STATISTICAL ANALYSIS PLAN

Protocol KCP-330-012

A Phase 2b, Open-Label, Single-Arm Study of Selinexor (KPT-330) Plus Low-Dose Dexamethasone (Sd) in Patients with Multiple Myeloma Previously Treated with Lenalidomide, Pomalidomide, Bortezomib, Carfilzomib, and Daratumumab, and Refractory to Prior Treatment with Glucocorticoids, an Immunomodulatory Agent, a Proteasome Inhibitor, and the anti-CD38 mAb Daratumumab

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STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

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DOCUMENT HISTORY

Version	Date	Author(s)	Brief Summary of Changes
1.0	December 13, 2017	PPD	Original
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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition	Abbreviation	Definition
AE	adverse event	mITT	modified intent-to-treat
ALT	alanine transaminase (SGPT)	MM	multiple myeloma
aPTT	activated partial thromboplastin time	MR	minimal response
AST	aspartate transaminase (SGOT)	MRD	minimal residual disease
ATC	Anatomic Therapeutic Class	NCI	National Cancer Institute
Bpm	beats per minute	OR	odds ratio
BSA	body surface area	ORR	overall response rate
BUN	blood urea nitrogen	OS	overall survival
C1D1	Cycle 1 Day 1	PD	progressive disease
CBR	clinical benefit rate	PDn	pharmacodynamic
CI	confidence interval	PFS	progression free survival
CR	complete response	PI	proteasome inhibitor
CSR	clinical study report	PK	pharmacokinetic
CTCAE	Common Terminology Criteria for Adverse Events	PP	per protocol
DCR	disease control rate	PR	partial response
DOR	duration of response	PT	preferred term
ECG	electrocardiogram	QoL	quality of life
ECOG	Eastern Cooperative Oncology Group	QRS	the portion of an electrocardiogram comprising the Q, R, and S waves, together representing ventricular depolarization
eCRF	electronic case report form	QTcB	QT interval corrected by Bazett's formula
EDTA	ethylenediaminetetraacetic acid	QTcF	QT interval corrected by Fridericia's formula
EFS	event-free survival	SAE	serious adverse event
EoS	eosinophil count - absolute	SAP	statistical analysis plan
EoT	End of Treatment	SAS	Statistical Analysis System
ETDRS	Early Treatment Diabetic Retinopathy Study	sCR	stringent complete response
FACT-G	Functional Assessment of Cancer Therapy – General	SD	stable disease
FACT-MM	Functional Assessment of Cancer Therapy – Multiple Myeloma	Sd	selinexor 80 mg plus dexamethasone 20 mg ("low-dose" dexamethasone)
FISH	fluorescent in situ hybridization	SI	International System of Units
FLC	free light chain	SOC	system organ class
GGT	gamma-glutamyl transferase	SPEP	serum protein electrophoresis
HCO3	bicarbonate	TEAE	treatment-emergent adverse event
Hgb	hemoglobin	TOI	trial outcomes index
IMiD	immunomodulatory drug	TSH	thyroid stimulating hormone
IMWG	International Myeloma Working Group	TTP	time to progression
INR	international normalization ratio	ULN	upper limit of normal
IRC	Independent Review Committee	UPEP	urine protein electrophoresis
ISS	International Staging System	VGPR	very good partial response
ITT	intent-to-treat	WBC	white blood cell
LDH	lactate dehydrogenase	WHO	World Health Organization
LLN	lower limits of normal	WHO DDE	World Health Organization Drug Dictionary Enhanced
MedDRA	Medical Dictionary for Regulatory Activities	XPO1	exportin 1
mg	Milligram		

1. OVERVIEW AND INVESTIGATIONAL PLAN

1.1. STUDY DESIGN

KCP-330-012 is a Phase 2b, single-arm, open-label, multicenter study of Sd (selinexor 80 mg plus dexamethasone 20 mg), both dosed twice weekly, for each week of a four-week cycle, in patients with multiple myeloma (MM) previously treated with alkylating agents, glucocorticoids, lenalidomide, pomalidomide, bortezomib, carfilzomib, and daratumumab, and refractory to prior treatment with glucocorticoids, at least one immunomodulatory agent (IMiD), at least one proteasome inhibitor (PI), and the anti-CD38 mAb daratumumab (i.e., penta-refractory MM). Note: refractory is defined as ≤ 25% response to therapy, progression during the previously described therapies, or progression within 60 days after completion of the therapy (per International Myeloma Working Group [IMWG] criteria 2016).

This study consists of two parts and will enroll approximately 210 patients overall. Part 1 (protocol V1.0-3.0) enrolled patients with both quad-refractory MM (i.e., previously treated with alkylating agents, glucocorticoids, lenalidomide, pomalidomide, bortezomib, carfilzomib, but not an anti-CD38 mAb, and refractory to prior treatment with glucocorticoids, at least one IMiD, and at least one PI) along with patients that had quad-refractory MM and whose disease was refractory to an anti-CD38 monoclonal antibody (i.e., penta-refractory MM). Part 2 (protocol V≥4.0) will enroll patients with penta-refractory MM only, and refractoriness to prior treatment with daratumumab (the only currently FDA approved anti-CD38 monoclonal antibody) is required.

The population for the primary efficacy analysis will contain only patients with penta-refractory MM enrolled in Part 2. Efficacy results for patients with quad-refractory MM and patients with penta-refractory MM enrolled in Part 1 will be analyzed separately. Safety analyses will be performed on the Part 2 patients with penta-refractory MM, the overall safety population of patients who received any amount of study treatment, presented together as well as separately by study part.

Patients receive oral selinexor 80 mg plus dexamethasone 20 mg (Sd), both dosed twice weekly, for each week of four-week cycles. Patients will receive treatment until progressive disease (PD), death, toxicity that cannot be managed by standard care, or withdrawal, whichever occurs first.

In select cases (e.g., for patients showing stable disease [SD] or partial response [PR] and tolerating treatment particularly well), the selinexor dose may be increased by 20 mg (up to a maximum of 100 mg per dose) after consultation with the Medical Monitor. The dose level for an individual patient may be escalated based on efficacy considerations only after a minimum of 2 cycles of study therapy. However, in no case may the dose for any patient exceed 70 mg/m^2. Prior to any potential dose increase, the BSA for the patient will be calculated and an individual patient's dose may not be increased if it would result in a dose > 70 mg/m^2.

Patient response at each time point will be assessed centrally by an Independent Review Committee (IRC) according to the IMWG response criteria (*Kumar 2016*) for MM. In Part 2, MM-specific assessments (i.e., serum protein electrophoresis [SPEP], urine protein electrophoresis [UPEP], serum/urine immunofixation, quantitative Ig levels, serum free light chain [FLC], and bone marrow aspirate) must be confirmed by a central laboratory to confirm

complete response (CR) or stringent complete response (sCR), per IMWG consensus criteria. Additional information is provided in the *IRC Charter* and *Study Manual*.

Patients may decide to discontinue study treatment for any reason. Patients who elect to discontinue study treatment should be encouraged to continue in the study so that follow-up information on disease progression, other antineoplastic therapy, symptoms and survival status may be obtained. However, patients may elect to withdraw consent and decline further participation in the trial at any time. The Investigator may remove a patient from study treatment using criteria described in Section 10.2 of Protocol V5.0.

The Investigator must determine the primary reason for a patient's discontinuation of study treatment and record this information on the electronic case report form (eCRF). Patients who are prematurely withdrawn from study treatment are not eligible to re-initiate study treatment on this protocol at a later date.

1.2. OBJECTIVES

1.2.1. Primary Objectives

Evaluate the efficacy (overall response rate [ORR] based on IRC assessment) for treatment with selinexor 80 mg plus low-dose dexamethasone (20 mg) (Sd) twice weekly (four-week cycles) in patients with penta-refractory MM previously treated with lenalidomide, pomalidomide, bortezomib, carfilzomib, and daratumumab; and refractory to prior treatment with glucocorticoids, an IMiD, a PI, and the anti-CD38 mAb daratumumab.

ORR will include patients who experience PR, very good partial response (VGPR), CR, or sCR, based on IMWG response criteria (*Kumar 2016*). The ORR for patients with penta-refractory MM in Part 2 will be compared to a minimal threshold level of 10%.

1.2.2. Secondary Objectives

The following endpoints will be analyzed separately for (a) Part 1 patients with quad-refractory MM, (b) Part 1 patients with penta-refractory MM, and (c) Part 2 patients with penta-refractory MM. Additionally, analyses of safety and tolerability will be performed on the overall population of patients from Parts 1 and 2 who received at least one dose of study treatment.

- Duration of response (DOR) = Duration from first observation of at least PR to time of PD, or death due to disease progression, whichever occurs first. DOR will be censored for death due to any causes other than disease progression.
- Clinical Benefit Rate (CBR = sCR + CR + VGPR + PR + minimal response [MR]), and duration of clinical benefit (Duration from first observation of at least MR to time of PD, or death due to disease progression, whichever occurs first. Duration of clinical benefit will be censored for death due to any cause other than disease progression.
- Disease Control Rate (DCR = CBR + SD [for a minimum of 12 weeks])
- Progression Free Survival (PFS = Duration from start of study treatment to PD or death [regardless of cause], whichever comes first)
- Time to Progression (TTP = Duration from start of study treatment to time of PD) obtained with selinexor plus dexamethasone vs. TTP on most recent prior therapy

- Time to Next Treatment (TTNT = Duration from start of study treatment to start of next anti-MM treatment or death due to disease progression, whichever occurs first)
- Overall Survival (OS = Duration from start of study treatment to death)
- Quality of Life (QoL) using the Functional Assessment of Cancer Therapy - Multiple Myeloma (FACT-MM)
- Safety and tolerability using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), v 4.03.
- Describe the Pharmacokinetics (PK) properties of selinexor in this patient population (Part 1 only)

1.2.3. CCI

CCI

1.4. STUDY PLAN

For each patient that signs the informed consent, the study consists of:

- Screening/baseline visit: occurs within 21 days prior to receiving the 1st dose of study treatment
- Treatment period: expected to be up to 12 months, but there is no maximum treatment duration. Patients will be treated until disease progression, death, toxicity that cannot be managed by standard care, or withdrawal from study, whichever occurs first
- Follow-up period: up to 12 months after last dose of study treatment, patients will be contacted approximately every 3 months for durability of response and survival follow-up

The End of Study (EoS) will occur when all patients have completed the 12-month follow-up period (i.e., when the last patient has expired, been followed for 12 months after last dose of study treatment, been lost to follow-up, or has withdrawn consent, whichever occurs first).

Please refer to Table 7-1 for detailed schedule of assessment and study activities.

1.5. INTERIM ANALYSIS

No interim analysis is planned for this study.

1.6. DATABASE LOCK

The primary analysis will be performed after all patients have completed the Cycle 2 MM Assessments, and will include a formal snapshot of database and analyses of efficacy, safety, and PK data. A clinical study report (CSR) will be prepared after the primary analysis. The data cut date for IRC-based MM response assessment may be later than the data cut date for other data points. All data points presented to IRC members for their assessment have been source verified.

At the time of the database snapshot for the primary analysis, the median DOR estimate may not be estimable with limited follow-up time. Therefore, an efficacy update on ORR and DOR among the Part 2 patients with penta-refractory MM will be provided before the submission of the New Drug Application (NDA) package.

The final analysis will be performed at the end of the study after all patients have completed the 12-month follow-up period (i.e., when the last patient has expired, been followed for 12 months after last dose of study treatment, been lost to follow-up, or has withdrawn consent, whichever occurs first). There will be a formal database lock and analyses of efficacy and safety data. A final CSR will be prepared summarizing the results from the full analysis.

1.7. MODIFICATIONS TO THE STATISTICAL SECTION OF THE PROTOCOL

The current SAP is based on Protocol v5.0. The following modifications were made to the statistical section of protocol.

Analysis Populations

- Additional analysis populations for efficacy endpoints and additional safety populations (Sections 3.1.1, 3.1.2, and 3.1.3) are defined to present data in a comprehensive manner.
- The definition of the modified intent-to-treatment (mITT) population is revised to include patients who did not meet all eligibility criteria but received Sponsor waiver to participate in the study. Waivers are not granted to patients who do not meet key eligibility criteria such as required prior therapies and measurable disease at baseline.
- The definition of the per-protocol population is revised (Section 3.1.1). The requirement of having completed at least one cycle of treatment is removed. Instead, patients are required to have at least one adequate post-baseline response assessment unless they died or withdrew from the study before that. Moreover, patients are required to have a compliance rate of at least 70% of selinexor instead of 80%.

Secondary Efficacy Endpoints

- The censoring rules for the secondary endpoints of duration of clinical benefits is revised to follow the TTP rule, such that it is consistent with the censoring rule for duration of response.
- The endpoint of duration of disease control is removed.

- The secondary endpoint of TTNT is added.

CCI [redacted]

- [redacted]

CCI [redacted]

- [redacted]

- [redacted]

1.8. STATISTICAL MODIFICATIONS MADE IN THE STATISTICAL ANALYSIS PLAN

Changes to Version 1.0

Section 1.2.3

- Clarified the definition of normal LDH at baseline (CCI [redacted]) to be "lower than or equal to upper limit normal"
- Clarified the hierarchical order of obtaining chromosomal abnormalities status: test results from central laboratories will be used if available, otherwise, test results from local laboratories will be used if available, otherwise, FISH results from initial diagnosis will be used if available.

Section 1.6

- The primary analysis will be performed after all patients have completed the Cycle 2 MM assessment, instead of Cycle 3 assessment
- Clarified the primary analysis will be performed based on a formal snapshot of database. In other words, data points in the database can still change after the primary analysis, but this snapshot will be frozen and will not change.

Section 2.6

- Revised the definition of visit windows for selected endpoints that are summarized/plotted by time points.

Section 2.7

- Added 2 subgroup factors on prior use of daratumumab

Section 3.1

- Added 2 additional analysis populations: the *All Penta-ref* population and the *Efficacy-Evaluable (EE) population*
- Removed the Part 1 six doses per cycle population and the Part 1 eight doses per cycle population

Section 3.1.2

- Corrected that the subset of safety population from Part 2 is different from the mITT population

Section 4.1.3

- CCI [redacted]
  - [redacted]
  - [redacted]
- CCI [redacted]

Section 4.2.1.3

- CCI [redacted]

Section 4.2.4-4.2.5

- Clarified that "missing 2 or more consecutively scheduled assessments" means a gap of 65 days or longer between 2 consecutive, adequate assessments.

Section 4.2.6.1

- Corrected the TTNT definition

Section 4.2.7.1

- Clarified for the calculation of overall survival, patients without on-study death events will be censored at the date of discontinuation from the study, or date of last participating visit (e.g., a telephone contact with patient status being alive), or database cut date, whichever is earlier.

Section 5.1.2.1

- Revised AE summary table

2. GENERAL STATISTICAL METHODS AND DATA HANDLING

2.1. GENERAL ANALYSIS METHODS

This is a single-arm, open-label study. All summary statistics will be computed and displayed among the corresponding analysis population, and by each scheduled assessment time point whenever applicable. Summary statistics for continuous variables will minimally include n, mean, standard deviation, minimum, median, and maximum. For categorical variables, frequencies and percentages will be presented. For time-to-event variables, the Kaplan-Meier method will be used for descriptive summaries. Graphical displays will be provided as appropriate. Data listings will be provided as appropriate.

2.2. MISSING DATA HANDLING IN DATA PRESENTATION

In general, missing baselines will not be imputed. The following approaches are default methods for missing data handling in summary tables.

- Categorical data at baseline will be summarized using counts (n) and percentages (%). Denominator will be the analysis population specified for the summary, unless otherwise specified. Missing data may be presented as a separate category.
- Continuous data: summaries will be based on observed data only.

2.2.1. Handling of Computation of Treatment Duration if Study Treatment End of Treatment Date is Missing

For the calculation of treatment duration, the date of the last dose of study treatment is equal to the date of last study treatment dosing reported on study treatment dosing form. If all the dosing dates are missing, then the duration is missing.

The last dose intake should be clearly identified on the eCRF dosing page and should not be approximated by the last returned package date.

2.2.2. Handling of Missing/partial Dates for Adverse Events or Concomitant Medications

In general, the imputation should be conservative such that onset dates should be imputed to be as early as possible and resolution dates will be imputed to be as late as possible. Impute resolution date first and then impute onset date using imputed resolution date. However, for categorization purpose, if the partial AE onset date information does not indicate whether the AE started prior to treatment or after the treatment-emergent adverse event (TEAE) period, the AE will be classified as treatment-emergent.

These data imputations are for categorization purpose or calculation of AE duration, and will not be used in listings. In data listings, an ongoing flag will be identified from the eCRF AE page.

Refer to the Karyopharm Biostatistics and Statistical Programming Rule Book for details on imputation methods.

2.2.3. Handling of Missing or Partial Birth Date for Calculation of Age

Refer to the Karyopharm Biostatistics and Statistical Programming Rule Book for details on imputation methods.

2.2.4. Handling of AEs When Date and Time of First Dose of Study Treatment Are Missing

When the date and time of the first dose of study treatment are missing, all AEs that occurred on or after signing the informed consent should be considered as TEAEs. The exposure duration should be kept as missing.

2.2.5. Handling of Missing Assessment of Relationship of AEs to Study Treatment

If the assessment of the relationship to study treatment is missing, then the relationship to study treatment in the frequency tables is considered as possibly related, but no imputation should be done at the data level or in data listings.

2.2.6. Handling of Missing Severity of AEs

If the severity is missing for one of the treatment-emergent occurrences of an AE, the maximal severity on the remaining occurrences will be considered. If the severity is missing for all the occurrences, a "missing" category will be added in the summary table.

2.3. STUDY TREATMENT DOSING DATE

Study treatment dosing date is the date on which a patient actually received study treatment (Sd, partial or complete).

The date of first study treatment is defined as the earliest date of non-zero dose of either selinexor or dexamethasone. The date of last study treatment is defined as the latest date of non-zero dose of either selinexor or dexamethasone.

2.4. STUDY DAY CALCULATION

Based on the study protocol, study Day 1 is the first study treatment dosing date. The day before Day 1 is considered Day -1; there is no Day 0.

A patient is considered as treated in a cycle if the patient received any non-zero dose of either selinexor or dexamethasone in that cycle.

Study day for a given assessment is defined as

- the assessment date – the date of first study treatment + 1 if the assessment date is on or after Day 1, or
- the assessment date – the date of first study treatment if the assessment date is before Day 1.

2.5. BASELINE MEASUREMENT

In general, the baseline value is defined as latest value prior to the first dose of study treatment. In the case an assessment performed on the same date as the first dose, but it is impossible to determine the evaluation time relative to the time of taking the first dose, the evaluation time will be assumed to be following the protocol-defined schedule.

Complete myeloma disease assessments are carried out during the Screening period and on Cycle 1 Day 1 (C1D1) prior to dosing Sd. In general, values on C1D1 are used as baseline. However, the IRC will determine which values are most clinically appropriate for use as

baseline, and if values are missing on C1D1, if the values obtained during the Screening period are appropriate as baseline.

2.6. VISIT WINDOWS

For safety data that are summarized/plotted by time points, non-missing assessments from all scheduled and unscheduled visits will be mapped to an appropriate analysis visit using a windowing scheme. Analysis visit windows are defined in Table 2-1. If there are 2 or more assessments mapped to the same analysis visit for a patient, the assessment that is closest to the target visit day will be used for analysis. If there are 2 or more assessments mapped to the same analysis visit with the same distance from the target visit day, then the latest one is selected for the analysis.

Table 2-1 Visit Windows for Clinical Laboratory Tests and Vital Signs

Analysis Visit Name	Target Visit Day	Study Day Range in Window
Baseline	Day 1	Prior to or on Day 1
Day 15	Day 15	Day 9 to 21
Day 29	Day 29	Day 23 to 35
Day 43	Day 43	Day 37 to 49
Day 57	Day 57	Day 51 to 63
Day 85	Day 85	Day 79 to 91
(every 28 days)		
…		
NOTE: Day 1 is the date of first study treatment dose. The visit window is +/- 6 days for post-baseline visits. Analysis visit and visit window may change for certain parameters depending on the data availability.		

2.7. SUBGROUPS

Subgroup analysis on selected efficacy endpoints will be conducted by

- R-ISS for MM (stage I, II, and III respectively)
- Region (US vs. non-US).
- FLC MM patient (yes vs. no), a FLC MM patient is defined as a patient without measurable disease in SPEP or UPEP, but with measurable disease in FLC, all based on baseline value.
- Prior daratumumab alone or in combination
    - ever received daratumumab in a combination therapy vs. as single agent ± dexamethasone

- received daratumumab in last line prior treatment (in combination therapy or as single agent ± dexamethasone) vs. did not receive daratumumab in last line prior treatment

2.8. POOLING OF CENTERS FOR STATISTICAL ANALYSES

All participating centers in the study will be pooled together for analysis.

2.9. COMPUTING AND CODING STANDARDS

Activities will be performed using the following tools:

Table, listing, and figure production	SAS Version 9.4 or higher
Coding	
AEs	MedDRA Version 20.1
Medical Histories	MedDRA Version 20.1
Prior and Concomitant Medications	WHO DDE Version March 2017
Grading	
AEs	CTCAE Version 4.0
Labs	CTCAE Version 4.03

3. PATIENT INFORMATION

3.1. DISPOSITION OF PATIENTS AND ANALYSIS POPULATIONS

This study consists of two parts. Part 1 (Protocol v1.0-3.0) enrolled patients with both quad-refractory MM and penta-refractory MM. Part 2 (Protocol v≥4.0) enroll patients with penta-refractory MM only.

Patient disposition will be summarized for Part 1 and Part 2 patients separately. Patient study status will be summarized in each of the following categories:

- Screened patients, defined as any patient who has signed the informed consent form
- Patients who met study eligibility criteria (including patients who did not meet all eligibility criteria per the protocol in effect at the time of enrollment but received waiver from Sponsor) but did not receive any dose of study treatment (partial or complete)
- Patients who met study eligibility criteria (including patients who did not meet all eligibility criteria per the protocol in effect at the time of enrollment but received waiver from Sponsor) and received at least one dose of study treatment (partial or complete)
- An end-of-treatment disposition:
    - Patients who were still on treatment
    - Patients who discontinued treatment and primary reason for treatment discontinuation
- An end-of-study disposition:
    - Patients who were still on study
    - Patients who withdrew from study and primary reason for study withdrawal

3.1.1. Efficacy Populations

The primary efficacy populations will only include patients from Part 2. Results for Part 1 patients will be summarized and analyzed separately.

The ***modified intent-to-treat (mITT) population*** will consist of Part 2 patients with penta-refractory MM who met all eligibility criteria (or did not meet all eligibility criteria but received waiver from Sponsor to enter the study), and received at least one dose of study treatment (partial or complete). This population will include patients who have discontinued therapy due to toxicity or PD and patients who have died from any cause, including those related to study treatment or disease. The mITT population will be used for the primary efficacy analyses.

The ***BCLPD-ref population*** will consist of patients in Part 2 who had MM *documented* to be refractory to bortezomib, carfilzomib, lenalidomide, pomalidomide, and daratumumab, and received at least one dose of study treatment (partial or complete).

The ***CLPD-ref population*** will consist of patients in Part 2 who had MM *documented* to be refractory to carfilzomib, lenalidomide, pomalidomide, and daratumumab, and received at least one dose of study treatment (partial or complete).

The ***BCPD-ref population*** will consist of patients in Part 2 who had MM *documented* to be refractory to bortezomib, carfilzomib, pomalidomide, and daratumumab, and received at least one dose of study treatment (partial or complete).

The ***CPD-ref population*** will consist of patients in Part 2 who had MM *documented* to be refractory to carfilzomib, pomalidomide, and daratumumab, and received at least one dose of study treatment (partial or complete). Note that this population has MM that is refractory to both second generation IMiDs (pomalidomide) and proteasome inhibitor (carfilzomib), as well as daratumumab.

The BCLPD-ref, CLPD-ref, BCPD-ref, CPD-ref populations will be used for supportive inferences concerning efficacy.

A patient is claimed to have documented refractory to a therapy if one of the following criteria is met:

- Best response on the therapy is SD or worse
- Patient progressed or relapsed during treatment
- Patient progressed or relapsed within 60 days after discontinuing this therapy.

If the date of treatment discontinuation or the date of disease progression/relapse is missing (partially or completely), unless it can be determined that one of the above criteria is met (e.g., both dates have day missing, but have the same year and month), the patient is determined to not have documented refractory.

3.1.2. Safety Population

The safety population will consist of all patients from Part 1 and Part 2, who have received at least one dose of study treatment (partial or complete) and have any post-baseline safety information.

Safety outputs will be presented by the following groups:

- Overall safety population
- The subset of safety population from Part 2
- The subset of safety population from Part 1

3.1.3. Additional Analysis Populations

Analysis of selected efficacy endpoints will be conducted in the following populations respectively:

The ***All Penta-ref*** population will consist of all patients from mITT (Part 2) and all Part 1 patients with penta-refractory MM who met all eligibility criteria (or did not meet all eligibility criteria but received waiver from Sponsor to enter the study), and received at least one dose of study treatment (partial or complete).

The ***high-risk population*** will consist of all Part 2 patients with penta-refractory MM with any of the following high-risk chromosomal abnormalities including del (17p)/p53, t(14; 16), t(4; 14), and 1q21, and received at least one dose of study treatment (partial or complete).

Chromosomal abnormalities are determined by the FISH test. If adequate test results from a central laboratory are available, such results will be used to determine the chromosomal abnormality status; otherwise, test results from the local site's laboratory will be used. If local laboratory results are not available either, FISH results from initial diagnosis (Disease History eCRF page) will be used if available. In the absence of test results indicating abnormality, a patient will be classified as normal for the corresponding mutation.

The ***Efficacy-Evaluable (EE) population*** will consist of all patients in the mITT population with at least one adequate post-baseline IRC-based MM response assessment.

The ***per-protocol (PP) population*** will consist of all patients in the mITT population who meet the following criteria:

- Have selinexor compliance ≥ 70%, see Section 3.4.2 for the definition of selinexor compliance rate.
- Have at least one adequate post-baseline response assessment unless died or withdrew from study before that.

The ***Part 1 quad-ref MM population*** (Part 1 – Quad) will consist of all quad-refractory patients in Part 1 who received at least one dose of study treatment (partial or complete).

The ***Part 1 penta-ref MM population*** (Part 1 – Penta) will consist of all penta-refractory patients in Part 1 who received at least one dose of study treatment (partial or complete).

Selected safety endpoints will be summarized within the Part 1 - Quad and Part 1 - Penta, populations respectively.

3.2. DEMOGRAPHICS AND BASELINE CHARACTERISTICS

In general, the baseline value is defined as latest value prior to the first dose of study treatment.

3.2.1. Demographic Data

Demographic variables include sex (female, male), race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Other), ethnicity, and age at study entry.

3.2.2. Prior Therapies

Prior therapies for MM will be summarized with the following variables:

- Exposure/refractory status to each individual MM treatment including lenalidomide, pomalidomide, bortezomib, carfilzomib, and daratumumab, alkylating agent, glucocorticoid, anthracyclines, and stem cell transplant
- Refractory status to at least one IMiD, one PI, and daratumumab
- Refractory status to all five therapies including bortezomib, carfilzomib, lenalidomide, pomalidomide, and daratumumab
- Refractory status to all five therapies except bortezomib
- Refractory status to all five therapies except lenalidomide
- Refractory status to carfilzomib, pomalidomide, and daratumumab

- Number of prior systemic therapies (summarized as a continuous variable and as a categorical variable) and months from most recent prior systemic therapy to start of study treatment

The duration to be summarized is defined as follows.

- Months from most recent prior systemic therapy to start of study treatment will be calculated as (date of first dose of study treatment – stop date of most recent systemic therapy +1)/ (365.25/12).

3.2.3. Medical/surgical History

Medical/surgical history will be summarized in the mITT population by system organ class (SOC) and preferred term (PT) using the number and percentage of patients who had at least one occurrence of a SOC and PT. The summary will be sorted by alphabetic order in SOC, and further by decreasing frequency of PT within each SOC in the mITT population. When more than one PT has the same frequency, the order of presentation will be alphabetical in PTs.

3.2.4. Disease History

Disease history includes disease stage at initial diagnosis, disease stage at active myeloma, current disease stage according to ISS (or R-ISS if parameters available) for MM, and the following results at initial diagnosis: β_2 microglobulin, albumin, immunoglobulin type, light chain type, availability of bone marrow results, % plasma cells, and availability of FISH results. Smoking history including status (Never used, Current, Former), and frequency when applicable will also be recorded.

3.2.5. Physical Examination and Vital Signs

At screening, a full physical examination will be performed including height (without shoes) in centimeters (cm), weight (indoor clothing without shoes) in kilograms (kg), temperature, heart rate, systolic and diastolic blood pressure, and oxygen saturation. Significant findings that were present prior to the signing of informed consent must be included on the eCRF medical history page. Significant new findings, including the presence of plasmacytomas, that begin or worsen after informed consent must be recorded on the eCRF AE or Plasmacytoma page.

3.2.6. Eastern Cooperative Oncology Group (ECOG) Score

The ECOG performance status (Grade 0-5) will be recorded at screening.

3.2.7. Analysis Methods

Continuous data will be summarized using the number of available observations, mean, standard deviation, median, minimum, and maximum. Categorical and ordinal data will be summarized using the number and percentage of patients with the denominators for the percentages determined based on the analysis population used, unless otherwise specified. Demographics and baseline characteristics will be summarized among mITT, PP, BCLPD-ref, CLPD-ref, BCPD-ref, and CPD-ref populations respectively. P-values on demographic and baseline characteristic data will not be calculated. No specific description of the safety parameters will be provided at baseline. If relevant, the baseline values will be described along with each safety analysis.

3.3. CONCOMITANT MEDICATIONS AND PROCEDURES

3.3.1. Concomitant Medications and Procedures

Concomitant medications are any treatments received by the patient concomitantly with study treatment, from first dose of study treatment to last dose of study treatment + 30 days.

Concomitant medications include all medications used to mitigate AEs such as nausea, for supportive care, to treat or prevent infection, or to maintain the use of dexamethasone in combination of selinexor in this study. All concomitant medication(s) must be reported on the eCRF. Any diagnostic, therapeutic, or surgical procedure performed during the study period should be recorded, including the dates, description of the procedure(s), and any clinical findings, if applicable.

All medications will be coded using the WHO DDE Version March 2017.

Please refer to the Karyopharm Biostatistics and Statistical Programming Rule Book on definitions on prior and post-treatment medications.

3.3.2. Analysis Methods

Concomitant medications will be summarized according to the WHO DDE dictionary using the mITT population, by the anatomic and therapeutic class (ATC) level 2 (therapeutic level) and level 4 (generic level). All ATC codes corresponding to a medication will be summarized, and patients will be counted once in each ATC category linked to the medication. Therefore, patients may be counted several times for the same medication. The summary will be sorted by decreasing frequency in ATC level 2 and then ATC level 4 in the mITT population.

Please refer to Section 2 for details on data handling rules related to computation, dates, imputation for missing dates.

3.4. EXTENT OF STUDY TREATMENT EXPOSURE AND COMPLIANCE

The extent of study treatment exposure and compliance will be summarized in safety population.

3.4.1. Extent of Study Treatment Exposure

The extent of exposure for the study treatment will be assessed using the following variables:

- Duration of study treatment exposure
- Number of selinexor doses received
- Number of dexamethasone dose received
- Number and percentage of patients with a selinexor dose reduction
- Number and percentage of patients with a dexamethasone dose reduction
- Number and percentage of patients with a selinexor dose interruption
- Number and percentage of patients with a dexamethasone dose interruption
- Number and percentage of patients with study treatment discontinued

Duration of study treatment exposure is defined as the date of last study treatment - date of first study treatment + 1, regardless of unplanned intermittent discontinuation.

3.4.2. Compliance

Study treatment compliance will be summarized descriptively as a quantitative variable among the mITT population, calculated as

$$\frac{\text{number of study treatment doses taken}}{\text{number of study treatment doses prescribed}} \times 100.$$

A study treatment dose is considered prescribed if selinexor and/or dexamethasone is prescribed. The number and percentage of patients with study treatment compliance ≥70% will be provided. Note that the number of prescribed study treatment doses does not include doses missed due to treatment interruption or other reasons not related to patient choice.

Selinexor compliance is defined similarly among the mITT population as

$$\frac{\text{number of selinexor doses taken}}{\text{number of selinexor doses prescribed}} \times 100.$$

The number and percentage of patients with selinexor compliance ≥70% will be provided. Similarly, the number of prescribed selinexor doses does not include doses missed due to treatment interruption or other reasons not related to patient choice. Patients with selinexor compliance < 70% will be excluded from the PP population.

4. EFFICACY

Patient response at each time point will be assessed centrally by an IRC according to the IMWG response criteria (*Kumar 2016*) for MM. Unless otherwise specified, MM response assessment refers to assessment determined by IRC. The primary endpoint (ORR) is based on these IRC assessed responses in the mITT population.

Documentation of response requires two consecutive readings of the applicable disease parameter (serum M-protein, urine M-protein, serum FLC, or quantitative immunoglobulin level), performed at any time with no minimum interval required between the two readings. The date of response or PD will be assigned to the earlier date of the two independent samples, unless PD is based on an unambiguous criterion such as a new plasmacytoma lesion.

If a patient had one PD assessment but was not subsequently confirmed, unless IRC considers the progression assessment unambiguous, it is not considered a PD (*Kumar 2016*).

Unless otherwise specified, efficacy analyses will use the mITT population. Analyses for the primary efficacy endpoint of ORR and the key secondary efficacy endpoints of DOR, CBR, and duration of clinical benefit will be repeated in the other efficacy populations and additional analysis populations. If relevant, selected efficacy analyses for other efficacy endpoints will be repeated in selected additional analysis populations.

4.1. PRIMARY EFFICACY ENDPOINT

4.1.1. Definition

The primary endpoint is ORR which is defined as the proportion of patients who achieve a confirmed PR or better (i.e., PR, VGPR, CR, or sCR), as assessed by the IRC, during or after the study treatment, before documented disease progression or initiating a new MM treatment.

4.1.2. Primary Analysis of ORR

For the primary analysis of superiority to the minimal threshold ORR, analysis will be performed using the 2-sided, exact 95% confidence interval (CI), calculated for the rate of ORR among the mITT population, and statistical significance will be declared if the lower bound of this interval is greater than 10%.

4.1.3. Supportive Analyses of ORR

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4.2. SECONDARY EFFICACY ENDPOINTS

Several of the secondary efficacy endpoints define durations based on either the progression free survival (PFS) status and time, or time to progression (TTP) status and time. In PFS, death with any cause is considered as an event. In TTP, only death due to disease progression is considered as an event. Please refer to Table 4-1 and Table 4-2 for details on censoring rules for PFS and TTP respectively.

4.2.1. Duration of Response (DOR)

4.2.1.1. Definition

DOR is defined for patients with a confirmed PR or better as the duration from first observation of at least PR to time of IRC-determined PD or death due to disease progression, whichever occurs first. The censoring method for DOR is the same as the censoring method for TTP in Table 4-2.

4.2.1.2. Analysis Methods

DOR will be summarized descriptively among those with a confirmed PR or better. Median DOR with 95% CI will be estimated based on the Kaplan-Meier method. The Kaplan-Meier curve for the duration of response will be provided.

4.2.1.3. Supportive Analyses of DOR

As supportive analyses, median DOR and 95% CI will be calculated:

- Using the BCLPD-ref, CLPD-ref, BCPD-ref, CPD-ref, all penta-ref, high-risk, EE, PP, Part 1 – Quad, Part 1 – Penta, populations respectively, if sufficient data exist
- In patients with R-ISS for MM stage I, II, and III respectively, if sufficient data exist
- In US vs. non-US patients, if sufficient data exist
- In FLC MM vs. non-FLC MM patients, if sufficient data exist.
- In patients ever received daratumumab as in combination therapy vs. as single-agent ± dexamethasone, if sufficient data exist.
- In patients received daratumumab in last line prior treatment vs. did not receive daratumumab in last line prior treatment, if sufficient data exist.

4.2.2. Best Overall Response and Clinical Benefit Rate (CBR)

4.2.2.1. Definition

The number and percentage of patients in the individual response categories (MR, PR, VGPR, CR, sCR) based on best response will be calculated respectively.

CBR is defined as the proportion of patients who achieve a confirmed MR or better, i.e., MR, PR, VGPR, CR, sCR. Duration of clinical benefit is defined as the duration from first observation of at least MR to time of IRC-determined PD or death due to disease progression, whichever occurs first. Responders without IRC-determined PD or death due to disease progression will be censored at the censored date for TTP.

4.2.2.2. Analysis Methods

The rate of CBR and the 2-sided, exact 95% CI will be calculated using the mITT population. Median duration of clinical benefit with 95% CI will be estimated based on the Kaplan-Meier method. The Kaplan-Meier curve for the duration of clinical benefit will be provided.

As supportive analyses, CBR rate and 95% CI will be calculated:

- Using the BCLPD-ref, CLPD-ref, BCPD-ref, CPD-ref, all penta-ref, high-risk, EE, PP, Part 1 – Quad, Part 1 – Penta, doses populations respectively.
- In patients with R-ISS for MM stage I, II, and III respectively
- In US vs. non-US patients
- In FLC MM vs. non-FLC MM patients.

Median duration of clinical benefit with 95% CI will be calculated in these analysis populations and subgroups when sufficient data exist.

4.2.3. Disease Control Rate (DCR)

4.2.3.1. Definition

DCR is defined as the proportion of patients who achieve SD for a minimum of 12 weeks, or better (i.e., SD for a minimum of 12 weeks, MR, PR, VGPR, CR, sCR).

4.2.3.2. Analysis Methods

The rate of DCR and the 2-sided, exact 95% CI will be calculated using the mITT population.

As supportive analyses, DCR rate and 95% CI will be calculated:

- Using the BCLPD-ref, CLPD-ref, BCPD-ref, and CPD-ref populations respectively, if sufficient data exist

4.2.4. Progression Free Survival (PFS)

4.2.4.1. Definition

PFS is defined as the duration from start of study treatment to time of IRC-determined PD or death from any cause, whichever occurs first. Please refer to Table 4-1 for details on PFS outcome status (PFS event vs. censored) and date definition. Unless otherwise specified, PD status refers to confirmed PD or PD by unambiguous criteria based on IRC assessment. If PD is based on 2 independent samples on an applicable disease parameter, date of PD refers to the earlier date of the 2 independent samples.

4.2.4.2. Analysis Methods

A duration is calculated as end date – start date + 1. For instance, if a PFS event occurs, then PFS time (in days) is defined as event date – start date of study treatment + 1. If a censoring event occurs, then PFS time is defined as the censoring date – start date of study treatment + 1.

Table 4-1 PFS outcome and censoring definition

Situation	Date of event or censoring	Outcome
No adequate post-baseline disease status assessment unless death occurs prior to first post-baseline assessment	Start of study treatment	Censored
Death before IRC-determined PD without a gap of 65 days or longer before death	Death date	PFS event
IRC-determined PD without a gap of 65 days or longer before progression	Date of PD	PFS event
No IRC-determined PD or death on or before a. database cut, b. withdrawal of informed consent, c. lost to follow-up, d. documented treatment discontinuation e. start of new MM treatment, whichever occurs first	Date of last adequate disease assessment prior to the earliest occurrence of the events (a. – e.) listed in the left column	Censored
No IRC-determined PD or death before a gap of 65 days or longer, which corresponds to 2 or more consecutively missed scheduled disease status assessment	Date of last adequate disease assessment prior to the gap	Censored

Median PFS with 95% CI will be estimated based on the Kaplan-Meier method. The Kaplan-Meier curve for PFS will be provided.

The following supportive analyses will be conducted:

- PFS based on Investigator assessment
- PFS in the BCLPD-ref, CLPD-ref, BCPD-ref, and CPD-ref populations respectively, if sufficient data exist

4.2.5. Time to Progression (TTP)

4.2.5.1. Definition

TTP is defined as the duration from start of study treatment to time of IRC-determined PD or death due to disease progression, whichever occurs first. Please refer to Table 4-2 for details on TTP outcome status and date definition. Unless otherwise specified, PD assessment refers to assessment determined by IRC. But for the cause of death, disease progression refers to investigator assessment as specified on the eCRF death report page.

4.2.5.2. Analysis Methods

Table 4-2 TTP outcome and censoring definition

Situation	Date of event or censoring	Outcome
No adequate post-baseline disease status assessment unless death due to disease progression occurs prior to first post-baseline assessment	Start of study treatment	Censored
Death due to disease progression before IRC-determined PD without a gap of 65 days or longer before death	Death date	TTP event
IRC-determined PD without a gap of 65 days or longer before progression	Date of disease progression	TTP event
No IRC-determined PD or death due to disease progression on or before 1. Death due to reasons other than disease progression 2. database cut, 3. withdrawal of informed consent, 4. lost to follow-up, 5. documented treatment discontinuation 6. start of new MM treatment, whichever occurs first	Date of last adequate disease assessment prior to the earliest occurrence of the events (1. – 6.) listed in the left column	Censored
No IRC-determined PD or death due to disease progression before a gap of 65 days or longer, which corresponds to 2 or more consecutively missed scheduled disease status assessment	Date of last adequate disease assessment prior to the gap	Censored

Median TTP with 95% CI will be estimated based on the Kaplan-Meier method. The Kaplan-Meier curve for TTP will be provided.

The following supportive analyses will be conducted:

- TTP based on Investigator assessment
- TTP in the BCLPD-ref, CLPD-ref, BCPD-ref, and CPD-ref populations respectively, if sufficient data exist
- TTP on most recent prior therapy

Note that MM response assessment is scheduled to be conducted every 28 days. The maximum allowed gap length of 64 days is selected to correspond to 2 scheduled response assessments while allowing small deviations from target dates.

4.2.6. Time to Next Treatment (TTNT)

4.2.6.1. Definition

TTNT is defined as the duration from start of study treatment to start of next anti-MM treatment or death, whichever occurs first. For patients without an event, their follow-up time will be censored at the date of discontinuation from study, or last participating visit.

4.2.6.2. Analysis Methods

Median TTNT with 95% CI will be estimated based on the Kaplan-Meier method. The Kaplan-Meier curve for TTNT will be provided.

The following supportive analyses will be conducted:

- TTNT in the BCLPD-ref, CLPD-ref, BCPD-ref, and CPD-ref populations respectively, if sufficient data exist
- TTNT on most recent prior therapy

4.2.7. Overall Survival (OS)

4.2.7.1. Definition

OS is defined as the duration from start of study treatment to death from any cause. If death event did not occur during the follow-up period, the patient is censored at the date of discontinuation from the study, or date of last participating visit (e.g., a telephone contact with patient status being alive), or database cut date, whichever is earlier.

4.2.7.2. Analysis Methods

The proportion of patients with death event and the 2-sided, exact 95% CI will be calculated using the mITT population. Median OS time with 95% CI will be estimated based on the Kaplan-Meier method. The Kaplan-Meier curve for OS will be provided.

The following supportive OS analyses will be conducted:

- Using the BCLPD-ref, CLPD-ref, BCPD-ref, CPD-ref populations respectively
- Using the all penta-ref, high-risk, EE, PP, Part 1 – Quad, Part 1 – Penta, respectively, if sufficient data exist

- The same as in primary OS analysis except additional censoring at the start date of a new MM treatment
- In patients with R-ISS for MM stage I, II, and III respectively, if sufficient data exist
- In US vs. non-US patients, if sufficient data exist
- In FLC MM vs. non-FLC MM patients, if sufficient data exist
- In patients with a best response of confirmed PR or better
- In patients with a best response of confirmed MR or better
- In patients with a best response of confirmed MR
- In patients with a best response of SD or worse (including patients whose disease is not evaluable)

4.2.8. Quality of life (QoL)

4.2.8.1. Definition

Health-related QoL and potential for improvement over the course of the study will be assessed using the Functional Assessment of Cancer Therapy – Multiple Myeloma (FACT-MM) patient-reported outcome questionnaire that is specifically relevant to MM. This instrument combines the general version of the FACT (FACT-G) with a MM-specific subscale (14 items). The subscales for the FACT-G are Physical Well-Being (7 items), Social/Family Well-Being (7 items), Emotional Well-Being (6 items), and Functional Well-Being (7 items). The trial outcomes index (TOI; total of 41 items) will be the primary measurement of interest, comprised of the Physical and Functional subscales plus the MM-specific subscale. Each item is rated on a 5-point Likert scale, ranging from 0 ("Not at all") to 4 ("Very much"), therefore the TOI has a score ranging from 0 to 120. The QoL assessment will be performed at Baseline (prior to first dose of study treatment), Day 1 of each cycle on or after the second, and at the Final visit.

4.2.8.2. Analysis Methods

The primary analysis for QoL will be based on the change from baseline on the TOI score at each assessment time point, which will be summarized using descriptive statistics including mean, standard deviation, median, minimum, and maximum. The total score considering all 5 subscales as well as the 5 individual subscale sums of scores will be summarized similarly. The same analysis windows as in Table 2-1 will be used with the only exception that C1D15 is not considered as the questionnaire was not scheduled to administer during that visit.

The following supportive analyses will be conducted:

- In patients with a best response of confirmed PR or better
- In patients with a best response of confirmed MR or better

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5. SAFETY

Safety analyses will use the safety population with the outputs presented by the following groups:

- Overall safety population
- The subset of safety population from Part 2
- The subset of safety population from Part 1

Safety analyses will be based on the reported AEs and other safety information, such as 12-lead electrocardiogram (ECG), ophthalmic exam, clinical laboratory assessments including hematology, serum chemistry, coagulation parameters, and urinalysis, vital signs, physical examination, and pregnancy testing.

Observation period

The observation period will be divided into the following periods:

- The pre-treatment period is defined as the time from the signed informed consent date up to first dose of study treatment.
- The treatment period is defined as the time from first dose of study treatment to last dose of study treatment + 30 days inclusive.
- The post-treatment period is defined as the time beyond the treatment period.

The on-study observation period is pre-treatment, treatment, and post-treatment period.

General rules

All safety analyses will be performed using the following common rules:

- Safety data in patients who do not belong to the safety population (e.g., enrolled but did not receive any dose of study treatment, partial or complete) will be listed separately.
- The baseline value is the last available value before the first dose of study treatment.
- The analyses of the safety variables will be essentially descriptive and no systematic testing is planned.

5.1. ADVERSE EVENTS

5.1.1. Definitions

An AE is defined as any undesired medical occurrence in a patient or clinical investigation patient receiving a pharmaceutical product regardless of a causal relationship with this treatment. An AE can therefore be any unfavorable sign and unintended sign (including an abnormal laboratory finding), symptom, or disease temporarily associated with the use of a study treatment, whether or not related to the study treatment.

AE observation period

- Pre-treatment AEs are AEs that developed or worsened or became serious from the signed informed consent up to first dose of study treatment.
- ***Treatment-emergent adverse events (TEAE)*** are defined as any AE that developed or worsened or became serious during the treatment period (time from first dose of study treatment to last dose of study treatment + 30 days inclusive); or any AE with a start date after the first dose of study treatment, and is considered related to study treatment by the Investigator. Note that any AE that was present at baseline but worsened in toxicity grade after first dose of study treatment, and is subsequently considered as related to study treatment shall be considered as TEAE.
- Post-treatment AEs are AEs that developed or worsened or became serious during post-treatment period and is not considered TEAE.

All AEs (including serious adverse events [SAEs]) will be coded to a PT and associated primary SOC using the MedDRA version 20.1.

The severity of all AEs will be graded according to the CTCAE Grading Scale. An AE with a CTCAE grade of 3 or higher is considered a severe AE. The severity of the AE is different from the seriousness of the AE which is defined below. For AEs not covered by CTCAE, the severity will be characterized as "mild," "moderate," or "severe" according to the following definitions:

- Mild events are usually transient and do not interfere with the patient's daily activities.
- Moderate events introduce a low level of inconvenience or concern to the patient and may interfere with daily activities.
- Severe events interrupt the patient's usual daily activities.

Serious adverse events

A SAE is any untoward medical occurrence that occurs at any dose (including after the informed consent form is signed and prior to dosing) that:

- Results in death
- Is life-threatening (patient is at immediate risk of death from the event as it occurred)
- Requires in-patient hospitalization (formal admission to a hospital for medical reasons) or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Results in a congenital anomaly/birth defect

SAE needs to be clearly documented on the patient's AE form.

5.1.2. Analysis Methods

The primary focus of AE reporting will be on TEAEs. Pre- and post-treatment AEs will be described separately.

If an AE date/time of onset (occurrence, worsening, or becoming serious) is incomplete, an imputation algorithm will be used to classify the AE as pre-treatment, treatment-emergent, or post-treatment. The algorithm for imputing date/time of onset will be conservative and will classify an AE as treatment-emergent unless there is definitive information to determine it is

pre-treatment or post-treatment. Details on classification of AEs with missing or partial onset dates are provided in Section 2.2.2.

AE summaries will include number (n) and percentage (%) of patients experiencing an AE. The denominator for computation of percentages is the number of patients in the corresponding population.

Unless otherwise specified, sorting order will follow the alphabetic order in SOC, and further by decreasing number of events in PTs within each SOC. When more than one PT has same number of events, the order of presentation will be alphabetical in PTs.

Multiple occurrences of the same event in the same patient will be counted only once in the tables.

Based on the entries on the eCRF AE page,

- An AE is considered potentially related to study treatment if:
  - the entry for "Relationship to selinexor" is either "Possibly Related" or "Related", or
  - the entry for "Relationship to Dexamethasone" is either "Possibly Related" or "Related".
- An AE is considered potentially related to selinexor if the entry for "Relationship to selinexor" is either "Possibly Related" or "Related".
- An AE is considered potentially related to dexamethasone if the entry for "Relationship to Dexamethasone" is either "Possibly Related" or "Related".

5.1.2.1. Analysis of TEAEs

An overview table summarizing the following will be presented:

- TEAEs
- TEAEs with CTCAE Grade 3 and 4
- Serious TEAEs
- TEAE leading to dose modification in selinexor, i.e., dose reduction or interruption in selinexor
- TEAEs leading to permanent treatment discontinuation
- TEAEs leading to death

- Treatment-related adverse events (TRAEs), i.e., TEAEs potentially related to either selinexor or dexamethasone
- Serious TRAEs
- TRAE leading to dose modification in selinexor, i.e., dose reduction or interruption in selinexor
- TRAEs leading to permanent treatment discontinuation
- TRAEs leading to death

TEAEs will be summarized by primary SOC and PT and will include the following categories:

- All TEAEs
- All TEAEs, by relatedness
    - TEAEs potentially related to either selinexor or dexamethasone
    - TEAEs potentially related to selinexor only
    - TEAEs potentially related to dexamethasone only
    - TEAEs not related to selinexor or dexamethasone
- All TEAEs, by maximum grade
- Grade 3 or higher TEAEs
- Grade 3 or higher TEAEs, by relatedness
    - Grade 3 or higher TEAEs potentially related to either selinexor or dexamethasone
    - Grade 3 or higher TEAEs potentially related to selinexor only
    - Grade 3 or higher TEAEs potentially related to dexamethasone only
    - Grade 3 or higher TEAEs not related to selinexor or dexamethasone
- TEAEs leading to selinexor dose reduced or drug interrupted
- TEAEs leading to dexamethasone dose reduced or drug interrupted
- Grade 3 or higher TEAEs leading to selinexor dose reduced or drug interrupted
- TEAEs leading to withdrawn from selinexor treatment
- Grade 3 or higher TEAEs leading to withdrawn from selinexor treatment

The most commonly reported (at least 10% of all patients) TEAEs will be presented by PT only and will include the following categories:

- The most commonly reported TEAEs
- The most commonly reported TEAEs potentially related to study treatment

5.1.2.2. Analysis of SAEs

Treat-emergent SAEs will be summarized by primary SOC and PT and will include the following categories:

- All treatment-emergent SAEs
- Treatment-emergent SAEs, by relatedness
    - Treatment-emergent SAEs potentially related to either selinexor or dexamethasone
    - Treatment-emergent SAEs potentially related to selinexor only

  - Treatment-emergent SAEs potentially related to dexamethasone only
  - Treatment-emergent SAEs not related to selinexor or dexamethasone
- Treatment-emergent SAEs leading to selinexor dose reduced or drug interrupted
- Treatment-emergent SAEs leading to dexamethasone dose reduced or drug interrupted
- Treatment-emergent SAEs leading to withdrawal from selinexor treatment

5.2. DEATH

The following summaries on death events will be provided:

- An overview of all death events and primary cause of death
- TEAEs leading to death (death as an outcome on the AE report page as reported by the Investigator), by primary SOC and PT
- TEAEs leading to death and are potentially related to selinexor or dexamethasone, by primary SOC and PT
- Listing of all death events

5.3. LABORATORY SAFETY VARIABLES

5.3.1. Definitions

Clinical laboratory data consists of blood analysis, including hematology, serum chemistry, coagulation parameters, and urinalysis. Clinical laboratory values in conventional units will be converted using the international system of units (SI).

Blood samples for clinical laboratory tests will be taken as specified in the study protocol. The laboratory parameters will be classified as follows:

- Hematology (blood sample: ethylenediaminetetraacetic acid [EDTA]) tests including hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, white blood cell (WBC) count, WBC differential, red blood cell count, lymphocytes, monocytes, neutrophils, eosinophils, basophils, and platelets. WBC differential may be automated or manual as per institutional standards.
- Serum Chemistry (blood sample: serum)
  - Complete Serum Chemistry will include sodium, potassium, chloride, bicarbonate (HCO_3^-), blood urea nitrogen (BUN), creatinine, glucose, calcium, phosphate, magnesium, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, total bilirubin and lactate dehydrogenase (LDH), total protein, albumin, amylase, lipase, creatine kinase and uric acid.
  - Limited Serum Chemistry will include sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, ALT, AST, alkaline phosphatase, total bilirubin and LDH, unless otherwise clinically indicated.
  - Thyroid-stimulating hormone (TSH)

- Coagulation parameters will include prothrombin time, international normalization ratio (INR), and activated partial thromboplastin time (aPTT).
- Urinalysis will include appearance, color, urine bilirubin, glucose, hemoglobin, ketones, pH, protein, specific gravity, and urobilinogen. Microscopy will only be performed if clinically indicated.

5.3.2. Analysis of Laboratory Variables

Whenever applicable, severity of selected clinical laboratory measures will be determined based on the CTCAE criteria. The worst toxicity grade in hematology and chemistry will be summarized by toxicity grade. Shift tables that present changes from baseline to worst on-study and baseline to last on-study values relative to CTCAE classification ranges will be presented.

For several key laboratory parameters (e.g., sodium, creatinine, platelet, hemoglobin, WBC, BUN-to-creatinine ratio, urea-to-creatinine ratio), box plots on measurements over time may be presented.

A listing of possible Hy's law cases (ALT or AST > 3 x upper limit of normal [ULN] with simultaneous total bilirubin > 2 x ULN) will be presented. The elevations of ALT/AST and total bilirubin must occur within 2 days of each other.

Thresholds/Range analyses for selected laboratory, vital signs, and ECG parameters will be conducted. Please refer to Appendix 7.2 for the definitions on thresholds/ranges for selected parameters. The number and percentage of patients classified into each category based on worst values will be presented.

5.4. VITAL SIGNS, ECOG, AND PHYSICAL EXAMINATION VARIABLES

Full physical examinations with vital signs are performed only during screening and end-of-treatment (EoT) visits, including height (without shoes) in centimeters (cm) [measured during screening visit only], weight (indoor clothing without shoes) in kilograms (kg), temperature, heart rate, systolic and diastolic blood pressure, and oxygen saturation.

At other visits, symptom-directed physical examinations are conducted with vital signs (temperature, heart rate, systolic and diastolic blood pressure).

An ECOG score assessment with grades 0-5 will be performed during screening, day 1 of each cycle, and the EoT visit.

Shift tables that present changes from baseline to worst on-study and last on-study for systolic blood pressure, diastolic blood pressure, and ECOG performance status values will be produced.

Abnormal vital signs results will be summarized in the threshold/range analyses as defined in Appendix 7.2.

5.5. ELECTROCARDIOGRAM (ECG)

Standard 12-lead ECGs will be performed during screening and EoT visits. Patients must rest for at least 5 minutes prior to the ECG recording. The Investigator will interpret the ECG using one of the following categories: normal, abnormal but not clinically significant, or abnormal and clinically significant. The following will be assessed: heart rate, rhythm, interval from start of

the Q wave to the end of the S wave (QRS), interval from the beginning of the P wave until the beginning of the QRS complex (PR Interval), interval between the start of the Q wave and the end of the T wave (QT), and QT corrected (QTc) using Bazett's formula or calculated by the Fridericia correction formula (*Bazett 1920, Fridericia 1920*). If Bazett correction is entered by the site, the Fridericia corrected QTc interval (QTcF) will be derived using the formula: QT/(RR^[1/3]), where RR = 60/heart rate.

Abnormal ECG results will be summarized in the threshold/range analyses as defined in Appendix 7.2.

5.6. OPHTHALMIC EXAM

A full ophthalmic examination will be performed during the Screening and EoT visits. Prior to dilation, best corrected visual acuity (Snellen's Equivalent based on either Snellen chart or Early Treatment Diabetic Retinopathy Study [ETDRS chart]), and slit lamp examination including tonometry will be conducted. Following dilation, fundoscopy will be conducted. Please refer to Protocol v5.0 for details on the grading of cataract if seen during the examination.

All ophthalmic examination findings will be presented in a data listing.

6. REFERENCES

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3. Mosteller RD. Simplified calculation of body-surface area. *N Engl J Med.* 1987;317:1098.

7. APPENDICE

7.1. Appendix I: Schedule of Assessments

Table 7-1 Schedule of Assessments and Study Activities

Activity/Assessment	Screening	Cycle 1				Cycle 2		Cycles ≥ 3	End-of-Treatment (EoT) Visit	Safety Follow-up Call	Durability of Response and Survival Follow-up[15]
	Day -21 to Day -1	Day 1	Day 3[14]	Day 8	Day 15	Day 1	Day 15	Day 1	≤ 14 Days Post Last Dose	30 Days Post-Last Dose	Every 3 mo.
		-1 day	+1 day	± 1 day	± 1 day	± 2 days	± 2 days	± 2 days		+ 7 days	± 14 days
Informed consent[1]	X										
Inclusion/exclusion criteria	X										
Demographics	X										
Medical history[2]	X	X									
Patient height	X										
Patient weight	X	X		X	X	X	X	X	X		
Body Surface Area (BSA)[3]	X										
Physical examination, full including vital signs[4]	X								X		

Activity/Assessment	**Screening**	**Cycle 1**				**Cycle 2**		**Cycles ≥ 3**	**End-of-Treatment (EoT) Visit**	**Safety Follow-up Call**	**Durability of Response and Survival Follow-up[15]**
	Day -21 to Day -1	**Day 1**	**Day 3[14]**	**Day 8**	**Day 15**	**Day 1**	**Day 15**	**Day 1**	**≤ 14 Days Post Last Dose**	**30 Days Post-Last Dose**	**Every 3 mo.**
		-1 day	**+1 day**	**± 1 day**	**± 1 day**	**± 2 days**	**± 2 days**	**± 2 days**		**+ 7 days**	**± 14 days**
Physical examination, symptom-directed, including vital signs[4]		X		X	X	X	X	X			
ECOG[5]	X					X		X	X		
Echocardiogram or MUGA[6]	X										
12-lead ECG	X								X		
Ophthalmic exam[7]	X								X		
Clinical Labs											
Urinalysis[5]	X								X		
CBC with differential[5]	X				X	X	X	X	X		
TSH[5]	X								X		
Complete serum chemistry[5]	X					X		X	X		

Activity/Assessment	**Screening**	**Cycle 1**				**Cycle 2**		**Cycles ≥ 3**	**End-of-Treatment (EoT) Visit**	**Safety Follow-up Call**	**Durability of Response and Survival Follow-up[15]**
	Day -21 to Day -1	**Day 1**	**Day 3[14]**	**Day 8**	**Day 15**	**Day 1**	**Day 15**	**Day 1**	**≤ 14 Days Post Last Dose**	**30 Days Post-Last Dose**	**Every 3 mo.**
		-1 day	**+1 day**	**± 1 day**	**± 1 day**	**± 2 days**	**± 2 days**	**± 2 days**		**+ 7 days**	**± 14 days**
Limited serum chemistry				X	X		X				
Coagulation tests[5]	X								X		
Serum hCG pregnancy test[8]	X					X (D1 of each cycle only)		X (D1 of each cycle only)	X		
C-reactive protein	X	X				X		X	X		
Multiple Myeloma Assessments											
SPEP and serum protein immunofixation[9]	X	X				X		X	X		X
UPEP (24-hr urine for total protein) and urine protein immunofixation[9]	X	X				X		X	X		X
Quantitative Ig levels[9]	X	X				X		X	X		X

Activity/Assessment	**Screening**	**Cycle 1**				**Cycle 2**		**Cycles ≥ 3**	**End-of-Treatment (EoT) Visit**	**Safety Follow-up Call**	**Durability of Response and Survival Follow-up[15]**
	Day -21 to Day -1	**Day 1**	**Day 3[14]**	**Day 8**	**Day 15**	**Day 1**	**Day 15**	**Day 1**	**≤ 14 Days Post Last Dose**	**30 Days Post-Last Dose**	**Every 3 mo.**
		-1 day	**+1 day**	**± 1 day**	**± 1 day**	**± 2 days**	**± 2 days**	**± 2 days**		**+ 7 days**	**± 14 days**
Serum FLC[9]	X	X			X	X	X	X	X		X
β_2-microglobulin	X								X		
Skeletal survey[10]	X					(X)		(X)	X		(X)
Plasmacytoma assessment[11]	X					(X)		(X)	X		(X)
CCI											
CCI											
FACT-MM questionnaire	X					X		X	X		
Study treatment dosing		Selinexor 80 mg + dexamethasone 20 mg (both twice weekly) for 4 weeks (each week) of 4-week cycles									
Adverse events[16]	X	X	X	X	X	X	X	X	X	X	
Concomitant medications	X	X	X	X	X	X	X	X	X		

Activity/Assessment	**Screening**	**Cycle 1**				**Cycle 2**		**Cycles ≥ 3**	**End-of-Treatment (EoT) Visit**	**Safety Follow-up Call**	**Durability of Response and Survival Follow-up[15]**
	Day -21 to Day -1	**Day 1**	**Day 3[14]**	**Day 8**	**Day 15**	**Day 1**	**Day 15**	**Day 1**	**≤ 14 Days Post Last Dose**	**30 Days Post-Last Dose**	**Every 3 mo.**
		-1 day	**+1 day**	**± 1 day**	**± 1 day**	**± 2 days**	**± 2 days**	**± 2 days**		**+ 7 days**	**± 14 days**
Nutritional consultation	X										
Telephone contact[14]			X							X	X
Antineoplastic therapy after EoT									X	X	X

(X) indicates that additional information is provided in the footnotes. Merged cells indicate that the procedure may be performed during either Screening or the C1D1 visit.

Abbreviations: BSA = body surface area; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EoT = End of Treatment; Ig = immunoglobulin; MM = multiple myeloma; SPEP = serum protein electrophoresis; UPEP = urine protein electrophoresis; CBC = complete blood count; FLC = free light chain.

[1] Prior to the first study-specific measure.

[2] Including details of all prior anti-myeloma therapies. Includes baseline symptoms as well as a detailed history of prior cancer therapies, especially MM therapies, including start and stop dates, disease progression during or after therapy, as well as discontinuations due to intolerability or any other serious illness.

[3] Body Surface Area (BSA) will be calculated by *Dubois 1916* or *Mosteller 1987* method during Screening and prior to any dose escalation. No patient may receive a dose of selinexor > 70 mg/m^2.

[4] Complete physical examination (PE) during Screening and EoT visit. Limited PEs during the study should be symptom directed. All PEs to include vital signs (blood pressure, pulse and body temperature).

[5] The following procedures may be performed at Screening or pre-dose on C1D1 and as shown in the Schedule during the study: ECOG performance assessment, echocardiogram or MUGA scan, 12-lead ECG, ophthalmic exam, urinalysis, CBC with differential, TSH, complete serum chemistry, coagulations tests, and nutritional consultation.

[6] Echocardiogram or MUGA scan at Screening and as clinically indicated during the study.

[7] A full ophthalmic examination will include, prior to dilation, best corrected visual acuity, slit lamp examination including tonometry, following dilation; fundoscopy and slit lamp to document lens clarity.

[8] For females of childbearing potential; negative serum hCG pregnancy test must be obtained within 3 days before the first dose of study treatment. Pregnancy testing (serum hCG or urine) is also required for females of childbearing potential prior to dosing on Day 1 of Cycles ≥ 2 and at the EoT Visit (serum hCG). Pregnancy testing may also be performed as clinically indicated during the study.

[9] Response criteria include SPEP, UPEP (24-hr urine), serum and urine immunofixation, quantitative Ig levels, and serum FLC assay on C1 D1 and must be taken either on Day -1 or pre-dose on C1D1. The assessments must be repeated at the time of disease progression or suspected response in order to confirm response. Note: For patients who achieve CR or sCR, as assessed by the local lab, assessments will be confirmed by a central lab using portions of the samples collected. See the *Study Manual* for additional information.

[10] Skeletal survey to be performed using x-rays per institutional guidelines. If x-rays are used, they should include a lateral radiograph of skull, anterioposterior and lateral views of the spine, and anterioposterior views of the pelvis, ribs, femora, and humeri. If clinically appropriate, MRI, CT, or PET/CT, with tumor measurements, may be used instead of, or in addition to, x-rays. If bone lesions or plasmacytomas are observed at baseline, their number and size should be recorded in the CRF. Bone lesions and/or plasmacytomas seen at baseline using imaging should be assessed as clinically appropriate per Investigator's discretion during the study. Skeletal survey results will be read by the local laboratory.

[11] If plasmacytomas are detected at baseline by PE, they should be measured and recorded, and re-assessed during the PE on Day 1 of each cycle, EoT visit, and every 3 months (if clinically appropriate) during follow-up.

[redacted]

[14] Telephone call (or visit) with patient to evaluate supportive care medications, concomitant medications and adverse events, and to adjust supportive care as appropriate. The telephone contact with the patient must take place on C1D3 (following administration of first dose of selinexor on C1D1).

[15] After treatment discontinuation, if possible, for patients who are not progressing, SPEP with serum immunofixation, UPEP (24 hr.) with urine protein immunofixation, serum FLC, and quantitative Ig levels (and physical examinations and imaging for bone lesions and plasmacytomas, if clinically appropriate) should be performed every 3 months for 1 year to assess durability of response. If these assessments cannot be performed, and for patients with PD, a telephone call will be made to the patient (or the patient's family) every 3 months for one year to inquire about the patient's survival, MM status, well-being, and information on any antineoplastic therapies utilized since discontinuation of selinexor study treatment.

[16] Serious adverse events that occur after signing patient signs the ICF (including prior to first dose on C1D1) and adverse events that occur after first dose on C1D1.

7.2. Appendix II: Thresholds/Range Analyses for Select Laboratory, Vital Sign, and ECG Parameters

Table 7-2 Definitions of thresholds and ranges for selected laboratory, vital signs, and ECG parameters.

Parameter	Thresholds/Ranges	Basis or Comments
Clinical Chemistry		
CPK	>ULN - ≤ 2.5 x ULN >2.5 - ≤ 5 x ULN >5 - ≤ 10x ULN >10 x ULN	CTCAE grades 1-4
Creatinine	>ULN - ≤ 1.5 x ULN >1.5 - ≤ 3.0 x ULN >3.0 - ≤ 6.0 x ULN >6.0 x ULN	CTCAE grades 1-4
Blood Urea Nitrogen	>ULN - ≤ 1.5 x ULN >1.5 - ≤ 3.0 x ULN >3.0 - ≤ 6.0 x ULN >6.0 x ULN	Same criteria as creatinine No CTCAE
Chloride	<LLN >ULN	No CTCAE
Sodium	Hyponatremia <LLN - ≥130 mmol/L <130 – ≥120 mmol/L <120 mmol/L	CTCAE grade 1, 3, 4 (No CTCAE grade 2)
	Hypernatremia >ULN - ≤ 150 mmol/L >150 mmol/L- ≤155 mmol/L >155 mmol/L - ≤ 160 mmol/L >160 mmol/L	CTCAE grade 1-4

Potassium	Hypokalemia <LLN – ≥ 3.0 mmol/L <3.0 – ≥ 2.5 mmol/L <2.5 mmol/L	CTCAE grade 1&2, 3, 4 (Grade 1 and 2 are the same)
	Hyperkalemia >ULN – ≤ 5.5 mmol/L >5.5 – ≤ 6.0 mmol/L >6.0 – ≤ 7.0 mmol/L >7.0 mmol/L	CTCAE grade 1-4
Total Cholesterol	>ULN – ≤ 7.75 mmol/L >7.75 – ≤ 10.34 mmol/L >10.34 – ≤ 12.92 mmol/L >12.92 mmol/L	CTCAE grade 1-4
Triglycerides	>1.71 – ≤ 3.42 mmol/L >3.42 – ≤ 5.7 mmol/L >5.7 – ≤ 11.4 mmol/L >11.4 mmol/L	CTCAE grade 1-4
Glucose	Hypoglycemia <LLN – ≥ 3.0 mmol/L <3.0 – ≥ 2.2 mmol/L <2.2 - ≥ 1.7 mmol/L <1.7 mmol/L	CTCAE grade 1-4
	Hyperglycemia >ULN - ≤ 8.9 mmol/L >8.9 – ≤ 13.9 mmol/L >13.9 – ≤ 27.8 mmol/L >27.8 mmol/L	CTCAE grade 1-4
Albumin	<LLN - ≥ 30 g/L <30 – ≥ 20 g/L <20 g/L	CTCAE grade 1-3

Amylase	>ULN - ≤ 1.5 x ULN >1.5 – ≤ 2.0 x ULN >2.0 – ≤ 5.0 x ULN >5.0 x ULN	CTCAE grade 1-4
Lipase	>ULN - ≤ 1.5 x ULN >1.5 – ≤ 2.0 x ULN >2.0 – ≤ 5.0 x ULN >5.0 x ULN	CTCAE grade 1-4
Direct bilirubin	>ULN - ≤ 1.5 x ULN >1.5 – ≤ 2 x ULN >2 – ≤ 3 x ULN >3 – ≤ 10 x ULN >10 x ULN	Same Criteria as Total Bilirubin No CTCAE Not in DILI Guidance
GGT	>ULN - ≤ 2.5 x ULN >2.5 – ≤ 5.0 x ULN >5.0 – ≤ 20.0 x ULN >20.0 x ULN	CTCAE grade 1-4
Total protein	<LLN >ULN	No CTCAE
LDH	<LLN >ULN	No CTCAE
Calcium	Hypercalcemia >ULN - ≤ 2.9 mmol/L >2.9 – ≤ 3.1 mmol/L >3.1 – ≤ 3.4 mmol/L >3.4 mmol/L	CTCAE grade 1-4
	Hypocalcemia <LLN - ≥ 2.0 mmol/L <2.0 – ≥1.75 mmol/L <1.75 – ≥ 1.5 mmol/L <1.5 mmol/L	CTCAE grade 1-4
Magnesium	Hypermagnesemia >ULN - ≤ 1.23 mmol/L	CTCAE grade 1, 3, 4

	>1.23 – ≤ 3.30 mmol/L >3.30 mmol/L	No CTCAE grade 2
	Hypomagnesemia <LLN - ≥ 0.5 mmol/L <0.5 – ≥ 0.4 mmol/L <0.4 – ≥ 0.3 mmol/L <0.3 mmol/L	CTCAE grade 1-4
Bicarbonate	<LLN >ULN	No CTCAE
Inorganic phosphate	Hypophosphatemia <LLN - ≥ 0.8 mmol/L <0.8 – ≥ 0.6mmol/L <0.6 – ≥ 0.3 mmol/L <0.3 mmol/L	CTCAE grade 1-4
Vitamins: A, D (25-hydroxy), E, K, B12	<LLN	No CTCAE
LDL	>ULN	No CTCAE
HDL	<LLN	No CTCAE
ALT	>ULN - ≤ 3 xULN >3 – ≤ 5 xULN >5 – ≤ 8 xULN >8 – ≤ 20.0 xULN >20.0 x ULN	Per FDA DILI Guidance Jul 2009 and CTCAE
AST	>ULN - ≤ 3 xULN >3 – ≤ 5 xULN >5 – ≤ 8 xULN >8 – ≤ 20.0 xULN >20.0 x ULN	FDA DILI Guidance and CTCAE
ALT or AST	ALT>3xULN or AST>3xULN	FDA DILI Guidance

Alkaline Phosphatase	>ULN - ≤ 1.5xULN >1.5 – ≤ 2.5 xULN >2.5 – ≤ 5.0 x ULN >5.0 – ≤ 20.0 x ULN >20.0 x ULN	FDA DILI Guidance and CTCAE
Total Bilirubin	>ULN - ≤ 1.5 x ULN >1.5 – ≤ 2 x ULN >2 – ≤ 3 x ULN >3 – ≤ 10 x ULN >10 x ULN	FDA DILI Guidance and CTCAE
ALT and Total Bilirubin	ALT>3xULN and TBILI>2xULN	FDA DILI Guidance Jul 2009
AST and Total Bilirubin	AST>3xULN and TBILI>2xULN	FDA DILI Guidance Jul 2009
(ALT or AST) and Total Bilirubin	(ALT>3xULN or AST>3xULN) and TBILI>2×ULN	FDA DILI Guidance Jul 2009
Hematology		
WBC	WBC decreased <LLN - ≥ 3.0 x 10e9 /L <3.0 – ≥ 2.0 x 10e9 /L <2.0 – ≥ 1.0 x 10e9 /L <1.0 x 10e9 /L	CTCAE grade 1-4
	Leukocytosis >100 x 10e9 /L	CTCAE grade 3 (only Grade available)
Lymphocytes	Lymphocyte decreased <LLN - ≥ 0.8 x10e9 /L <0.8 – ≥ 0.5 x10e9 /L <0.5 – ≥ 0.2 x10e9 /L <0.2 x10e9 /L	CTCAE grade 1-4
	Lymphocyte increased >4 – ≤ 20 x10e9/L >20 x10e9/L	CTCAE grade 2, 3 (only Grades available)
Neutrophils	Neutrophil decreased <LLN - ≥ 1.5 x10e9 /L	CTCAE grade 1-4

	<1.5 – ≥ 1.0 x10e9 /L <1.0 – ≥ 0.5 x10e9 /L <0.5 x10e9 /L	
Monocytes	>ULN	No CTCAE
Basophils	>ULN	No CTCAE
Eosinophils	>ULN	No CTCAE
Hemoglobin	Hgb decreased (anemia) <LLN - ≥ 100 g/L <100 – ≥ 80 g/L < 80 g/L	CTCAE grade 1-3
	Hgb increased >ULN - ≤ 20 g/L above ULN >20 g/L above ULN - ≤ 40 g/L above ULN >40 g/L above ULN	CTCAE grade 1-3
RBC	<LLN >ULN	No CTCAE
Platelets	Platelet decreased <LLN - ≥ 75.0 x 10e9 /L <75.0 – ≥ 50.0 x 10e9 /L <50.0 – ≥ 25.0 x 10e9 /L <25.0 x 10e9 /L	CTCAE grade 1-4
	Platelet increased >ULN	No CTCAE available
Mean corpuscular hemoglobin	<LLN >ULN	No CTCAE

Mean corpuscular hemoglobin concentration	<LLN >ULN	No CTCAE
Mean corpuscular volume	<LLN >ULN	No CTCAE
Reticulocytes	<LLN >ULN	No CTCAE
Coagulation		
Activated partial thromboplastin time (PTT)	>ULN - ≤ 1.5 x ULN >1.5 – ≤ 2.5 x ULN >2.5 x ULN	CTCAE grade 1-3
Prothrombin time (PT) International Normalized Ratio (INR)	>ULN - ≤ 1.5 x ULN >1.5 – ≤ 2.5 x ULN >2.5 x ULN	CTCAE grade 1-3
ECGs		
HR	Bradycardia <50 bpm Decrease from baseline ≥10 bpm Decrease from baseline ≥20 bpm <50 bpm and decrease from baseline ≥10 bpm <50 bpm and decrease from baseline ≥20 bpm	Per HV grade 2, 3, plus shift change
	Tachycardia >120 bpm Increase from baseline ≥20 bpm >120 bpm and increase from baseline ≥20 bpm	Per HV grade 1, 2, 3, plus shift change
PR	≥240 ms ≥200 ms and increase from baseline ≥40 ms ≥200 ms and increase from baseline ≥100 ms	

QRS	>120 ms Increase from baseline ≥20 ms Increase from baseline ≥40 ms	
QTc	>450 ms (Male) >470 ms (Female) ≥500 ms Increase from baseline >10 ms Increase from baseline >30 ms Increase from baseline >60 ms	
Vital Signs		
HR	Same PCS as above in ECG category	
SBP	SBP increased >140 mmHg >160 mmHg >10 mmHg increase from baseline >20 mmHg increase from baseline >160 mmHg & >10 mmHg increase from baseline >160 mmHg & >20 mmHg increase from baseline	
	SBP decrease <100 mmHg >10 mmHg decrease from baseline >20 mmHg decrease from baseline <100 mmHg and >10 mmHg decrease from baseline	Per HV grade 1, 3, plus shift change

	<100 mmHg and >20 mmHg decrease from baseline	
DBP	DBP increased >90 mmHg >100 mmHg >5 mmHg increase from baseline >10 mmHg increase from baseline >100 mmHg and >5 mmHg increase from baseline >100 mmHg and >10 mmHg increase from baseline	
	DBP decreased <60 mmHg >5 mmHg decrease from baseline >10 mmHg decrease from baseline <60 mmHg and >5 mmHg decrease from baseline <60 mmHg and >10 mmHg decrease from baseline	
Weight	Weight gain ≥5 % increase from baseline ≥10 % increase from baseline ≥ 20% increase from baseline	CTCAE grade 1-3
	Weight loss ≥5 % decrease from baseline ≥10 % decrease from baseline ≥ 20% decrease from baseline	CTCAE grade 1-3