbers of subjects achieving CR, VGPR, and PR

10.1.3 Analysis Set

DLT Analysis Set:

The DLT analysis set will consist of DLT evaluable subjects who received at least one dose of MLN9708 (see 6.7.2).

Safety Analysis Set:

The safety analysis set will consist of all subjects who received at least one dose of MLN9708.

Response Evaluable Analysis Set:

The response evaluable analysis set will consist of all subjects who received at least one dose of MLN9708, have measurable disease at baseline, and at least one postbaseline response assessment.

Pharmacokinetic analysis set:

The pharmacokinetic analysis set will consist of all subjects who received at least one dose of MLN9708 and has evaluable pharmacokinetic data.

10.2 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.

10.3 Interim Analysis and Early Stopping Guidelines

No interim analysis is planned in this study.

10.4 Statistical Methods of Analysis

The demographic data and all endpoints data will be analyzed. Summary statistics (numbers of subjects, mean, median, standard deviation, maximum, minimum) will be calculated for continuous data. Frequencies and proportions will be tabulated for categorical data.

Details are presented in the statistical analysis plan.

10.4.1 Safety endpoints

Unless otherwise specified, the following safety endpoints will be analyzed for the subjects in the safety analysis set.

10.4.1.1 DLT

DLTs will be summarized in the DLT analysis set.

10.4.1.2 Adverse events

The incidence and percentage of treatment-emergent adverse events will be summarized by system organ class (SOC) and preferred term (PT) of ICH Medical Dictionary for Regulatory Activities (MedDRA) and by grade. In addition, the following adverse events will be summarized by the same method. Severity will be graded with CTCAE version 4.03.

- Serious adverse events
- Adverse events leading to permanent discontinuation of study treatment
- Treatment-related adverse events

- Treatment-related serious adverse events
- Treatment-related adverse events leading to permanent discontinuation of study treatment

10.4.1.3 Laboratory tests

Summary statistics will be calculated for the changes in continuous data from baseline to postdose assessment. In addition, the shift from baseline to the postdose worst grade will be tabulated for selected laboratory parameters in accordance with CTCAE version 4.03.

10.4.1.4 Other safety analyses

Vital signs, 12-lead ECGs, body weight, ECOG performance status, etc. will be summarized.

10.4.2 Efficacy endpoints

Unless otherwise specified, the following efficacy endpoint analyses will be performed for subjects in the response evaluable analysis set.

10.4.2.1 Tumor response

The numbers of patients achieving CR, VGPR and PR will be assessed in accordance with the International Myeloma Working Group Uniform Response Criteria for Multiple Myeloma. Where possible, the objective response rate (CR + VGPR + PR) will also be summarized.

10.4.3 Pharmacokinetic analysis

In the pharmacokinetic analysis set, non- compartment model analysis will be performed based on the MLN2238 plasma concentration profile, and the pharmacokinetic parameters (e.g., C_{max}, AUC) will be calculated. The summary statistics will also be calculated for each parameter by dose. In addition to calculating the summary statistics of the MLN2238 plasma concentration at each blood sample collection time, specified in the study protocol, by dose, figures of profiles (both individual and mean concentration) will also be prepared by dose. Furthermore, a compartment model analysis may be performed based on the MLN2238 plasma concentration profile.

11. REGULATORY OBLIGATIONS

11.1 Quality Control of Data and Quality Assurance

This study will be conducted in compliance with "Ministerial Ordinance Concerning the Standards for the Conduct of Clinical Trials of Medicinal Products" (Ministry of Health, Labour and Welfare [MHLW] Ordinance No. 28, 27 March 1997) including relevant MHLW notifications (J-GCP), Pharmaceutical Affairs Law, and the protocol of this study, and based on the Helsinki Declaration, the protection of the human rights of subjects will be given first priority.

Quality control of data will be conducted following the sponsor's standard operating procedures related to the conduct of clinical studies. The sponsor's audit, which is independent of and separate from routine monitoring or quality control functions, will ascertain, for quality assurance of a clinical trial, whether the clinical trial is conducted in compliance with the J-GCP, the protocol, and the operating procedures.

11.2 Informed Consent

An initial generic informed consent template form is provided for the principal investigator to prepare the informed consent document to be used at the site. Updates to the template will be communicated by letter from the sponsor to the principal investigator. The written informed consent document should be prepared in Japanese.

Before a subject's participation in the clinical study, the investigator is responsible for obtaining written informed consent from the subject after fully informing the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol-specific screening procedures or any investigational products are administered.

The acquisition of informed consent should be documented in the subject's medical records, and the informed consent form should be signed and personally dated by the subject, by the investigator and by the person who conducted the informed consent discussion. The original signed informed consent form should be retained in accordance with institutional policy, and a copy of the signed consent form should be provided to the subject or legally acceptable representative.

If a potential subject is illiterate or visually impaired, the investigator must provide an impartial witness to read the informed consent form to the subject and must allow for questions. Thereafter, both the subject and the witness must sign the informed consent form to attest that informed consent was freely given and understood.

11.3 Institutional Review Board

A copy of the protocol, proposed informed consent form, other written subject information, and any proposed advertising material must be submitted to the institutional review board (IRB) for written approval. A copy of the written approval of the protocol and informed consent document must be received by the sponsor before recruitment of subjects into the study and shipment of investigational product.

The sponsor must submit and, where necessary, obtain approval from the IRB for protocol amendments and changes to the informed consent document if applicable. The investigator should notify the head of the medical institution of deviations from the protocol or serious adverse events occurring at the site and other adverse event reports received from the sponsor, in accordance with local procedures.

The investigator will be responsible for obtaining annual approval/renewal of the head of the medical institution throughout the duration of the study. Copies of the investigator's reports and the head of the medical institution's continuance of approval must be sent to the sponsor.

11.4 Subject Confidentiality

The investigator must ensure that the subject's confidentiality is maintained:

- On the eCRFs or other documents submitted to the sponsor, subjects should be identified by the subject identification number only.
- On the serious adverse event forms submitted to the sponsor, subjects should be identified by a subject study number only.
- Documents that are not for submission to the sponsor (e.g., signed informed consent forms) should be kept in strict confidence by the investigator.

In compliance with J-GCP, it is required that the investigator and institution permit authorized representatives (study monitors or auditors) of the company, of the regulatory

agency(s), and the IRB direct access to review the subject's original medical records for verification of study-related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study. The investigator is obligated to inform and obtain the consent of the subject to permit named representatives to have access to his/her study-related records without violating the confidentiality of the subject.

11.5 Dissemination of New Information

When information important to the proper conduct of the clinical study becomes available such as on diseases, impairment, and deaths suspected to be due to the effect of the investigational product, onset of infections suspected to be due to the use of the investigational product, and other information related to the investigational product quality, efficacy, and safety, the sponsor will promptly notify the investigators, the heads of medical institution, medical experts, and the ESEC in writing and take necessary measures. Of note, the sponsor will finish the report to the ESEC at the end of October 2016.

Once it is determined that the information provided by the sponsor may affect a subject's willingness to continue participation, the investigator should promptly provide the information to the subjects, document, and ensure his/her willingness to continue participation. When the sponsor requires the investigator to ensure the subject's willingness to continue participation, or the investigator obtains information that may affect a subject's willingness to continue participation as well, the investigator will ensure the subject's willingness to continue participation.

12. ADMINISTRATIVE AND LEGAL OBLIGATIONS

12.1 Protocol Amendments and Study Termination

Protocol amendments, except where necessary to eliminate an immediate hazard to subjects, must be made only with the prior approval by the sponsor. The head of the medical institution must be informed of amendments and give approval if applicable. The medical institution must send a copy of the approval letter from the head of the medical institution to the sponsor.

Both the sponsor and the principal investigator reserve the right to terminate the study, according to the study contract. The principal investigator should notify the head of the medical institution in writing of the study's completion or early termination and send a copy of the notification to the sponsor.

12.2 Source Data and Essential Documents

The study center must comply with inspection by sponsor's study monitors, auditors, IRB, and regulatory authorities and make available for direct inspection all clinical study-related records.

After coordinating the method, timing, and schedule for source data verification beforehand with the investigator and clinical study management office of the study center, the study monitor will confirm through direct access that all clinical study-related records are in order and are stored appropriately and that the contents are accurate and complete.

Source data verification by study monitors will be conducted in accordance with "Monitoring Plan" to be provided separately.

In this study, an eCRF may be used as source data.

- eligibility
- medical and surgical history
- reason for discontinuation or change of study treatment
- purpose of the use of concomitant medications
- reason for study termination

- investigator's comments
- presence or absence of adverse events, intermittence (repeated appearance and disappearance), severity, seriousness, and relationship with investigational product

No study document should be destroyed without prior written agreement between the sponsor and the medical institution. Should the medical institution wish to assign the management of study records to another party or move them to another location, he/she must notify the sponsor in writing of the new responsible person and/or the new location.

12.3 Data Handling and Retention of Records

12.3.1 Data Handling

All data capture for this study will be eCRF using electronic data capture (EDC) system. Case report form is taken as synonymous with eCRF. The sponsor offers the training to investigators and clinical research coordinators for eCRF completion guidelines and/or acquiring EDC access privileges.

The sponsor ensures that the data is compliance with the protocol and J-GCP and creates electronic queries for the medical institution to resolve any questions.

The principal investigator review all eCRF data including the response to queries and data changes, then the principal investigator will sign off eCRF electronically (eSignature) as indicating approval for the all entries on eCRF. The principal investigator is responsible for the accuracy and reliability of eCRF data.

Sponsor's clinical data management department may correct the data for the following eCRF issues with notification to the sites.

- Revision of administrative data such as visit no. on eCRF generated by unscheduled visit or re-examination.
- Deletion of the entry in "Other" option and change to another option if the entry in "Other" option should be filled in correct option.

12.3.2 Retention of Records

The medical institution must maintain the following records (including documents) till the day on which manufacturing or import approval of the test product is obtained (or the

day 3 years after the date of notification in case of a notification pursuant to Article 24, Paragraph 3) or the day 3 years after the date of premature termination or completion of the clinical study, whichever is the later.

1) Source documents
2) The contract, informed consent forms, written information and other documents prepared by persons engaged in the medical institution pursuant to the J-GCP or their copies.
3) The protocol, documents obtained from the institutional review board pursuant to Article 32, Paragraphs 1, 2, and 3, and other documents obtained pursuant to the J-GCP.
4) Records of investigational product control and other study-related duties.

The sponsor will obtain the following data via electronic means from a third-party measurement service. The electronic data provided by the third-party measurement service will be used as source documents.

12.4 Language

The eCRF must be completed in English.

All written information and other material to be used by subjects and investigative staff must use vocabulary and language that are clearly understood.

12.5 Publication Policy

Authorship of any publications resulting from this study will be determined on the basis of the Uniform Requirement for Manuscripts Submitted to Biomedical Journals, which states:

- Authorship credit should be based on (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; (3) final approval of the version to be published. Authors should meet conditions 1, 2, and 3.
- When a large, multicenter group has conducted the work, the group should identify the individuals who accept direct responsibility for the manuscript. These individuals should fully meet the criteria for authorship defined above.
- Acquisition of funding, collection of data, or general supervision of the research group, alone, does not justify authorship.

- All persons designated as authors should qualify for authorship, and all those who qualify should be listed.
- Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content.

All publications (e.g., manuscripts, abstracts, oral/slide presentations, book chapters) based on this study must be submitted to the sponsor for corporate review. The Clinical Study Agreement among the institution, the principal investigator, and the sponsor will detail the procedures for, and timing of, sponsor's review of publications.

12.6 Compensation

Subjects will be treated and/or compensated for any study-related illness/injury pursuant to the information provided in the compensation for injury section of the informed consent document, which describes any compensation that will be provided during the study. However, if the liability for damages is determined to be due to deliberateness or negligence on the he part of research facilities and/or due to deliberateness or gross negligence on the part of subjects, the compensation will be adjusted accordingly or waived altogether.

12.7 Financing

The financial aspects of the study should be documented in an agreement between the sponsor and the institution.

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Summary of Changes for Protocol Amendment

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

Version 3.2 → Version 3.3

Protocol Number: TB-MC010034

Date of Amendment: 22 November 2016

Protocol Change Memo

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

Date for version 3.3: 22 November 2016

Section	Replaced	With	Rationale
Header	Date: 18 November 2015	Date: 22 November 2016	New version.
Title Page	Version/Date: Version 3.2 18 November 2015	Version/Date: Version 3.3 22 November 2016	New version.
Document History	Document History Version 1: 12 January 2012 Version 2: 7 February 2012 Version 2.1: 7 March 2012 Version 2.2: 11 September 2012 Version 3: 4 December 2013 Version 3.1: 4 December 2014	Document History Version 1: 12 January 2012 Version 2: 7 February 2012 Version 2.1: 7 March 2012 Version 2.2: 11 September 2012 Version 3: 4 December 2013 Version 3.1: 4 December 2014 Version 3.2: 18 November 2015	Document history is updated.
3. EXPERIMENTAL PLAN 3.4 Estimated Study Duration	The study will be conducted between March 2012 and March 2017.	The study will be conducted between March 2012 and March 2019.	Extended the estimated study duration according to the progress of the study.
6. TREATMENT PROCEDURES 6.9 Excluded Concomitant Medications and Procedures	• Systemic treatment with strong inhibitors of CYP1A2 (fluvoxamine, enoxacin), strong inhibitors of CYP3A (clarithromycin, telithromycin, itraconazole, voriconazole, ketoconazole) or strong CYP3A inducers (rifampicin, rifabutin, carbamazepine, phenytoin, phenobarbital), or use/ intake of foods containing Ginkgo biloba extract, St. John's wort, or grapefruit during the study.	• Systemic treatment with strong CYP3A inducers (rifampicin, rifabutin, carbamazepine, phenytoin, phenobarbital), or use/ intake of foods containing St. John's wort during the study.	The inhibitors of CYP1A2 and CYP3A does not affect on pharmacokinetics of MLN 9708 based on the study results.

____ : Amended texts

Protocol Change Memo

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

Date for version 3.3: 22 November 2016

Section	Replaced	With	Rationale
11. REGULATORY OBLIGATIONS 11.5. Dissemination of New Information	When information important to the proper conduct of the clinical study becomes available such as on diseases, impairment, and deaths suspected to be due to the effect of the investigational product, onset of infections suspected to be due to the use of the investigational product, and other information related to the investigational product quality, efficacy, and safety, the sponsor will promptly notify the investigators, the heads of medical institution, medical experts, and the ESEC in writing and take necessary measures.	When information important to the proper conduct of the clinical study becomes available such as on diseases, impairment, and deaths suspected to be due to the effect of the investigational product, onset of infections suspected to be due to the use of the investigational product, and other information related to the investigational product quality, efficacy, and safety, the sponsor will promptly notify the investigators, the heads of medical institution, medical experts, and the ESEC in writing and take necessary measures. <u>Of note, the sponsor will finish the report to the ESEC at the end of October 2016.</u>	Report of new information to ESEC was finished.

____ : Amended texts

Summary of Changes for Protocol Amendment

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

Version 3.1 → Version 3.2

Protocol Number: TB-MC010034

Date of Amendment: 18 November 2015

Protocol Change Memo

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

Date for version 3.2: 18 November 2015

Section	Replaced	With	Rationale
Header	Product: MLN9708 Protocol Number: TB-MC010034 Date: 4 December 2014	Product: MLN9708 Protocol Number: TB-MC010034 Date: 18 November 2015	New version.
Document History	Document History Version 1: 12 January 2012 Version 2: 7 February 2012 Version 2.1: 7 March 2012 Version 2.2: 11 September 2012 Version 3: 4 December 2013	Document History Version 1: 12 January 2012 Version 2: 7 February 2012 Version 2.1: 7 March 2012 Version 2.2: 11 September 2012 Version 3: 4 December 2013 Version 3.1: 4 December 2014	Document history is updated.
3. EXPERIMENTAL PLAN 3.4 Estimated Study Duration	The study will be conducted between March 2012 and March 2016.	The study will be conducted between March 2012 and March 2017.	Extended the estimated study duration according to the progress of the study.

____ : Amended texts

Summary of Changes for Protocol Amendment

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

Version 3 → Version 3.1

Protocol Number: TB-MC010034

Date of Amendment: 4 December 2014

Protocol Change Memo

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

Date for version 3.1: 4 December 2014

Section	Replaced	With	Rationale
Header	Product: MLN9708 Protocol Number: TB-MC010034 Date: 4 December 2013	Product: MLN9708 Protocol Number: TB-MC010034 Date: 4 December 2014	New version.
Title Page	Clinical Study Sponsor: Takeda Bio Development Center Company Limited 1-7-12, Marunouchi, Chiyoda-ku, Tokyo, 100-0005, Japan PPD PPD Version/Date: Version 3 4 December 2013 Confidentiality Notice This document contains confidential information of Takeda Bio Development Center Limited. This document must not be disclosed to anyone other than the study staff and members of the institutional review board. The information in this document cannot be used for any purpose other than the evaluation or conduct of the clinical study without the prior written consent of Takeda Bio Development Center Limited. If you have questions regarding how this document may be used or shared, or other study-related questions, contact the Clinical Study Sponsor.	Clinical Study Sponsor: Takeda Pharmaceutical Company Limited 1-1, Doshomachi 4-chome, Chuo-ku, Osaka, 540-8645, Japan Version/Date: Version 3.1 4 December 2014 This document contains confidential information of Takeda Pharmaceutical Company Limited. This document must not be disclosed to anyone other than the study staff and members of the institutional review board. The information in this document cannot be used for any purpose other than the evaluation or conduct of the clinical study without the prior written consent of Takeda Pharmaceutical Company Limited. If you have questions regarding how this document may be used or shared, or other study-related questions, contact the Clinical Study Sponsor.	Description adjustment and new version.

____ : Amended texts

Protocol Change Memo

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

Date for version 3.1: 4 December 2014

Section	Replaced	With	Rationale
Document History	Document History Version 1: 12 January 2012 Version 2: 7 February 2012 Version 2.1: 7 March 2012 Version 2.2: 11 September 2012	Document History Version 1: 12 January 2012 Version 2: 7 February 2012 Version 2.1: 7 March 2012 Version 2.2: 11 September 2012 Version 3: 4 December 2013	Document history is updated.
Protocol Summary	**Sponsor:** Takeda Bio Development Center Limited	**Sponsor:** Takeda Pharmaceutical Company Limited	Description adjustment.
3. EXPERIMENTAL PLAN 3.4 Estimated Study Duration	The study will be conducted between March 2012 and March 2015.	The study will be conducted between March 2012 and March 2016.	Extended the estimated study duration according to the progress of the study.
5. SUBJECT ENROLLMENT 5.1 Enrollment Procedures	MLN9708 (TB-MC010034) Subject Registration Center Takeda Bio Development Center Limited Sapia Tower, 1-7-12 Marunouchi, Chiyoda-ku, Tokyo, Japan PPD PPD PPD	MLN9708 (TB-MC010034) Subject Registration Center Takeda Pharmaceutical Company Limited Marunouchi Eiraku Building, 1-4-1 Marunouchi, Chiyoda-ku, Tokyo, Japan PPD PPD PPD	Description adjustment.

____ : Amended texts

Protocol Change Memo

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

Date for version 3.1: 4 December 2014

Section	Replaced	With	Rationale
6. TREATMENT PROCEDURES 6.1 MLN9708	MLN9708 is manufactured (including packaging and labeling) by MPI and supplied by Takeda Bio Develoment Center.	MLN9708 is manufactured (including packaging and labeling) by MPI and supplied by Takeda Pharmaceutical Company.	Description adjustment.
14. APPENDICES Appendix D. Pregnancy Notification Worksheet	Fax to: Clinical Development DIV, Takeda Bio Development Center Company Limited	Fax to: Clinical Development DIV, Takeda Pharmaceutical Company Limited	Description adjustment.

____ : Amended texts

Summary of Changes for Protocol Amendment

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

Version 2.2 → Version 3

Protocol Number: TB-MC010034

Date of Amendment: 4 December 2013

Protocol Change Memo

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

Date for version 3: 4 December 2013

Section	Replaced	With	Rationale
Header	Product: MLN9708 Protocol Number: TB-MC010034 Date: 11 September 2012	Product: MLN9708 Protocol Number: TB-MC010034 Date: 4 December 2013	New version.
Title Page	Version/Date: Version 2.2 11 September 2012	Version/Date: Version 3 4 December 2013	New version.
Document History	Document History Version 1: 12 January 2012 Version 2: 7 February 2012 Version 2.1: 7 March 2012	Document History Version 1: 12 January 2012 Version 2: 7 February 2012 Version 2.1: 7 March 2012 Version 2.2: 11 September 2012	Document history is updated.
Overview of Study Design	The sponsor will evaluate the tolerability of MLN9708 dosage 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 plus Rd), 3 (MLN9708 5.5 mg alone), and 4 (MLN9708 5.5 mg plus Rd).	The sponsor will evaluate the tolerability of MLN9708 dosage 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 plus Rd), 3 (MLN9708 5.5 mg alone), and 4 (MLN9708 5.5 mg plus 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.	Added description for the case where the next cohort will not be studied.

____ : Amended texts

Protocol Change Memo

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

Date for version 3: 4 December 2013

Section	Replaced	With	Rationale
3. EXPERIMENTAL PLAN 3.1 Study Design	The sponsor will evaluate the tolerability of MLN9708 dosage 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 plus Rd), 3 (MLN9708 5.5 mg alone), and 4 (MLN9708 5.5 mg plus Rd).	The sponsor will evaluate the tolerability of MLN9708 dosage 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 plus Rd), 3 (MLN9708 5.5 mg alone), and 4 (MLN9708 5.5 mg plus 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.	Added description for the case where the next cohort will not be studied.
3. EXPERIMENTAL PLAN 3.4 Estimated Study Duration	The study will be conducted between March 2012 and September 2014.	The study will be conducted between March 2012 and March 2015.	Extended the estimated study duration according to the progress of the study.
6. TREATMENT PROCEDURES 6.6 Cohort Transition and Early Stopping Guidelines 6.6.1 Cohort Transition	N/A	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.	Added description for the case where the next cohort will not be studied.

____ : Amended texts

Summary of Changes for Protocol Amendment

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

Version 2.1 → Version 2.2

Protocol Number: TB-MC010034

Date of Amendment: 11 September 2012

Protocol Change Memo

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

Date for version 2.2: 11 September 2012

Section	Replaced	With	Rationale
Header	Product: MLN9708 Protocol Number: TB-MC010034 Date: 7 March 2012	Product: MLN9708 Protocol Number: TB-MC010034 Date: 11 September 2012	New version.
Title Page	Key Sponsor Contact: PPD PPD PPD PPD	Deleted	New template.
Title Page	Version/Date: Version 2.1 7 March 2012	Version/Date: Version 2.2 11 September 2012	New version.
Document History	Document History Version 1: 12 January 2012 Version 2: 7 February 2012	Document History Version 1: 12 January 2012 Version 2: 7 February 2012 Version 2.1: 7 March 2012	Document history is updated.
6. TREATMENT PROCEDURES 6.5.2.2.2 Dose Modification for Neutropenia	If ANC count is less than 1,000/mm^3 in Cycle 2 or subsequent cycles, lenalidomide dose should be interrupted. ...*snip*... G-CSF is not permitted in Cycle 1 unless Grade 4 neutropenia occurs (See section 6.8 Excluded Concomitant Medications and Procedures).	If ANC count is less than 1,000/mm^3 in Cycle 2 or subsequent cycles, lenalidomide dose should be interrupted. ...*snip*... G-CSF is not permitted in Cycle 1 unless Grade 4 neutropenia occurs (See section 6.9 Excluded Concomitant Medications and Procedures).	Description amendment

____ : Amended texts

Protocol Change Memo

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

Date for version 2.2: 11 September 2012

Section	Replaced	With	Rationale
6. TREATMENT PROCEDURES 6.5.2.3.2 MLN9708 Treatment Modification	Table 6-9 Adverse Event (Severity): Grade 2 peripheral neuropathywith pain, Grade 3 non-hematological toxicity Action on MLN9708: Reduce MLN9708 by 1 dose level	Table 6-9 Adverse Event (Severity): Grade 2 peripheral neuropathywith pain, Grade 3 non-hematological toxicity Action on MLN9708: MLN9708 may be reinitiated with one dose level reduction.	Clear explanation
6. TREATMENT PROCEDURES 6.7.3 Definitions of DLT	7. Any other Grade 3 or greater nonhematologic toxicities with the following exceptions: ...*snip*... •Grade 3 or greater nausea and/or emesis without the use of optimal anti-emetic prophylaxis. Optimal anti-emetic prophylaxis is defined as an anti-emetic regimen that employs a 5-HT3 antagonist given in standard doses and according to standard schedules. Dexamethasone should not be administered as an anti-emetic. •Diarrhea that does not require treatment	7. Any other Grade 3 or greater nonhematologic toxicities with the following exceptions: ...*snip*... •Grade 3 nausea and/or emesis which can be controlled with anti-emetic therapies including anti-emetic prophylaxis. Anti-emetic prophylaxis is defined as an anti-emetic regimen that employs a 5-HT3 antagonist given in standard doses and according to standard schedules. Dexamethasone should not be administered as an anti-emetic. • Grade 3 Diarrhea that is controlled with appropriate supportive care	In ver 2.1 PRT, the sponsor's intention was not described clear enough. Therefore to avoid any potential misinterpratation, we decided to amend the description to be more specific.
6. TREATMENT PROCEDURES 6.8 Permitted Concomitant Medications and Procedures	N/A	6.8 Permitted Concomitant Medications and Procedures Throughout the study, investigators may prescribe any concomitant medications or perform procedures deemed necessary to provide adequate supportive care except for those listed in "6.9 Excluded Concomitant Medications and Procedures"	Added new section for clarification

____ : Amended texts

Protocol Change Memo

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

Date for version 2.2: 11 September 2012

Section	Replaced	With	Rationale
7. STUDY PROCEDURES 7.2.2 Treatment period	· Body weight – Cycle 1: Before MLN9708 dosing on Day 1. If a patient's body weight has been measured within 3 days before the first dose, then this measurement may be used for the Cycle 1 Day 1 data.	· Body weight – Cycle 1: Before MLN9708 dosing on Day 1. If a patient's body weight at screening is measured within 3 days before the first dose, then this measurement may be used for the Cycle 1 Day 1 data.	Clear explanation
7. STUDY PROCEDURES 7.2.2 Treatment period	• Urine M-protein (electrophoresis protein fraction test): ...*snip*... **Subjects whose urine M-protein has been detected in serum and urine at screening** –Measurement by 24-hour urine collection. • If a response assessment requires confirmation or disease progression is suspected (see Appendix G), a urine M-protein measurement will be collected as appropriate using 24-hour urine collection.	• Urine M-protein (electrophoresis protein fraction test): ...*snip*... **Subjects whose urine M-protein has been detected in serum and urine at screening** –Measurement by 24-hour urine collection. · Urine samples will be collected prior to MLN9708 dosing on Cycle 1 Day 1. If a screening test is performed within 7 days before the first dose, the results may be used as the Cycle 1 Day 1 data. · If a response assessment requires confirmation or disease progression is suspected (see Appendix G), a urine M-protein measurement will be collected as appropriate using 24-hour urine collection.	Clear explanation
7. STUDY PROCEDURES 7.2.3 End of study	• Urine M-protein by 24-hour urine collection (protein fraction test by electrophoresis): Performed only for subjects whose urine M-protein was detected by immunofixation and electrophoresis protein fraction test at screening.	• Urine M-protein by 24-hour urine collection (protein fraction test by electrophoresis): Performed only for subjects whose urine M-protein is detected at screening.	Correction of errors.

____ : Amended texts

Protocol Change Memo

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

Date for version 2.2: 11 September 2012

<table>
<tr><th>Section</th><th>Replaced</th><th>With</th><th>Rationale</th></tr>
<tr><td>7. STUDY PROCEDURES
7.2.6 Pharmacokinetic sample collection time points</td><td>Table 7-2
<table><tr><td>Cycle 2</td><td>Day 1</td><td>Predose</td></tr></table></td><td>Table 7-2
<table><tr><td>Cycle 2</td><td>Day 1</td><td>Predose <u>(336 hours postdose)</u></td></tr></table></td><td>Clear explanation</td></tr>
<tr><td>8. REMOVAL AND REPLACEMENT OF SUBJECTS
8.1 Removal of Subjects</td><td>Subjects have the right to withdraw fully or partially from the study at any time and for any reason.
...*snip*...
In this case, the missing of protocol-specified tests or assessments on the 29th day after the last dose of the investigational product will not be considered as any protocol deviations.</td><td>Subjects have the right to withdraw fully or partially from the study at any time and for any reason.
...*snip*...
In this case, the missing of protocol-specified tests or assessments <u>between the day of the last dose of the investigational product and</u> the 29th day after the last dose will not be considered as any protocol deviations.</td><td>Clear explanation</td></tr>
<tr><td>14. APPENDICES
Appendix A. Schedule of Assessments</td><td><table><tr><td></td><td>Cycle 1
Day1</td><td>EOS</td></tr><tr><td>Urine M-protein Measurement (24hr Urine Collection)</td><td>X[m]</td><td>X</td></tr></table></td><td><table><tr><td></td><td>Cycle 1
Day 1</td><td>EOS</td></tr><tr><td>Urine M-protein Measurement (24hr Urine Collection)</td><td>▲[m]</td><td>▲</td></tr></table></td><td>Correction of errors.</td></tr>
<tr><td>14. APPENDICES
Appendix A. Schedule of Assessments</td><td><table><tr><td></td><td>EOS</td></tr><tr><td>CT/MRI (chest,abdomen)[o]</td><td>X</td></tr></table></td><td><table><tr><td></td><td>EOS</td></tr><tr><td>CT/MRI (chest,abdomen)[o]</td><td>X[o]</td></tr></table></td><td>Description amendment.</td></tr>
</table>

____ : Amended texts

Protocol Change Memo

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

Date for version 2.2: 11 September 2012

Section	Replaced	With	Rationale
14. APPENDICES Appendix A. Schedule of Assessments Note	Footnote ▲For a patient with M-protein detected only in urine at screening, spot urine is to be performed every 2 cycles for urine M-protein predose of MLN9708 on Day 1 of Cycle 3 and subsequent cycles (Cycle 3, 5, 7, 9, 11, and so on [odd-numbered cycles]) (Urine collection during Days 23 through 28 of previous cycle is acceptable). For subjects whose M-protein has been detected in serum and urine at screening, if a response assessment requires confirmation or disease progression (see Appendix G) is suspected, a urine M-protein measurement will be collected as appropriate	Footnote ▲For a patient with M-protein detected only in urine at screening, spot urine is to be performed every 2 cycles for urine M-protein predose of MLN9708 on Day 1 of Cycles 1, 3 and subsequent cycles (Cycle 3, 5, 7, 9, 11, and so on [odd-numbered cycles]) (Urine collection during Days 23 through 28 of previous cycle is acceptable). Also conduct at EOS visit. For subjects whose M-protein is detected in serum and urine at screening, urine samples will be collected prior to MLN9708 dosing on Cycle 1 Day 1. If a response assessment requires confirmation or disease progression (see Appendix G) is suspected, a urine M-protein measurement will be collected as appropriate. Also conduct at EOS visit.	Clear explanation

____ : Amended texts

Summary of Changes for Protocol Amendment

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

Version 2 → Version 2.1

Protocol Number: TB-MC010034

Date of Amendment: 7 March 2012

Protocol Change Memo

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

Date for version 2.1: 7 March 2012

Section	Replaced	With	Rationale
Header	Product: MLN9708 Protocol Number: TB-MC010034 Date: 7 February 2012	Product: MLN9708 Protocol Number: TB-MC010034 Date: 7 March 2012	New version.
Title Page	Key Sponsor Contact: Development Operations 2, Clinical Development Division	Key Sponsor Contact: Development Operations, Clinical Development	Reorganization due to conversion of business entity.
Title Page	Version/Date: Version 2 7 Febuary 2012	Version/Date: Version 2.1 7 March 2012	New version.
Document History	Document History Version 1: 12 January 2012	Document History Version 1: 12 January 2012 Version 2: 7 February 2012	Document history is updated.
1.6.1 Lenalidomide	In this study, subjects will be registered in accordance with the CCI [redacted] proper management procedures	In this study, subjects will be registered in accordance with the lenalidomide proper management procedures	Description amendment.
5.2 CCI [redacted] Registration	The CCI [redacted] procedures must be followed when providing CCI [redacted] to the subjects in the MLN9708 with Rd cohort in the study.	The CCI [redacted] procedures must be followed when providing lenalidomide to the subjects in the MLN9708 with Rd cohort in the study.	Description amendment.
6. TREATMENT PROCEDURES 6.5.2.3.4 Dexamethasone Treatment Modification	Table 6-11 Adverse Events: Others; CTCAE: ≥ Grade 3; Action: Hold dexamethasone until toxicity has resolved to ≤ Grade 2	Table 6-11 Deleted	Correction of errors
7 STUDY PROCEDURES 7.2.1 Screening period	· Subject background (including medical history, concomitant disease, details of multiple myeloma diagnosis [date of diagnosis, histological type, current clinical stage], history of prior-treatment for multiple myeloma [chemotherapy, radiotherapy, transplantation, surgery])	· Subject background (including medical history, concomitant disease, details of multiple myeloma diagnosis [date of diagnosis, histological type, current clinical stage] (see Appendix H), history of prior-treatment for multiple myeloma [chemotherapy, radiotherapy, transplantation, surgery])	Clear explanation

____ : Amended texts

Protocol Change Memo

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

Date for version 2.1: 7 March 2012

Section	Replaced	With	Rationale
7 STUDY PROCEDURES 7.2.1 Screening period	· CT/MRI (chest, abdomen) Unless a patient shows hypersensitivity to contrast, all CT/MRI should be performed with contrast.	· CT/MRI (chest, abdomen) Unless a patient shows hypersensitivity to contrast or concern for potential aggravation of renal dysfunction, all CT/MRI should be performed with contrast.	Clear explanation
7 STUDY PROCEDURES 7.2.2 Treatment period	· Vital signs (sitting blood pressure, pulse rate and axillary temperature, SpO2) – Cycle 1: Days 1, 8 and 15 – Cycles 2 and subsequent cycles: Days 1 and 15	· Vital signs (sitting blood pressure, pulse rate and axillary temperature, SpO2) – Cycle 1: Days 1, 8 and 15 – Cycles 2 to 12: Days 1 and 15 – Cycle 13 and subsequent cycles: Day 1	Clear explanation
7 STUDY PROCEDURES 7.2.2 Treatment period	· Body weight Cycle 1: Before MLN9708 dosing on Day 1. If a patient's body weight has been measured within 3 days before the first dose, then this measurement may be used as the Cycle 1 Day 1 measurement.	· Body weight Cycle 1: Before MLN9708 dosing on Day 1. If a patient's body weight has been measured within 3 days before the first dose, then this measurement may be used for the Cycle 1 Day 1 data.	Clear explanation t
7 STUDY PROCEDURES 7.2.2 Treatment period	· Laboratory tests: Hematology tests – Cycles 4 and subsequent cycles: Days 1 and 15	· Laboratory tests: Hematology tests – Cycles 4 to 12: Days 1 and 15 – Cycle 13 and subsequent cycles: Day 1	Clear explanation
7 STUDY PROCEDURES 7.2.2 Treatment period	· Laboratory tests: Hematology test If a screening test has been performed within 3 days before the first dose, the test may be used as Cycle 1 Day 1 test.	· Laboratory tests: Hematology test If a screening test has been performed within 3 days before the first dose, the result may be used as Cycle 1 Day 1 data.	Clear explanation
7 STUDY PROCEDURES 7.2.2 Treatment period	· Laboratory tests: Chemistry tests – Cycles 4 and subsequent cycles: Days 1 and 15	· Laboratory tests: Chemistry tests – Cycles 4 to 12: Days 1 and 15 – Cycle 13 and subsequent cycles: Day 1	Clear explanation
7 STUDY PROCEDURES 7.2.2 Treatment period	· Laboratory tests: Chemistry test If a screening test has been performed within 3 days before the first dose, the test may be used as Cycle 1 Day 1 test.	· Laboratory tests: Chemistry test If a screening test has been performed within 3 days before the first dose, the result may be used as Cycle 1 Day 1 data.	Clear explanation

____ : Amended texts

Protocol Change Memo

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

Date for version 2.1: 7 March 2012

Section	Replaced	With	Rationale
7 STUDY PROCEDURES 7.2.2 Treatment period	· Urine M-protein (electrophoresis protein fraction test): For subjects whose urine M-protein has been detected at screening, a urine M-protein measurement will be collected using 24-hour urine collection according to the schedule presented below. For subjects whose M-protein has been detected only in the urine, urine M-protein will be measured by casual urine. – Measurement by 24-hour urine collection (Subjects whose urine M-protein has been detected in the urine at screening. *snip* · Urine samples will be collected prior to MLN9708 dosing on Day 1 of Cycles 3, 5, 7, 9, and 11. It will be acceptable to collect samples between Days 23 and 28 of the preceding cycle. – Measurement by casual urine (Subjects whose M-protein has been detected only in urine at screening) · Samples will be collected prior to MLN9708 dosing on Day 1 of Cycles 2, 4, 6, 8, 10, and 12. – If disease progression is suspected (see Appendix G), a urine M-protein measurement will be collected as appropriate using 24-hour urine collection.	· Urine M-protein (electrophoresis protein fraction test): **Subjects whose urine M-protein has been detected only in urine at screening** – Measurement by 24-hour urine collection · Urine samples will be collected prior to MLN9708 dosing on Cycle 1 Day 1. If a screening test has been performed within 7 days before the first dose, the results may be used as the Cycle 1 Day 1 data. · Samples will be collected every 2 cycles prior to MLN9708 dosing on Day 1 of Cycles 3 and subsequent cycles (Cycles 3, 5, 7, 9, 11 and on [odd-numbered cycles]). It will be acceptable to collect samples between Days 23 and 28 of the preceding cycle. – Measurement by casual urine · Samples will be collected every 2 cycles prior to MLN9708 dosing on Day 1 of Cycles 2 and subsequent cycles (Cycles 2, 4, 6, 8, 10, 12 and on [even-numbered cycles]). **Subjects whose urine M-protein has been detected in serum and urine at screening** – Measurement by 24-hour urine collection. · If a response assessment requires confirmation or disease progression is suspected (see Appendix G), a urine M-protein measurement will be collected as appropriate using 24-hour urine collection.	Clear explanation

____ : Amended texts

Protocol Change Memo

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

Date for version 2.1: 7 March 2012

Section	Replaced	With	Rationale
7 STUDY PROCEDURES 7.2.2 Treatment period	· CT/MRI (head, abdomen): – If soft tissue plasmacytoma is found at screening, a CT/MRI scan will be performed every 2 cycles before MLN9708 dosing on Day 1 of Cycle 3, 5, 7, 9, and 11. It will be acceptable to perform the scan between Days 23 and 28 of the preceding cycle. A scan may be performed as appropriate if disease progression is suspected or a response assessment requires confirmation (see Appendix G) if necessary outside a specified cycle. – All diagnostic imaging scans will be performed using contrast media, except for subjects who are hypersensitive to contrast media.	· CT/MRI (head, abdomen): – If soft tissue plasmacytoma is found at screening, a CT/MRI scan will be performed every 2 cycles before MLN9708 dosing on Day 1 of Cycle 3 and subsequent cycles (Cycles 3, 5, 7, 9, 11 and on [odd-numbered cycles]). It will be acceptable to perform the scan between Days 23 and 28 of the preceding cycle. A scan may be performed as appropriate if disease progression is suspected or a response assessment requires confirmation if necessary outside a specified cycle (see Appendix G). – All diagnostic imaging scans will be performed using contrast media, except for subjects who are hypersensitive to contrast media or shows concern for potential aggravation of renal dysfunction.	Clear explanation
7 STUDY PROCEDURES 7.2.2 Treatment period	· Bone marrow aspiration: Percentage of plasma cells in bone marrow (Note: When collecting the sample, anatomical locations that have been irradiated in the past should be avoided.) Bone marrow puncture will be performed as appropriate when disease progression is suspected (see Appendix G).	· Bone marrow aspiration: Percentage of plasma cells in bone marrow (Note: When collecting the sample, anatomical locations that have been irradiated in the past should be avoided.) Bone marrow puncture will be performed as appropriate if a response assessment requires confirmation or when disease progression is suspected (see Appendix G).	Clear explanation
7 STUDY PROCEDURES 7.2.3 End of study	The following assessments will be performed on Day 29 after the last dose (acceptable time window) for subjects who have received MLN9708.	The following assessments will be performed on Day 29 after the last dose (acceptable time window + 21days) for subjects who have received MLN9708.	Correction of errors

____ : Amended texts

Protocol Change Memo

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

Date for version 2.1: 7 March 2012

Section	Replaced	With	Rationale
7 STUDY PROCEDURES 7.2.3 End of study	· CT/MRI (chest, abdomen) – If soft tissue plasmacytoma is found at screening, a CT/MRI scan will be performed. – All diagnostic imaging scans will be performed using contrast media, except for subjects who are hypersensitive to contrast media.	· CT/MRI (chest, abdomen) – If soft tissue plasmacytoma is found at screening, a CT/MRI scan will be performed. – All diagnostic imaging scans will be performed using contrast media, except for subjects who are hypersensitive to contrast media or shows concern for potential aggravation of renal dysfunction.	Clear explanation
7 STUDY PROCEDURES 7.2.4 Laboratory tests	Table 7-1. Study Test Parameters Others Serum M-protein (protein fractionation by electrophoresis)	Table 7-1. Study Test Parameters Others Serum M-protein (protein fractionation by electrophoresis, immunofixation)	Correction of errors
7 STUDY PROCEDURES 7.2.4 Laboratory tests	Table 7-1. Study Test Parameters Others Urine M-protein (protein fractionation by electrophoresis)	Table 7-1. Study Test Parameters Others Urine M-protein (protein fractionation by electrophoresis, immunofixation)	Correction of errors
9. SAFETY DATA COLLECTION, RECORDING, AND REPORTING 9.3 Serious Adverse Event Reporting Procedures	PPD PPD	PPD	Change to reflect the new company name.
13. REFERENCES	N/A	Durie BG. Staging and kinetics of multiple myeloma. *Semin Oncol* 1986;13:300-309. Durie BG, Salmon SE. A clinical staging system for multiple myeloma. Correlation of measured myeloma cell mass with presenting clinical features, response to treatment, and survival *Cancer* 1975;36:842-854. Greipp PR, Miguel JS, Durie BG, Crowley JJ, Barlogie B, Bladé J, et al. International staging system for multiple myeloma. *J Clin Oncol* 2005;23(15):3412-3420.	Refernece in newly added Appendix H.

____ : Amended texts

Protocol Change Memo

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

Date for version 2.1: 7 March 2012

Section	Replaced	With	Rationale
14. APPENDICES Appendix A. Schedule of Assessments	Day: EOS Visit Windows (Day): +14	Day: EOS Visit Windows (Day): +21	Correction of errors
14. APPENDICES Appendix A. Schedule of Assessments	Chemistry: X (Screening)	Chemistry[j]: X[h] (Screening)	Clear explanation
14. APPENDICE Appendix A. Schedule of Assessments	Tests and Observation: Cycle 2 and thereafter; Day 1 FLC: X[k]	Tests and Observation: Cycle 2 and thereafter; Day 1 FLC[k]: (X)[k]	Clear explanation
14. APPENDICE Appendix A. Schedule of Assessments	Tests and Observation: Cycle 2 and thereafter Day: 15 Vital Signs: X Hematology: X Chemistry: X	Tests and Observation: Cycle 2 and thereafter Day: 15 Vital Signs: X[q] Hematology: X[q] Chemistry[i]: X[q]	Clear explanation
14. APPENDICE Appendix A. Schedule of Assessments	Tests and Observation: Cycle 2 and thereafter; Day 1; EOS Immunofixation (serum and urine)[o]: NA; X[o]	Tests and Observation: Cycle 2 and thereafter; Day 1; EOS Immunofixation (serum and urine)[l]: (X)[l]; (X)[l]	Clear explanation
14. APPENDICE Appendix A. Schedule of Assessments	Tests and Observation: Cycle 2 and thereafter; Day 1 Urine M-protein Measurement: X 24hr Urine Collection[m]: X	Tests and Observation: Cycle 2 and thereafter; Day 1 Urine M-protein Measurement (Casual Urine Collection): ● Urine M-protein Measurement (24hr Urine Collection): ▲	Clear explanation

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Protocol Change Memo

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

Date for version 2.1: 7 March 2012

<table>
<tr><th>Section</th><th>Replaced</th><th>With</th><th>Rationale</th></tr>
<tr><td>14. APPENDICE
Appendix A. Schedule of Assessments</td><td>
<table>
<tr><th>Tests and Observation</th><th>Screening</th><th>Cycle 2 and thereafter; Day 1</th><th>EOS</th></tr>
<tr><td>Radiographic assessment (systemic) [q]</td><td>X[q]</td><td></td><td>X</td></tr>
<tr><td>CT/MRI (chest, abdomen) [r]</td><td>X[r]</td><td>X[r]</td><td>X</td></tr>
<tr><td>Bone Marrow Aspiration [k]</td><td>X</td><td>X[k]</td><td></td></tr>
</table>
</td><td>
<table>
<tr><th>Tests and Observation</th><th>Screening</th><th>Cycle 2 and thereafter; Day 1</th><th>EOS</th></tr>
<tr><td>Radiographic assessment (systemic) [n]</td><td>X[n]</td><td></td><td>X[n]</td></tr>
<tr><td>CT/MRI (chest, abdomen) [o]</td><td>X[o]</td><td>X[o]</td><td>X</td></tr>
<tr><td>Bone Marrow Aspiration [k]</td><td>X</td><td>(X)[k]</td><td></td></tr>
</table>
</td><td>Clear explanation</td></tr>
<tr><td>14. APPENDICE
Appendix A. Schedule of Assessments</td><td>
<table>
<tr><th>Tests and Observation</th><th>Cycle 2 and thereafter</th><th>EOS</th></tr>
<tr><td>Response Assessment</td><td>X[s]</td><td>X[s]</td></tr>
</table>
</td><td>
<table>
<tr><th>Tests and Observation</th><th>Cycle 2 and thereafter</th><th>EOS</th></tr>
<tr><td>Response Assessment</td><td>X[p]</td><td>X[p]</td></tr>
</table>
</td><td>Clear explanation</td></tr>
<tr><td>14. APPENDICE
Appendix A. Schedule of Assessments
Note</td><td>N/A</td><td>Footnote
●For a patient with M-protein detected only in urine at screening, spot urine is to be performed every 2 cycles for urine M-protein predose of MLN9708 on Day 1 of Cycle 2 and subsequent cycles (Cycle 2, 4, 6, 8, 10, 12, and so on [even-numbered cycles]).
▲For a patient with M-protein detected only in urine at screening, spot urine is to be performed every 2 cycles for urine M-protein predose of MLN9708 on Day 1 of Cycle 3 and subsequent cycles (Cycle 3, 5, 7, 9, 11, and so on [odd-numbered cycles]) (Urine collection during Days 23 through 28 of previous cycle is acceptable).
For subjects whose M-protein has been detected in serum and urine at screening, if a response assessment requires confirmation or disease progression (see Appendix G) is suspected, a urine M-protein measurement will be collected as appropriate</td><td>Add footnotes</td></tr>
</table>

____ : Amended texts

Protocol Change Memo

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

Date for version 2.1: 7 March 2012

Section	Replaced	With	Rationale
14. APPENDICE Appendix A. Schedule of Assessments Footnote	l For a patient with urine M-protein detected at screening, after Cycyle 2, samples will be collected every 2 cycles prior to MLN9708 dosing on Day 1 of Cycles 3, 5, 7, 9, and 11. It will be acceptable to collect samples between Days 23 and 28 of the preceding cycle. For a patient with M-protein detected only in urine at screenng, casual urine sample will be collected prior to MLN9708 dosing on Day 1 of Cycles 2, 4, 6, 8, 10, and 12 for urine M-protein.	l To be conducted if a response assessment requires confirmation (see Appendix G) during the MLN9708 treatment.	Clear explanation
14. APPENDICE Appendix A. Schedule of Assessments Note	m When assessing response, measure a urine M-protein using 24-hour urine collection.	m If a screening test has been performed within 7 days before the first dose, the results may be used as the Cycle 1 Day 1 data.	Clear explanation
14. APPENDICE Appendix A. Schedule of Assessments Note	n To be performed every 2 cycles predose of MLN9708 on Day 1 of Cycle 2, 3, 5, 7, 9, and 11. It will be acceptable to collect samples between Days 23 and 28 of the preceding cycle. Samples may be colleced as appropriate outside a specified cycle if a response assessment requires confirmation or disease progression is suspected.	n If bone X-rays have been performed within 8 weeks before the first dose, the X-ray results may be used as screening data. Chest X-ray is to be performed only during the screening. For any patient with documented osteolytic disease at screening, repeat the assessment again at EOS. If there are symptoms or signs that suggest increased or new bone lesions during the study treatment, repeat the procedure as necessary at any point. Repeat scans should use the same imaging modality throughout the study.	Clear explanation

____ : Amended texts

Protocol Change Memo

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

Date for version 2.1: 7 March 2012

Section	Replaced	With	Rationale
14. APPENDICE Appendix A. Schedule of Assessments Note	r When CT scans and MRIs are performed within 8 weeks of the first dose of MLN9708, the scans maybe used as the screening data. For patients with documented plasma cell neoplasms (plasmacytoma) in soft tissues, CT/MRI are to be performed predose of MLN9708 on Day 1 of Cycles 3, 5, 7, 9, and 11. (CT scans and MRIs may be conducted on Days 23 through 28 of previous cycle). Also conduct at EOS visit. If there are symptoms or signs that suggested increases or new bone lesions in the specified cycles, scans may be repeated at any point during the study. Unless a patient shows hypersensitivity to contrast, CT/MRT should be performed with contrast. Repeat scans should use the same imaging modality throughout the study. Unless a patient shows hypersensitivity to contrast, CT/MRT should be performed with contrast. Repeat scans should use the same imaging modality throughout the study.	o When CT scans and MRIs are performed within 8 weeks of the first dose of MLN9708, the scans maybe used as the screening data. For patients with documented plasma cell neoplasms (plasmacytoma) in soft tissues, CT/MRI are to be performed predose of MLN9708 on Day 1 of Cycle 3 and subsequent cycles (Cycles 3, 5, 7, 9, 11, and so on [odd-numbered cycles]). (CT scans and MRIs may be conducted on Days 23 through 28 of previous cycle). Also conduct at EOS visit. If there are symptoms or signs that suggested increases or new bone lesions (See Appendix G) in the specified cycles, scans may be repeated at any point during the study. Unless a patient shows hypersensitivity to contrast or concerns for potential aggravation of renal dysfunction, CT/MRT should be performed with contrast. Repeat scans should use the same imaging modality throughout the study. Unless a patient shows hypersensitivity to contrast or potentiality for aggravated renal dysfunction, CT/MRT should be performed with contrast. Repeat scans should use the same imaging modality throughout the study.	Clear explanation
14. APPENDICE Appendix A. Schedule of Assessment Note	s To be conducted at Cycles 3, 5, 7, 9, and 11 and at EOS as much as possible.	p To be conducted every 2 cycles at Cycle 3 and subsequent cycles (Cycles 3, 5, 7, 9, 11 [odd-numbered cycles]) and at EOS as much as possible.	Correction of errors and clear explanation
14. APPENDICE Appendix A. Schedule of Assessments Note	N/A	q To be conducted until/up to 12 cycles.	Clear explanation

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Protocol Change Memo

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

Date for version 2.1: 7 March 2012

Section	Replaced	With	Rationale
14. APPENDICE Appendix H. International Staging System for Multiple Myeloma and Durie & Salmon Myeloma Staging System	N/A	Added H. International Staging System and Durie & Salmon Myeloma Staging System	Added staging system for clarity.

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Summary of Changes for Protocol Amendment

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

Version 1 → Version 2

Protocol Number: TB-MC010034

Date of Amendment: 7 February 2012

Protocol Change Memo

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

Date for version 2: 7 February 2012

Section	Replaced	With	Rationale
Header	Product: MLN9708 Protocol Number: TB-MC010034 Date: 12 January 2012	Product: MLN9708 Protocol Number: TB-MC010034 Date: 7 February 2012	New version.
Title Page	Version/Date: Version 1 12 January 2012	Version/Date: Version 2 7 February 2012	New version.
Document History	-	Document History Version 1 7 February 2012	Document history is updated.
Protocol Summary Inclusion Criteria:	4) Measurable disease defined by at least one of the following 3 measurements • Serum M-protein: ≥ 1 g/dL (≥ 10 g/L) • Urine M-protein: ≥ 200 mg/24 hours • Serum free light chain (FLC) assay: involved FLC level ≥ 10 mg/dL.	4) Measurable disease defined by at least one of the following 3 measurements • Serum M-protein: ≥ 1 g/dL (≥ 10 g/L) • Urine M-protein: ≥ 200 mg/24 hours • Serum free light chain (FLC) assay: involved FLC level ≥ 10 mg/dL (≥ 100 mg/L), provided that the serum FLC ratio is abnormal.	Clear explanation.
Protocol Summary Exclusion Criteria:	8) Systemic treatment with potent CYP1A2 inhibitors (fluvoxamine, enoxacin), potent CYP3A inhibitors (clarithromycin, telithromycin, itraconazole, voriconazole, ketoconazole), or potent CYP3A inducers (rifampin, rifabutin, carbamazepine, phenytoin, phenobarbital), or use of foods containing Ginkgo biloba extract, or St. John's wort within 14 days before enrollment.	8) Systemic treatment with potent CYP1A2 inhibitors (fluvoxamine, enoxacin), potent CYP3A inhibitors (clarithromycin, telithromycin, itraconazole, voriconazole, ketoconazole), or potent CYP3A inducers (rifampin, rifabutin, carbamazepine, phenytoin, phenobarbital), or use of foods containing Ginkgo biloba extract, St. John's wort, or grapefruit within 14 days before enrollment.	Response to the PMDA queries.
Protocol Summary Exclusion Criteria:	20) Uncontrolled diabetes mellitus. 21) Prior or current complications of deep vein thrombosis or pulmonary embolism (MLN9708 with Rd cohort only).	20) Uncontrolled diabetes mellitus. 21) A history of interstitial lung disease or lung fibrosis, or a current complication of interstitial lung disease or lung fibrosis diagnosed by diagnostic chest imaging. 22) Prior or current complications of deep vein thrombosis or pulmonary embolism (MLN9708 with Rd cohort only).	Response to the PMDA queries.

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Protocol Change Memo

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

Date for version 2: 7 February 2012

Section	Replaced	With	Rationale
Protocol Summary Exclusion Criteria:	23) Patients who do not consent to use adequate contraceptive precautions (e.g. condoms and oral contraceptives) from when giving their consent through 3 months after the last dose of MLN9708, dexamethasone, or lenalidomide for women with childbearing potential and from giving their consent through 4 months after last dose of MLN9708, dexamethasone, or lenalidomide for men having their partners with childbearing potential. Menopause is defined as the time when there has been no menstrual periods for at least 1 year. The menstruation is possibly interrupted by chemotherapy not defined as menopause.	24) Patients who do not consent to use adequate contraceptive precautions (e.g. condoms and oral contraceptives) during the following term: • For women with childbearing potential*, from when giving their consent through 3 months after the last dose of MLN9708, dexamethasone, or lenalidomide • For men having their partners with childbearing potential, from giving their consent through 4 months after last dose of MLN9708, dexamethasone, or lenalidomide * Women with child-bearing potential are those who are premenopausal (menopause is defined as the time when there has been no menstrual periods for at least 1 year), or who have not had a bilateral tube ligation, bilateral oophorectomy, or hysterectomy. The menstruation is possibly interrupted by chemotherapy not defined as menopause.)	Response to the PMDA queries.
Protocol Summary Exclusion Criteria:	24) Pregnant (e.g. positive for pregnancy test) or lactating.	25) Pregnant (e.g. positive for pregnancy test) or lactating. Lactation is prohibited from the first dose through 6 weeks after the last dose of MLN9708, dexamethasone, and lenalidomide	Response to the PMDA queries.
Study Glossary	NA	SpO2 transcutaneous oxygen saturation	Response to the PMDA queries.
1. BACKGROUND AND RATIONALE 1.7.2 Rationale for using a fixed dose	When converting the dose from a body surface area dose to a fixed dose, we used 1.86 m2, which was the median body surface area of the subjects who participated in overseas clinical studies of bortezomib in multiple myeloma that were conducted by MPI.	When converting the dose from a body surface area dose to a fixed dose, we used 1.86 m2, which was the mean body surface area of the subjects who participated in overseas clinical studies of bortezomib in multiple myeloma that were conducted by MPI.	Response to the PMDA queries.

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Protocol Change Memo

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

Date for version 2: 7 February 2012

Section	Replaced	With	Rationale
4. SUBJECT ELIGIBILITY 4.1 Inclusion Criteria	4) Measurable disease defined by at least one of the following 3 measurements • Serum M-protein: ≥ 1 g/dL (≥ 10 g/L) • Urine M-protein: ≥ 200 mg/24 hours • Serum free light chain (FLC) assay: involved FLC level ≥ 10 mg/dL.	4) Measurable disease defined by at least one of the following 3 measurements • Serum M-protein: ≥ 1 g/dL (≥ 10 g/L) • Urine M-protein: ≥ 200 mg/24 hours • Serum free light chain (FLC) assay: involved FLC level ≥ 10 mg/dL (≥ 100 mg/L), provided that the serum FLC ratio is abnormal.	Clear explanation.
4. SUBJECT ELIGIBILITY 4.2 Exclusion Criteria	8) Systemic treatment with potent CYP1A2 inhibitors (fluvoxamine, enoxacin), potent CYP3A inhibitors (clarithromycin, telithromycin, itraconazole, voriconazole, ketoconazole), or potent CYP3A inducers (rifampin, rifabutin, carbamazepine, phenytoin, phenobarbital), or use of foods containing Ginkgo biloba extract, or St. John's wort within 14 days before enrollment.	8) Systemic treatment with potent CYP1A2 inhibitors (fluvoxamine, enoxacin), potent CYP3A inhibitors (clarithromycin, telithromycin, itraconazole, voriconazole, ketoconazole), or potent CYP3A inducers (rifampin, rifabutin, carbamazepine, phenytoin, phenobarbital), or use of foods containing Ginkgo biloba extract, St. John's wort, or grapefruit within 14 days before enrollment.	Response to the PMDA queries.
4. SUBJECT ELIGIBILITY	20) Uncontrolled diabetes mellitus. 21) Prior or current complications of deep vein thrombosis or pulmonary embolism (MLN9708 with Rd cohort only).	20) Uncontrolled diabetes mellitus. 21) A history of interstitial lung disease or lung fibrosis, or a current complication of interstitial lung disease or lung fibrosis diagnosed by diagnostic chest imaging. 22) Prior or current complications of deep vein thrombosis or pulmonary embolism (MLN9708 with Rd cohort only).	Response to the PMDA queries.

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Protocol Change Memo

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

Date for version 2: 7 February 2012

Section	Replaced	With	Rationale
4.2 Exclusion Criteria	23) Patients who do not consent to use adequate contraceptive precautions (e.g. condoms and oral contraceptives) from when giving their consent through 3 months after the last dose of MLN9708, dexamethasone, or lenalidomide for women with childbearing potential and from giving their consent through 4 months after last dose of MLN9708, dexamethasone, or lenalidomide for men having their partners with childbearing potential. Menopause is defined as the time when there has been no menstrual periods for at least 1 year. The menstruation is possibly interrupted by chemotherapy not defined as menopause.	24) Patients who do not consent to use adequate contraceptive precautions (e.g. condoms and oral contraceptives) during the following term: • For women with childbearing potential*, from when giving their consent through 3 months after the last dose of MLN9708, dexamethasone, or lenalidomide • For men having their partners with childbearing potential, from giving their consent through 4 months after last dose of MLN9708, dexamethasone, or lenalidomide * Women with child-bearing potential are those who are premenopausal (menopause is defined as the time when there has been no menstrual periods for at least 1 year), or who have not had a bilateral tube ligation, bilateral oophorectomy, or hysterectomy. The menstruation is possibly interrupted by chemotherapy not defined as menopause.)	Response to the PMDA queries.
4. SUBJECT ELIGIBILITY	24) Pregnant (e.g. positive for pregnancy test) or lactating[3]	25) Pregnant (e.g. positive for pregnancy test) or lactating. Lactation is prohibited from the first dose through 6 weeks after the last dose of MLN9708, dexamethasone, and lenalidomide[3]	Response to the PMDA queries.
6. TREATMENT PROCEDURES 6.1 MLN9708	Packaging: PTP Packaging Unit: Three capsules per PTP, which is contained by 1 unit carton.	Packaging: foil-foil blisters Packaging Unit: Three capsules per foil-foil blister, which is contained by 1 unit carton.	Correction of errors.

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Protocol Change Memo

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

Date for version 2: 7 February 2012

Section	Replaced	With	Rationale
6. TREATMENT PROCEDURES 6.5.1.1.2 Dose Modification for Non-hematological Toxicity	If non-hematological toxicities shown in Table 6-4 occur in <u>within a cycle</u>, MLN9708 should be interrupted.	If non-hematological toxicities shown in Table 6 4 occur in <u>Cycle 2 and subsequent cycles</u>, MLN9708 should be interrupted.	Correction of errors.
6. TREATMENT PROCEDURES 6.5.2.1 Criteria for Dose Modification	Table 6-5. <u>4.0 mg/day</u>	Table 6-5. <u>4.0 mg</u> <u>All "mg/day" was replaced with "mg".</u>	Correction of errors.
6. TREATMENT PROCEDURES 6.5.2.2.1 Dose Modification for Thrombocytopenia	Table 6-6. Fourth fall Resume MLN9708 at reduced dose by 1 level (Level 2). Do not dose MLN9708 <u>2.3 mg or below.</u>	Table 6-6. Fourth fall Resume MLN9708 at reduced dose by 1 level (Level 2). Do not dose MLN9708 <u>below 2.3 mg.</u>	Correction of errors.
6. TREATMENT PROCEDURES 6.5.2.2.1 Dose Modification for Thrombocytopenia	Table 6-6. Fifth fall Resume lenalidomide at 5 mg. Do not dose lenalidomide <u>5 mg or below.</u>	Table 6-6. Fifth fall Resume lenalidomide at 5 mg Do not dose lenalidomide <u>below 5 mg.</u>	Correction of errors.
6. TREATMENT PROCEDURES 6.5.2.2.2 Dose Modification for Neutropenia	Table 6-7. Fourth fall Resume MLN9708 at reduced dose by 1 level (Level 2). Do not dose MLN9708 <u>2.3 mg or below.</u>	Table 6-7. Fourth fall Resume MLN9708 at reduced dose by 1 level (Level 2). Do not dose MLN9708 <u>below 2.3 mg.</u>	Correction of errors.

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Protocol Change Memo

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

Date for version 2: 7 February 2012

Section	Replaced	With	Rationale
6. TREATMENT PROCEDURES 6.5.2.2.2 Dose Modification for Neutropenia	Table 6-7. Fifth fall Resume lenalidomide at 5 mg. Do not dose lenalidomide <u>5 mg or below.</u>	Table 6-7. Fifth fall Resume lenalidomide at 5 mg Do not dose lenalidomide <u>below 5 mg.</u>	Correction of errors.
6. TREATMENT PROCEDURES 6.5.2.3.1 Dose Modification for Rash	Table 6-8. Fourth event Resume MLN9708 at reduced dose by 1 level (Level 2). Do not dose MLN9708 <u>2.3 mg or below.</u>	Table 6-7. Fourth fall Resume MLN9708 at reduced dose by 1 level (Level 2). Do not dose MLN9708 <u>below 2.3 mg.</u>	Correction of errors.
6. TREATMENT PROCEDURES 6.5.2.3.1 Dose Modification for Rash	Table 6-8. Fifth event Resume lenalidomide at 5 mg. Do not dose lenalidomide <u>5 mg or below.</u>	Table 6-7. Fifth event Resume lenalidomide at 5 mg Do not dose lenalidomide <u>below 5 mg.</u>	Correction of errors.
6. TREATMENT PROCEDURES 6.5.2.3.1 Dose Modification for Rash	Table 6-8. Second thorough fifth event Recovers to < Grade 2.	Table 6-8. Second thorough fifth event Recovers to < Grade 2 <u>within 2 weeks.</u>	Correction of errors.
6. TREATMENT PROCEDURES 6.5.2.3.3 Lenalidomide Treatment Modification	Table 6-11. Dyspepsia, gastric, or duodenal ulcer, gastritis Grade 1-2 (requiring medical management) <u>Grade 4</u>	Table 6-11. Dyspepsia, gastric, or duodenal ulcer, gastritis Grade 1-2 (requiring medical management) <u>> Grade 2</u>	Correction of errors.

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Protocol Change Memo

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

Date for version 2: 7 February 2012

Section	Replaced	With	Rationale
6. TREATMENT PROCEDURES 6.8 Excluded Concomitant Medications and Procedures	Systemic treatment with strong inhibitors of CYP1A2 (fluvoxamine, enoxacin), strong inhibitors of CYP3A (clarithromycin, telithromycin, itraconazole, voriconazole, ketoconazole) or strong CYP3A inducers (rifampicin, rifabutin, carbamazepine, phenytoin, phenobarbital), or use/ intake of foods containing Ginkgo biloba extract, or St. John's wort during the study.	Systemic treatment with strong inhibitors of CYP1A2 (fluvoxamine, enoxacin), strong inhibitors of CYP3A (clarithromycin, telithromycin, itraconazole, voriconazole, ketoconazole) or strong CYP3A inducers (rifampicin, rifabutin, carbamazepine, phenytoin, phenobarbital), or use/ intake of foods containing Ginkgo biloba extract, St. John's wort, or grapefruit during the study.	Response to the PMDA queries.
6. TREATMENT PROCEDURES 6.8 Excluded Concomitant Medications and Procedures	Any antineoplastic treatment for multiple myeroma other than Rd administered concomitantly with MLN9708 in the Rd combination cohort. Treatment with corticosteroids 10 mg of prednisolone per day or less is permitted.	Any antineoplastic treatment other than Rd administered concomitantly with MLN9708 in the Rd combination cohort. Treatment with corticosteroids 10 mg of prednisolone per day or less is permitted.	Clear explanation.
7. STUDY PROCEDURES 7.2.1 Screening period	Subject background (including medical history, concomitant disease, details of multiple myeloma diagnosis [date of diagnosis, histological type, current clinical stage], history of prior-treatment)	Subject background (including medical history, concomitant disease, details of multiple myeloma diagnosis [date of diagnosis, histological type, current clinical stage], history of prior-treatment for multiple myeloma [chemotherapy, radiotherapy, transplantation, surgery])	Clear explanation.
7. STUDY PROCEDURES 7.2.1 Screening period	Vital signs (sitting blood pressure, pulse rate, and axillary temperature)	Vital signs (sitting blood pressure, pulse rate, axillary temperature, and transcutaneous oxygen saturation [SpO2])	Response to the PMDA queries.
7. STUDY PROCEDURES 7.2.1 Screening period	• Laboratory tests: (snip) - Virus tests	• Laboratory tests: (snip) - Virus tests (HIV antibody, HBs antigen, HCV antibody. The test results will not be recorded in the eCRF.)	Clear explanation.

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Protocol Change Memo

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

Date for version 2: 7 February 2012

Section	Replaced	With	Rationale
7. STUDY PROCEDURES 7.2.1 Screening period	• X-rays - Chest, bone (head, cervical vertebrae, thoracic vertebrae, lumbar vertebrae, pelvis, both upper arms, both forearms, both femurs, both lower legs); in two directions for each, except for the pelvis - If bone X-ray is performed within 8 weeks before the first dose, the X-ray results may be used as screening data.	• X-rays - Chest - Bone (head, cervical vertebrae, thoracic vertebrae, lumbar vertebrae, pelvis, both upper arms, both forearms, both femurs, both lower legs); in two directions for each, except for the pelvis - If bone X-ray is performed within 8 weeks before the first dose, the X-ray results may be used as screening data.	Clear explanation.
7. STUDY PROCEDURES 7.2.2 Treatment period	• Vital signs (sitting blood pressure, pulse rate, and axillary temperature)	• Vital signs (sitting blood pressure, pulse rate, axillary temperature, and SpO2)	Response to the PMDA queries.
7. STUDY PROCEDURES 7.2.2 Treatment period	• X-rays - Chest, bone (head, cervical vertebrae, thoracic vertebrae, lumbar vertebrae, pelvis, both upper arms, both forearms, both femurs, both lower legs); in two directions for each, except for the pelvis - X-rays will be performed as appropriate if osteolytic lesions are found at screening and there are concerns about bone lesions increasing or new bone lesions developing during the study.	• X-rays - Bone (head, cervical vertebrae, thoracic vertebrae, lumbar vertebrae, pelvis, both upper arms, both forearms, both femurs, both lower legs); in two directions for each, except for the pelvis - X-rays will be performed as appropriate if osteolytic lesions are found at screening and there are concerns about bone lesions increasing or new bone lesions developing during the study.	Correction of errors.
7. STUDY PROCEDURES 7.2.3 End of study	Vital signs (sitting blood pressure, pulse rate, and axillary temperature)	Vital signs (sitting blood pressure, pulse rate, axillary temperature, and SpO2)	Response to the PMDA queries.

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Protocol Change Memo

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

Date for version 2: 7 February 2012

Section	Replaced	With	Rationale
7. STUDY PROCEDURES 7.2.3 End of study	• X-rays - Chest, bone (head, cervical vertebrae, thoracic vertebrae, lumbar vertebrae, pelvis, both upper arms, both forearms, both femurs, both lower legs); in two directions for each, except for the pelvis - X-rays will be performed as appropriate if osteolytic lesions are found at screening.	• X-rays - Bone (head, cervical vertebrae, thoracic vertebrae, lumbar vertebrae, pelvis, both upper arms, both forearms, both femurs, both lower legs); in two directions for each, except for the pelvis - X-rays will be performed as appropriate if osteolytic lesions are found at screening.	Correction of errors.
7. STUDY PROCEDURES 7.2.4 Laboratory tests	Table 7-1 footnote [i] β2-microglobulin, HIV antibody, HBs antigen, and HCV antibody test are performed only at screening	Table 7-1 footnote [i] β2-microglobulin test is performed only at screening	Clear explanation.
9. SAFETY DATA COLLECTION, RECORDING, AND REPORTING 9.3 Serious Adverse Event Reporting Procedures	Emergency center for safety information (available 24 hours 365 days) PPD PPD PPD	Emergency center for safety information (available 24 hours 365 days) PPD PPD PPD PPD	Clear explanation.
14. APPENDICES Appendix A. Schedule of Assessments	Radiographic assessment (systemic)[q] [q] If bone X-rays is performed within 8 weeks before the first dose, the X-ray results may be used as screening data. For any patient with documented osteolytic disease at screening, repeat the assessment again at EOS. If there are symptoms or signs that suggest increased or new bone lesions during the study treatment, repeat the procedure as necessary at any point. Repeat scans should use the same imaging modality throughout the study.	Radiographic assessment[q] [q] If bone X-rays is performed within 8 weeks before the first dose, the X-ray results may be used as screening data. Chest X-ray is to be performed only during the screening. For any patient with documented osteolytic disease at screening, repeat the assessment again at EOS. If there are symptoms or signs that suggest increased or new bone lesions during the study treatment, repeat the procedure as necessary at any point. Repeat scans should use the same imaging modality throughout the study.	Clear explanation.

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