Title: A Phase 1b, Randomized, Double-Blind, Placebo-Controlled, Safety, Tolerability and Pharmacokinetic Study of Multiple Rising Doses of MLN9708 for the Treatment of Subjects With ISN/RPS Class III or IV Lupus Nephritis

NCT Number: NCT02176486

SAP Approve Date: 6 March 2018

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

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

- Named persons or organizations associated with the study.
- Proprietary information, such as scales or coding systems, which are considered confidential information under prior agreements with license holder.
- Other information as needed to protect confidentiality of Takeda or partners, personal information, or to otherwise protect the integrity of the clinical study.

STATISTICAL ANALYSIS PLAN

STUDY NUMBER: MLN9708_101

A Phase 1b, Randomized, Double-Blind, Placebo-Controlled, Safety, Tolerability and Pharmacokinetic Study of Multiple Rising Doses of MLN9708 for the Treatment of Subjects With ISN/RPS Class III or IV Lupus Nephritis

MRD Study in Lupus Nephritis

PHASE 1b

Version**: Final**

Date**:** 6 March 2018

Prepared by:

Personal Protected Data

Based on:

Protocol Version: Amendment 9

Protocol Date: 24 May 2016

1.1 Approval Signatures

Electronic signatures can be found on the last page of this document.

Study Title: A Phase 1b, Randomized, Double-Blind, Placebo-Controlled, Safety, Tolerability and Pharmacokinetic Study of Multiple Rising Doses of MLN9708 for the Treatment of Subjects With ISN/RPS Class III or IV Lupus Nephritis

Approvals:

Personal Protected Data _____ Date

Personal Protected Data _____ Date

Personal Protected Data _____ Date

Personal Protected Data _____ Date

Personal Protected Data _____ Date

2.0 TABLE OF CONTENTS

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3.0 LIST OF ABBREVIATIONS

[redacted]	[redacted]
AE	adverse event
ACR	American College of Rheumatology
ALT	alanine aminotransferase
[redacted]	[redacted]
anti-dsDNA	antibody to double-stranded DNA
AST	aspartate aminotransferase
[redacted]	[redacted]
AUC(0-168)	area under the plasma concentration-time curve from time 0 to 168 hours postdose
AUC(0-t)	area under the plasma/blood/serum concentration-time curve from time 0 to time t
AUC(0-tlqc)	area under the plasma concentration-time curve from time 0 to time of last quantifiable concentration (tlqc)
AZA	azathioprine
[redacted]	[redacted]
BMI	body mass index
BSA	body surface area
CI	confidence interval
Cmax	maximum observed plasma concentration
CrCl	creatinine clearance
CS	clinically significant
CTCAE	Common Terminology Criteria for Adverse Events
CYC	cyclophosphamide
CYP	cytochrome P-450
DDI	drug-drug interaction
DLT	dose-limiting toxicity
dsDNA	double-stranded deoxyribonucleic acid
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
ECG	electrocardiogram
ESRD	end-stage renal disease
EOT	End of Treatment
ET	Early Termination
FACT	functional assessment of cancer therapy
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GFR	glomerular filtration rate
GI	gastrointestinal
GN	Glomerulonephritis
HBsAg	hepatitis B surface antigen

hCG	human chorionic gonadotropin
HCV	hepatitis C virus
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
IEC	independent ethics committee
Ig	Immunoglobulin
IgA	Immunoglobulin A
IgG	immunoglobulin G
IgM	immunoglobulin M
IRB	institutional review board
ISN	International Society of Nephrology
ISV	insufficient sample volume
IVRS/IWRS	interactive voice response system/interactive web response system
K2EDTA	dipotassium ethylenediamine-tetraacetic acid
LLN	lower limit of normal
LN	lupus nephritis
MedDRA	Medical Dictionary for Regulatory Activities
MMF	mycophenolate mofetil
MRD	multiple-rising dose
MTD	maximum tolerated dose
NCS	not clinically significant
NOAEL	no-observed-adverse-effect level
NSAID	nonsteroidal anti-inflammatory drug
PGx	pharmacogenomics
PK	pharmacokinetic(s)
PO	Orally
PT	preferred term
PTE	pretreatment event
QTcF	QT interval with Fridericia's correction method
RBC	red blood cell
[redacted]	[redacted]
RPS	Renal Pathology Society
RRMM	relapsed refractory multiple myeloma
SAE	serious adverse event
SAP	statistical analysis plan
sCR	serum creatinine
SLE	systemic lupus erythematosus
[redacted]	[redacted]
SNP	single nucleotide polymorphism
SOC	system organ class
SRC	Safety Review Committee

TB	tuberculosis
TEAE	treatment-emergent adverse event
Tmax	time to reach Cmax
ULN	upper limit of normal
UPCR	urine protein to creatinine ratio
WBC	white blood cell
WHO	World Health Organization

4.0 OBJECTIVES

4.1 Primary Objective

To characterize the safety and tolerability of ixazomib when administered as multiple oral doses at escalating dose levels in subjects with lupus nephritis (LN).

4.2 Secondary Objective

- To assess changes from Baseline in urine protein to creatinine ratio (UPCR) in LN subjects following multiple administrations of ixazomib.
- To evaluate the effect of ixazomib on kidney function, as assessed by changes from Baseline in serum creatinine (sCR), and estimated glomerular filtration rate (eGFR).
- To evaluate the effect of ixazomib on anti-dsDNA antibody titers and complement C3/C4 levels.
- To characterize the plasma PK of ixazomib in LN subjects when ixazomib is administered over 3 cycles consisting of 3 doses per cycle.

4.3 Additional Objectives

Not applicable.

4.4 Study Design

See Protocol Section 6.

5.0 ANALYSIS ENDPOINTS

5.1.1 Primary Endpoint

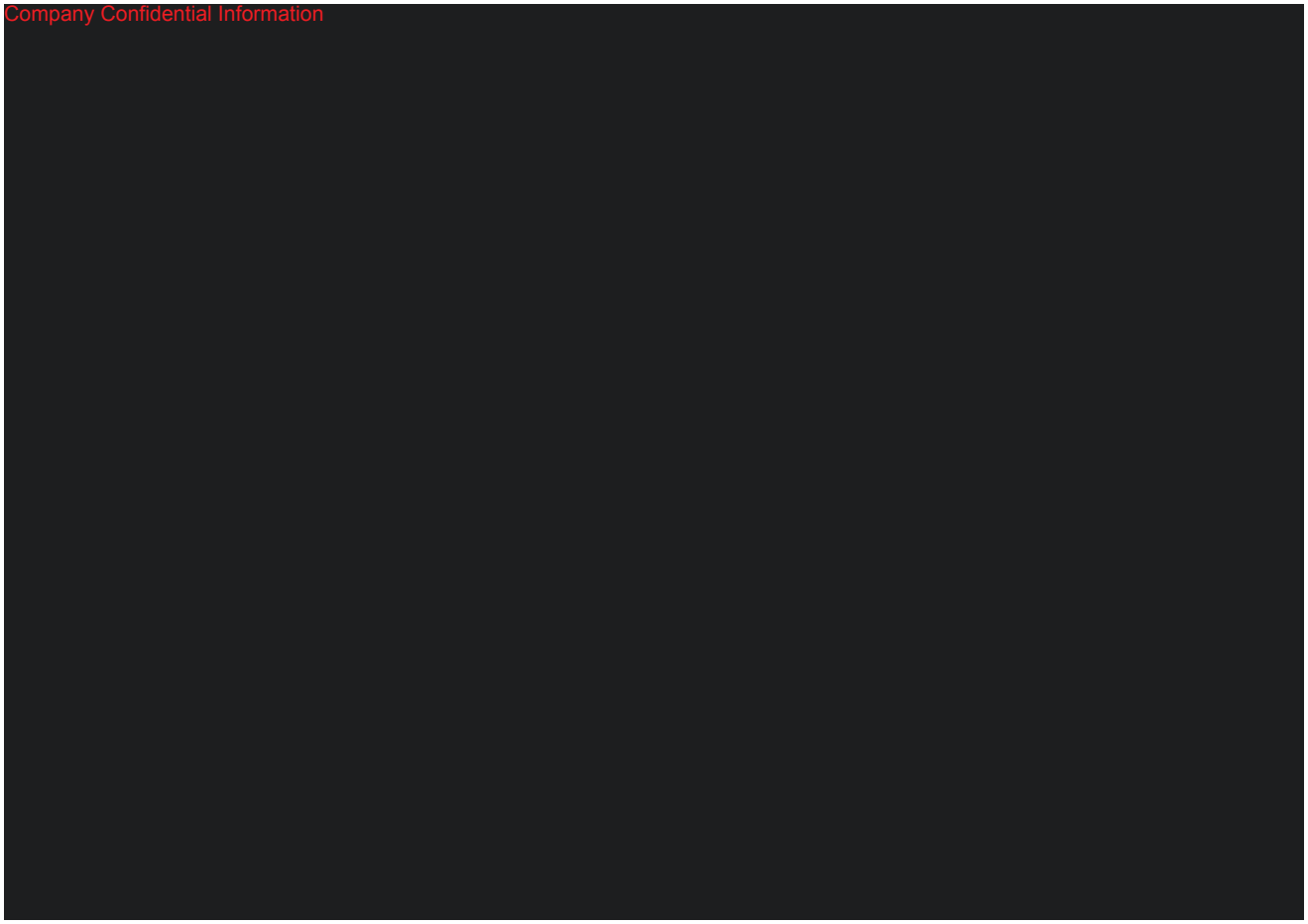
- Percentage of study subjects with at least 1 Grade ≥2 treatment emergent adverse event (TEAE) according to CTCAE.
- Percentage of study subjects with at least 1 serious adverse event (SAE).
- Percentage of study subjects with at least 1 adverse event leading to discontinuation of investigational study medication.
- Percentage of subjects with at least 1 markedly abnormal laboratory criteria for hematologic parameters.

5.1.2 Secondary Endpoints

- Change from Baseline to Final Visit of treatment period in UPCR.
- Change from Baseline to Final Visit of treatment period in sCR level.
- Change from Baseline to Final Visit of treatment period in eGFR measurement.
- Change from Baseline to Final Visit of treatment period in levels of autoantibodies (anti-dsDNA) and complement (C3 and C4).
- Plasma PK of ixazomib in subjects with LN following administration of ixazomib.
  - Plasma PK endpoints will be the following PK parameters of ixazomib in all cohorts:
    - Maximum plasma concentration (C_{max}).
    - Time to reach Cmax (T_{max}).
    - Area under the plasma concentration-time curve from time 0 to the last quantifiable concentration ($AUC_{(0\text{-}tlqc)}$); or $AUC_{(0\text{-}168)}$, if measurable.

5.1.3 Exploratory Endpoints

- Company Confidential Information [redacted]



5.1.4 Additional Safety Endpoints

Other safety assessments include vital sign measurements, ECGs, physical examinations and clinical laboratory tests.

6.0 DETERMINATION OF SAMPLE SIZE

This study is not statistically powered for any hypothesis testing. The sample size of at least 4 active and 1 placebo subjects for each of the 0.5 mg and 2.0 mg dose groups (Cohorts A and B, respectively), 6 active and 2 placebo subjects for each of the 3.0 and 4.0 mg dose groups (Cohorts C and D, respectively) is considered to be sufficient to fulfill the study objectives of the evaluation of safety, tolerability, and pharmacokinetics of each cohort.

7.0 METHODS OF ANALYSIS AND PRESENTATION

7.1 General Principles

Continuous data will be summarized using the following descriptive statistics: number of subjects (N), mean, standard deviation (SD), median, minimum, and maximum, where appropriate. Where indicated, the coefficient of variation (%CV) and geometric mean will also be included in the summary of continuous data. Categorical data will be summarized using the number and percent of subjects for each category, where appropriate.

Unless otherwise stated, baseline value is defined as the last observed value before the first dose of study medication.

Subjects who receive placebo in each cohort will be pooled across the cohorts. All study-related raw data for randomized subjects will be presented in listings. All summaries will be presented by the pooled placebo group, ixazomib doses, ixazomib overall, and overall subjects in the study separately. All data analyses and figures will be generated using SAS System® Version 9.2 or higher.

7.1.1 Study Definitions

There are no study-specific definitions.

7.1.2 Definitions of Study Days

Study day will be calculated relative to the date of the first dose of the study drug. Study days prior to the first dose of study drug will be calculated as: {date of assessment/event – date of first dose of study drug of the subject}. Study days on or after the first dose of study drug will be calculated as: {date of assessment/event – date of first dose of study drug of the subject + 1}.

7.1.3 Definition of Study Visit Windows

There will be no visit windows.

7.1.4 Conventions for Missing Adverse Event Dates

There will be no imputation of incomplete, or missing adverse event dates.

7.1.5 Conventions for Missing Concomitant Medication Dates

There will be no imputation of incomplete, or missing concomitant medication dates.

7.1.6 Conventions for Missing Data

There will be no imputation of incomplete or missing data.

7.2 Analysis Sets

Safety Set:

The Safety Analysis Set will consist of all subjects who are enrolled and received at least 1 dose of study drug. Subjects in this analysis set will be used for demographic, baseline characteristics and safety summaries.

Pharmacokinetic Set:

The PK set will consist of all subjects who receive study drug and have at least 1 measurable plasma concentration.

Pharmacodynamic Set:

The PD set will consist of all subjects who receive study drug and have at least 1 postdose PD measurement.

7.3 Disposition of Subjects

Disposition of all screened subjects (denominator) will be tabulated (count and percent); there will be no inferential analysis of subject disposition data.

Summaries will be presented by the pooled placebo group, ixazomib doses, ixazomib overall, and overall subjects in the study.

Disposition of all randomized subjects will be tabulated for each part of the study:

- All subjects received at least one dose of study drug (denominator).
- Subjects who completed the study drug.
- Subjects who prematurely discontinued study drug.
- Subjects who completed all study visits.
- Subjects who prematurely discontinued study visits.

Primary reasons for discontinuation of study drug/visits, as entered on the electronic case report form (eCRF), will be tabulated. The date of first dose, date of last dose, duration of treatment and the reason for premature discontinuation of study drug/study visit will be presented for each subject in listings.

Primary reasons for failure will be summarized and will be presented in a data listing.

7.4 Demographic and Other Baseline Characteristics

Demographic and baseline characteristics will be summarized using the safety set by pooled placebo group, ixazomib doses, ixazomib overall, and overall subjects in the study.

Summary statistics will be presented for continuous variables (age, height, weight, and body mass index [BMI]). The number and percentage subjects within each category will be presented

for categorical variables (for example, gender, race, etc.). Individual subject demographic and baseline characteristic data will be listed.

Demographic variables of screen failure subjects and reasons for screen failures will be summarized overall for subjects who are screened but not enrolled in the study.

7.5 Medical History and Concurrent Medical Conditions

Medical history refers to the significant conditions or diseases relevant to the disease under study that resolved at or prior to signing of informed consent. Concurrent medical conditions are those significant ongoing conditions or diseases present at signing of informed consent.

Medical history and concurrent medical conditions will be coded using the latest version of Medical Dictionary for Regulatory Activities (MedDRA, version 20.0) will be presented in listings based on safety analysis set.

7.6 Medication History and Concomitant Medications

Medication history information to be obtained includes any medication relevant to eligibility criteria and the efficacy or safety evaluations stopped at or within 28 days before signing of informed consent. Medications used from signing of informed consent through the end of each study part will be considered as concomitant medications for each study part, respectively.

Concomitant medication is defined as the medication that the patient started taking before first dose and ongoing in the study. Missing, partial, incomplete date/time for concomitant mediations won't be imputed; these will be listed as such.

All medication history and concomitant medications data will be presented in listing. This listing will be based on safety set.

7.7 Study Drug Exposure and Compliance

The date and time of each dose for each subject will be reported in a data listing.

Summaries of ixazomib PK concentration data will be provided (See Section 7.9.1). No other summary statistics for the extent of exposure to study drug or compliance calculations will be performed.

7.8 Efficacy Analysis

Not applicable.

7.8.1 Primary Efficacy Endpoint(s)

Not applicable.

7.8.2 Secondary Efficacy Endpoint(s)

Not applicable.

7.9 Pharmacokinetic and Pharmacodynamic Analysis

7.9.1 Pharmacokinetic Analysis

7.9.1.1 Pharmacokinetic Concentrations

Individual subject plasma and [redacted] concentration data for ixazomib will be listed for all subjects in the safety set. Both scheduled and actual PK sample collection times will be presented in listings.

For the pharmacokinetic set, plasma and [redacted] ixazomib concentration data will be summarized by time point for each ixazomib dosing cohort using descriptive statistics (N, mean, SD, %CV, median, maximum, and minimum). Summary statistics will be calculated by assigning a value of 0 to all values below the limit of quantification (BLQ).

7.9.1.2 Pharmacokinetic Parameters

No PK parameters will be derived due to early termination of the study.

7.9.2 Pharmacodynamic Analysis

All PD summaries will be based on the PD set.

7.9.2.1 Pharmacodynamic Concentrations

Pharmacodynamic measures will include hematologic measures of serum anti dsDNA antibody, other autoantibodies and complement C3/C4 levels. Samples will be collected as noted in Appendix A in the Protocol. These assays are routinely performed in the central laboratory.

Baseline value, final visit value, and change from baseline to final visit of the levels of autoantibodies (anti-dsDNA) and complement (C3 and C4) will be summarized by pooled placebo, ixazomib dose and ixazomib overall (N, mean, SD, median, minimum, and maximum). Individual data for each subject will be provided in the listing.

[redacted]

For serum and urine cytokine samples, the values at each time point, change from baseline to each visit of the levels of each analyte, except analyates in which all values are below LLOQ, will be summarized by pooled placebo, ixazomib dose and ixazomib overall (N, mean, SD, median, minimum, and maximum). Individual data for each subject will be provided in the listing.

7.10 Other Outcomes (Secondary Endpoints and Exploratory Endpoints)

Other secondary endpoints include change from baseline to final visit of treatment period in Urine Protein to Creatinine Ratio (UPCR), serum creatinine (SCr) level and estimated glomerular filtration rate (eGFR) measurement.

Observed values of UPCR, SCr and eGFR will be listed for each subject by visit. Baseline, final visit values and change from baseline at final visit will be summarized by pooled placebo, ixazomib dose and ixazomib overall (N, mean, SD, median, minimum and maximum) using the safety set.

Due to the fact that the study was terminated before the finalization of this statistical analysis plan, no summaries nor analysis will be performed for the exploratory endpoints. Data collected on eCRF or from study procedures that are related to the exploratory endpoints will be listed if appropriate.

7.11 Safety Analysis

Safety measures include AEs, clinical laboratory parameters, vital sign parameters, 12-lead ECG results, and other safety parameters. The safety analysis set will be used for all summaries of safety parameters.

7.11.1 Adverse Events

A Pre-Treatment Event (PTE) is defined as any untoward medical occurrence in a clinical investigation subject who has signed informed consent to participate in a study, but prior to administration of any study medication; it does not necessarily have to have a causal relationship with study participation.

An AE is defined as any untoward medical occurrence in a clinical investigation subject administered a drug; it does not necessarily have to have a causal relationship with this treatment. PTE and AE verbatim terms will be coded by SOC and PT using MedDRA (version 20.0 or later).

Treatment-Emergent Adverse Events (TEAE)s will be defined as AEs that occur after the first dose of study drug received in the treatment period and up to 30 days (onset date – last date of dose + 1 $\leq$ 30) after the last dose of study drug or early termination.

TEAEs will be presented by severity (mild, moderate, and severe). Serious TEAEs, TEAEs leading to study drug discontinuation, and TEAEs leading to death will also be summarized using SOC and PT.

When calculating the frequency and percentage of subjects who reported TEAEs, a subject will be counted only once for each SOC or PT when multiple TEAEs are coded to the same SOC or PT. For the intensity or relatedness summaries, if a subject reports multiple TEAEs coded to the same SOC or PT, the TEAE with maximum intensity or strongest relationship will be included in the summary.

AEs with missing severity will be listed as such in the AE listings, however, will be summarized as severe in summary tables. Similarly, if the relationship of an event is missing, the event will be considered as related but in listings it will be presented as missing.

In general, AEs will be tabulated at the following levels: overall summary (subjects with at least 1 AE in any dose or treatment), the MedDRA SOC, and the MedDRA PT. The tables will

include the number and percentage (N[%]) of subjects. The following summary tables will be generated for all cohorts:

- Overview of Treatment-Emergent Adverse Events.
- Treatment-Emergent Adverse Events by System Organ Class and Preferred Term.
- Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term.
- Most Frequent (>5% or N>2) Non-Serious Adverse Events by Preferred Term.
- Most Frequent (>5% or N>2) Non-Serious Adverse Events by System Organ Class and Preferred Term.
- Relationship of Treatment-Emergent Adverse Events to Study Drug by System Organ Class and Preferred Term.
- Drug-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term.
- Severity of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term.

In addition, the following summary tables, number and percentage of subjects, will be generated for the following primary endpoints in all cohorts:

- At least 1 Grade ≥2 treatment emergent adverse event (TEAE) according to CTCAE.

Subject mappings for the TEAEs by SOC and PT will be generated.

Data listings will be provided for PTEs, TEAEs, TEAEs leading to study drug discontinuation AEs leading to discontinuation of investigational study medication, SAEs and AEs that resulted in death.

7.11.2 Clinical Laboratory Evaluations

Clinical laboratory tests will be assessed using the safety analysis set and will be evaluated and presented using International System of Units (SI) unless otherwise stated. Table 7.a shows a list of all clinical laboratory tests.

Table 7.a Clinical Laboratory Tests

Hematology	Serum Chemistry	Urinalysis	Special
Red blood cells Reticulocytes White blood cells with differential Hemoglobin Hematocrit Platelets	Alanine aminotransferase Alkaline phosphatase Aspartate aminotransferase γ-Glutamyl transferase Total bilirubin Direct bilirubin Albumin Total protein Creatinine Blood urea nitrogen Creatine kinase Potassium Sodium Glucose Chloride Phosphorus Calcium	**To be done at local laboratory** pH Specific gravity Protein Glucose Blood Nitrite Microscopic Analysis: RBC/high power field WBC/high power field Epithelial cells, casts, etc **To be done at central laboratory** Urine protein and creatinine for UPCR Urine Biomarkers **To be done at the site** Standard urinalysis using dipstick (protein only)	**To be done at local laboratory** Coomb's test Platelets, red blood cells, white blood cells with differential **To be done at central laboratory** Lipid panel (fasted): Total cholesterol LDL-cholesterol HDL-cholesterol Triglycerides Serum complement C3 and C4 Total IgM, IgG and IgA Autoantibodies: Anti-double-stranded DNA Anti-nuclear antibody Anti-Ro (SS-A) Anti-La (SS-B) Anti-RNP Anti-Sm Anti-phospholipids Serum biomarkers Tetanus antibody titers HBsAb titers
Serum			
Serum hCG (a) **At Screening Only:** Hepatitis panel, including HBsAg, anti-HCV and HIV FSH (b)			

DNA=deoxyribonucleic acid, FSH=follicle-stimulating hormone, HBsAb=hepatitis B surface antibody, hCG=human chorionic gonadotropin, HDL=high-density lipoprotein, HIV=human immunodeficiency virus, LDL=low-density lipoprotein.
(a) Serum hCG pregnancy test will be done on all female subjects of childbearing potential at Screening.
(b) The FSH level will be obtained for female subjects at Screening if they are postmenopausal by history (ie, last regular menstrual cycle >2 years) and not surgically sterile. The FSH result must be >40 IU/L for the subject to be permitted not to use adequate contraception.

All laboratory test parameters will be displayed in individual subject data listings in both SI units and conventional (CV) units. For test results not in SI units, the conversion to SI units will be done in derived analysis data sets using the known conversion factors. If necessary, SI units from the central laboratory may be converted to Takeda's preferred SI units in the derived dataset. All summaries and analyses will be based on the values using these preferred SI units.

Descriptive statistics (N, mean, SD, median, minimum, and maximum) for the observed baseline, post-baseline and change from baseline values will be presented by pooled placebo group, ixazomib doses, and ixazomib overall for the following laboratory tests:

- Red blood cells.
- White blood cells with differential.
- Platelets.
- Alanine aminotransferase.
- Alkaline phosphatase.
- Aspartate aminotransferase.
- γ-Glutamyl transferase.
- Total bilirubin.
- Creatinine.
- Blood urine nitrogen.
- Urine protein and creatinine for UPCR.
- C3 and C4.
- Total IgM, IgG and IgA.
- Anti-double-stranded DNA.
- Tetanus antibody titers.
- HBsAb titers.

Study baseline will be used for change from baseline.

Laboratory Markedly Abnormal Values (MAVs), identified by the criteria defined in Appendix A, will be tabulated. If a subject has a MAV for a particular laboratory test, all visits for that subject for that parameter will be listed. The number and percentage of subjects with at least 1 post-dose markedly abnormal laboratory test result will be summarized. The mapping of the subjects who meet the MAV criteria will be listed as a table. All observations, including ones at unscheduled visits, will be included in the MAV evaluation and summaries if MAV criteria are satisfied.

All clinical laboratory data will be presented in both SI and conventional units in data listings.

7.11.3 Vital Signs

Vital sign MAVs, identified by the criteria defined in Appendix B, will be tabulated. If a subject has a MAV for a particular vital signs parameter, all visits for that subject for that parameter will be listed. The number and percentage of subjects with at least 1 post-dose markedly abnormal vital signs measurement will be summarized. The mapping of the subjects who meet the MAV criteria will be listed as a table. All observations, including ones at unscheduled visits, will be included in the MAV evaluation and summaries if MAV criteria are satisfied.

All vital signs will be listed in a data listing.

7.11.4 12-Lead ECGs

ECG MAVs, identified by the criteria defined in Appendix C, will be tabulated. If a subject has a MAV for a particular 12-lead ECG parameter, all visits for that subject for that parameter will be listed. The number and percentage of subjects with at least 1 post-dose markedly abnormal 12-lead ECG measurement will be summarized. The mapping of the subjects who meet the MAV criteria will be listed as a table. All observations, including ones at unscheduled visits, will be included in the MAV evaluation and summaries.

Overall ECG interpretation category (normal, abnormal not clinically significant, abnormal clinically significant, not evaluable) is collected by eCRF at baseline and at each scheduled post-baseline visit. Shifts in ECG interpretation will be presented as cross-tabulations (baseline versus each post-baseline visit) of numbers of subjects with normal, abnormal not clinically significant, and abnormal clinically significant interpretations, not evaluable, with missing, if applicable, and total categories overall.

All ECG parameters will be listed in a data listing.

7.12 Interim Analysis

There is no interim analysis.

7.13 Changes in the Statistical Analysis Plan

Only analysis on Cohort A and B, and Double-Blind treatment period of the study will be presented because study has been terminated early.

Due to the fact that the study was terminated before the finalization of this statistical analysis plan, no summaries nor analysis will be performed for the exploratory endpoints. Data collected on eCRF or from study procedures that are related to the exploratory endpoints will be listed if appropriate. Additionally, no PK parameters will be derived due to early termination of the study.

8.0 REFERENCES

1. A Phase 1b, Randomized, Double-Blind, Placebo-Controlled, Safety, Tolerability and Pharmacokinetic Study of Multiple Rising Doses of MLN9708 for the Treatment of Subjects With ISN/RPS Class III or IV Lupus Nephritis, Takeda, Protocol Amendment No.9 for MLN9708_101, dated 24 May 2016.

Appendix A Criteria for Identification of Markedly Abnormal Laboratory Values

Hematology – Criteria for Markedly Abnormal Values (SI units)

Parameter	Unit	Low Abnormal	High Abnormal
Hemoglobin	Both	< 0.8 × LLN	> 1.2 × ULN
Hematocrit	Both	< 0.8 × LLN	> 1.2 × ULN
RBC count	Both	< 0.8 × LLN	> 1.2 × ULN
WBC count	Both	<0.5 × LLN	>1.5 × ULN
Platelet count	Conventional	$<75 \times 10^3/\mu L$	$>600 \times 10^3/\mu L$
	SI	$<75 \times 10^9/L$	$>600 \times 10^9/L$
Reticulocytes	Conventional	--	>3 % of erythrocytes
	SI	--	>0.030 Fraction of 1

LLN=lower limit of normal, RBC=red blood cell, ULN=upper limit of normal, WBC=white blood cell.

Serum Chemistry – Criteria for Markedly Abnormal Values (SI units)

Parameter	Unit	Low Abnormal	High Abnormal
ALT	Both	--	>3 × ULN
AST	Both	--	>3 × ULN
GGT	Both	--	>3 × ULN
Alkaline phosphatase	Both	--	>3 × ULN
Calcium	Conventional	<7.0 mg/dL	>11.5 mg/dL
	SI	<1.75 mmol/L	>2.88 mmol/L
Chloride	Conventional	<75 mEq/L	>126 mEq/L
	SI	<75 mmol/L	>126 mmol/L
Total bilirubin	Conventional	--	>2.0 mg/dL
	SI	--	>34.2 μmol/L
Albumin	Conventional	<2.5 g/dL	--
	SI	<25 g/L	--
Total protein	Both	<0.8 × LLN	>1.2 × ULN
Creatinine	Conventional	--	>2.0 mg/dL
	SI	--	>177 μmol/L
Blood urea nitrogen	Conventional	--	>30 mg/dL
	SI	--	>10.7 mmol/L
Sodium	Conventional	<130 mEq/L	>150 mEq/L
	SI	<130 mmol/L	>150 mmol/L
Potassium	Conventional	<3.0 mEq/L	>6.0 mEq/L
	SI	<3.0 mmol/L	>6.0 mmol/L
Glucose	Conventional	< 50 mg/dL	>350 mg/dL
	SI	< 2.8 mmol/L	>19.4 mmol/L
Bicarbonate	Conventional	<8.0 mEq/L	--
	SI	<8.0 mmol/L	--
Creatine kinase	Conventional	--	>5 × ULN
	SI	--	>5 × ULN
Total Cholesterol	Conventional	--	>300 mg/dL
	SI	--	>7.72 mmol/L
Triglycerides	Both	--	>2.5 × ULN
LDL Cholesterol	Conventional	< 50 mg/dL	>160 mg/dL
	SI	<1.30 mmol/L	>4.14 mmol/L
HDL Cholesterol	Conventional	<40 mg/DL	>60mg/DL
	SI	<1.04 mmol/L	>1.55 mmol/L
Direct Bilirubin	Conventional	--	>2 x ULN
Phosphorus	Conventional	<1.6mg/dL	>6.2 mg/dL
	SI	<0.52 mmol/L	>2mmol/L

ALT=alanine aminotransferase, AST=aspartate aminotransferase, GGT=γ-glutamyl transferase, LLN=lower limit of normal, ULN=upper limit of normal.

Appendix B Criteria for Markedly Abnormal Vital Signs

Parameter	Unit	Lower Criteria	Upper Criteria
Pulse	bpm	<50	>120
Systolic blood pressure	mm Hg	<85	>180
Diastolic blood pressure	mm Hg	<50	>110
Body temperature	^{o}C	< 35.6	>37.7

Appendix C Criteria for Markedly Abnormal 12-Lead ECG Parameters

Parameter	Unit	Lower Criteria	Upper Criteria
Heart Rate	bpm	< 50	> 120
PR	msec	≤ 80	≥ 200
RR	msec	≤ 600	≥ 1440
QRS	msec	≤ 80	≥ 180
QT Interval	msec	≤ 50	≥ 460
QTcB Interval	msec	≤ 50	≥ 500 OR ≥ 30 change from baseline and ≥ 450
QTcF Interval	msec	≤ 50	≥ 500 OR ≥ 30 change from baseline and ≥ 450

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
Personal Protected Information	Biostatistics Approval	07-Mar-2018 18:01 UTC
	Pharmacovigilance Approval	07-Mar-2018 18:27 UTC
	Clinical Approval	07-Mar-2018 18:35 UTC
	Clinical Pharmacology Approval	07-Mar-2018 19:39 UTC
	Biostatistics Approval	08-Mar-2018 15:02 UTC