Official Title of Study:

A MULTICENTER, SINGLE-ARM, OPEN-LABEL STUDY WITH POMALIDOMIDE IN COMBINATION WITH LOW DOSE DEXAMETHASONE IN SUBJECTS WITH REFRACTORY OR RELAPSED AND REFRACTORY MULTIPLE MYELOMA

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STATISTICAL ANALYSIS PLAN

A MULTICENTER, SINGLE-ARM, OPEN-LABEL
STUDY WITH POMALIDOMIDE IN COMBINATION
WITH LOW DOSE DEXAMETHASONE IN SUBJECTS
WITH REFRACTORY OR RELAPSED AND
REFRACTORY MULTIPLE MYELOMA

STRATUS

STUDY DRUG:	Pomalidomide (CC-4047)
PROTOCOL NUMBER:	CC-4047-MM-010
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Prepared by:
Celgene Corporation
[redacted]

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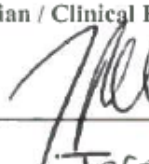
Signature 

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ABBREVIATIONS

Abbreviation	Explanation
AE	Adverse Event
AMA	American Medical Association
ATC	Anatomical Therapeutic Chemical
AUC	Area under the curve
BP	Blood Pressure
CIs	Confidence Intervals
CR	Complete Response
CRF	Case Report Form
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DDI	Delivered Dose Intensity
DoR	Duration of response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EE	Efficacy Evaluable
FCBP	Female of child bearing potential
FISH	Fluorescence in situ Hybridization
IMWG	International Myeloma Working Group
ICD	Informed consent document
IP(s)	Investigational Product(s)
ITT	Intention-to-treat
IVRS	Interactive voice response system
IWRS	Interactive web response system
LD-DEX	Low-Dose Dexamethasone
MedDRA	Medical Dictionary for Regulatory Activities
MM	Multiple Myeloma
mmHg	millimeter of mercury
NCI	National Cancer Institute

Abbreviation	Explanation
ORR	Overall Response Rate
OS	Overall Survival
PD	Progressive Disease / Pharmacodynamics
PDI	Planned Dose Intensity
PFS	Progression Free Survival
PK	Pharmacokinetics
POM	Pomalidomide
PP	Per-protocol
PR	Partial Response
RDI	Relative Dose Intensity
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Systems
sCR	Stringent Complete Response
SD	Stable Disease
SPM	Second Primary Malignancy
TEAE	Treatment-Emergent Adverse Event
TTP	Time to Progression
TTR	Time to Response
VGPR	Very Good Partial Response
WHO	World Health Organization

1. INTRODUCTION

[redacted]

1.1. Summary of Change

Major revisions from the 19 September 2013 version to the current version are:

- The efficacy evaluable population has been substituted for the per-protocol population for the analysis of the following endpoints: overall response rate (ORR), time to response (TTR), duration of response (DoR), time to progression (TTP), progression free survival (PFS) and overall survival (OS).
- Removal of all sub-group analyses.

The following aspects of data handling methods are modified with more details added:

- Additional censoring and event rules for PFS and DoR.
- Correction of the calculation for cycle length.
- Clarification of the definition of 'baseline'.

The following points are additions to this SAP version:

- Clarification that the PK and PD related table, figures and listings will be provided in a separate delivery document.
- Clarification that the cytogenetic sub-group analysis will be provided in a separate report.
- Identification of drug classification groups of prior anti-multiple myeloma (MM) drugs.
- Additional imputation rules for incomplete dates with regards to diagnosis date, prior and subsequent anti-myeloma therapy dates.

2. OBJECTIVES

The primary objective of the study is to evaluate the safety of the combination of POM and LD-DEX in a large cohort of subjects with refractory MM or relapsed and refractory MM.

The secondary objectives of the study are to:

- Analyze the population pharmacokinetics of POM and assess POM exposure response relationships in subjects with refractory MM or relapsed and refractory MM administered POM and LD-DEX.
- Evaluate efficacy of the combination of POM and LD-DEX in subjects with refractory MM or relapsed and refractory MM.
- Evaluate the relationship between cytogenetic profiles and the combination of POM and LD-DEX in terms of response and outcome.

[redacted]

3. INVESTIGATIONAL PLAN

3.1. Overall Study Design and Plan

This study is a multicenter, single-arm, open label study of POM in combination with LD-DEX in subjects with refractory or relapsed and refractory MM. Approximately 720 subjects who satisfy study inclusion and exclusion criteria will be enrolled into the study (for detailed subject eligibility see sections 7.2 and 7.3 of Protocol CC-4047-MM-010). There are three periods to this study: The screening period (defined as days -28 to 0 prior to start of the investigational product [IP]), the Treatment period starting at the moment of first administration of the IP defined as Cycle 1 Day 1 until start of follow-up, and the Follow-up period which starts at the time of the permanent IP discontinuation and which continues until all subjects have been followed for up to 5 years after the last issued interactive voice/web response system (IVRS/IWRS) enrollment date if still alive and not lost-to-follow-up, or longer if clinically relevant.

Subjects will undergo screening within 28 days prior to Cycle 1 Day 1 and be treated in 28-day cycles. Subjects will remain on treatment with the IP until a specific event, including, but not limited to, progressive disease (PD), intolerance due to toxicity, death, withdrawal of consent, non-compliance with the IP, and becoming lost-to-follow-up.

An outline of study time points and corresponding assessments due at those times are presented in Table 1: Table of Events (see section 5 of Protocol CC-4047-MM-010). Safety assessments will be performed during the Screening period and on Day1 (± 1 day) of each cycle as well as the time of IP discontinuation. Additional safety assessments (hematology, serum chemistry and estimation of renal function) shall be performed on day 15 (± 2 days) of cycles 1 to 6 while vital signs shall also be collected at a follow-up visit to take place within 28 days post discontinuation of the IP.

Pregnancy testing for females of child bearing potential (FCBP) and pregnancy counseling shall be assessed during the Screening period, Day 1 (± 1 day) of each cycle and at the time of the IP discontinuation. An additional pregnancy test for FCBP shall be conducted within 28 days post IP discontinuation.

Efficacy measurements shall be collected during the Screening period, at Day 1 (± 1 day) of each cycle and within 28 days post IP discontinuation, with the exception of response assessments which will not be collected during the Screening period. Survival status and recording of subsequent anti-myeloma regimens will be recorded within 28 days post IP discontinuation and during the Follow-up period every 3 months (84 ± 14 days).

Note that the visit (or assessment) occurring just prior to initiation of the IP is defined as “baseline” (i.e., Day 1 of Cycle 1). However, data from the Screening period will be substituted for a given measure if data at Day 1 Cycle 1 is not available.

Dose modifications and interruptions of the IP are permitted throughout the study.

Subjects will remain on study until a specific event, including, but not limited to, becoming lost-to-follow-up, death and withdrawal of consent.

The first full analysis of the primary and secondary endpoint will be conducted once all enrolled subjects have completed up to 2 cycles of the IP if having not stopped therapy earlier.

A final, updated, analysis will be conducted at the time of study close, the point when all subjects will have discontinued from the study, i.e. 5 years from the last issued IVRS enrollment date if having not discontinued from the study before this point.

3.2. Study Populations

The study population includes refractory MM subjects or relapsed and refractory MM subjects. All subjects must have documented progressive disease (PD) on or within 60 days of their last treatment, after receiving at least 2 lines of treatment, and must have received a minimum of 2 consecutive cycles of prior treatment regimens that included bortezomib and lenalidomide, either in combination or in separate regimens. These include:

- Subjects classified as *refractory* must have progressed during or within 60 days of treatment with bortezomib and/or lenalidomide.
- Subjects classified as *relapsed*, who previously responded to bortezomib and/or lenalidomide with at least partial response (PR) must have progressed within 6 months of ending treatment with bortezomib and/or lenalidomide.
- Subjects who have not achieved at least minimal response (MR) who have developed *intolerance or toxicity* after a minimum of 2 cycles of bortezomib.
- Subjects who are eligible for or who are planning to receive bone marrow transplant are not eligible for this study.

3.3. Study Endpoints

The primary endpoint is:

- The incidence of adverse events (AE) (type, frequency, seriousness, severity, relationship to POM and /or DEX, and outcomes), including second primary malignancy (SPM).

The secondary endpoints are:

- POM exposure
- POM population PK and exposure response
- Overall response rate (ORR)

- Time to response (TTR)
- Duration of response (DoR)
- Progression free survival (PFS)
- Time to progression (TTP)
- Overall survival (OS)
- Analysis of cytogenetic profiles

3.4. Stratification , Randomization and Blinding

Subjects will not be randomized or blinded due to the study being a single-arm study.

3.5. Sample Size

Approximately 720 subjects across twenty-one European countries will be enrolled into this study. This sample size has been determined to enable the characterisation of currently infrequent AEs. As such, a sample size of 720 subjects will allow detection of any infrequent AE, defined as an AE with a frequency of 0.4% (3/720), assuming a study power of 95%. Under this calculation, an infrequent event with a frequency of 0.4% will be confirmed if at least 1 of 720 evaluable subjects experiences such an event.

4. GENERAL STATISTICAL CONSIDERATIONS

In general and unless otherwise noted, continuous variables will be summarised using the following summary statistics; N, Mean, Standard Deviation, Median, Minimum and Maximum. Categorical variables will be summarized using frequency tabulations (i.e., counts and percentages). In the case of missing categorical data, an "unknown" category will be created for reporting purposes, but subjects or records included in this category will not be included in the denominator when calculating percentages.

4.1. Reporting Conventions

Summary tables, listings, and any supportive SAS output will include a "footer" of explanatory notes that will indicate, at a minimum, the following:

- Program source (e.g., SAS program name and the path that generates the output)
- Data extraction date (e.g., the database lock date, run date)

The purpose of the data extraction date is to link the output to a final database, either active or archived, that is write-protected for replication and future reference. An output date will also appear on each output page and will indicate the date the output was generated by the analysis program. Individual source listings will display all the relative values supporting corresponding tables and figures.

4.1.1. Dates Handling

Dates will be stored as numeric variables in the SAS analysis files and reported in DDMMMYYYY format (i.e., the Date9. datetime format in SAS). Dates in the clinical database are classified into the categories of procedure dates, log dates, milestone dates, outcome dates, and special dates.

- **Procedure Dates** are the dates on which given protocol-specified procedure are performed. They include the dates of laboratory testing, physical examinations, tumor scans, etc. They should be present whenever data for a protocol-specified procedure is present and should only be missing when a procedure is marked as NOT DONE in the database. Procedure dates will not be imputed.
- **Log Dates** are dates recorded in the case report form (CRF) data logs. Specifically, they are the start and end dates for AEs and concomitant medications/procedures. They should not be missing unless an event or medication is marked as *ongoing* in the database. Otherwise, incomplete log dates will be imputed according to the rules in Appendix A of this SAP: Date Imputation Guideline (e.g., for duration or cycle assignment etc.). However, in listings, log dates will be shown as recorded without imputation.

- **Milestone Dates** are dates of protocol milestones such as enrollment date, study drug start date, study termination, etc. They should not be missing if the milestone occurs for a subject. They will not be imputed.
- **Outcome Dates** are dates corresponding to study endpoints such as survival, disease progression, etc. In most cases they are derived either from a milestone (e.g., the survival date is derived from the death date), or a procedure date (e.g., the progression date is derived from the date of the tumor scan that was used to determine progression). They may be subject to endpoint-specific censoring rules if the outcome event, for instance, did not occur; otherwise they are not subject to imputation.
- **Special Dates** cannot be classified in any of the above categories and they include, for example, the date of birth. They may be subject to variable-specific censoring and imputation rules (see Section 4.1.2. below).

Dates recorded in comment fields will not be imputed or reported in any specific format.

4.1.2. Calculation Using dates

Calculations using dates (e.g., subject's age or relative day after the first dose of the IP) will adhere to the following conventions:

- Study days after the start day of study drug will be calculated as the difference between the date of interest and the first date of dosing of the IP plus 1 day. The generalised calculation algorithm for a relevant day is:

  STUDY DAY = [(TARGET DATE – DSTART) + 1], where DSTART = the start day of study drug.

  Study days before the start day of study drug will be calculated as the difference between the date of interest and the first date of the IP.

  Note that Study Day 1 is the first day of treatment of study drug. Negative and zero study days are reflective of observations obtained during the baseline/screening period. Note: Partial date for the first study drug is not imputed in general. All effort should be tried to avoid incomplete study drug start date.

- For all efficacy analyses, time-to-event days for efficacy endpoints will be calculated as the difference between the date of event and the enrollment date plus 1 day.
- Age (expressed in days) is calculated as:

  AGE = [CONSENT – DATE OF BIRTH + 1], where CONSENT = the date the informed consent document (ICD) was signed.

  In practice, age will be transformed into years by dividing the difference by 365.25 days, then truncating the divided difference to the nearest year.

  - Prefer using calculated age from clinical database. When not available, may use calculated age from the CRF or the IVRS

- Partial birth date: impute a missing day as the 15th day of the month; impute a missing month as July; set age as missing if year is missing

- Intervals that are presented in weeks will be transformed from days (as calculated above) to weeks by using (without truncation) the following conversion formula:

  WEEKS = DAYS /7

- Intervals that are presented in months will be transformed from days (as calculated above) to months by using (without truncation) the following conversion formula:

  MONTHS = DAYS /30.4167

4.1.3. Calculation of Cycles

The start date of each treatment cycle will be calculated based on study drug exposure records for each subject. The start date of the first cycle will be the date when the subject receives any study drug.

Once the start dates, e.g., S_1, S_2, S_3… are calculated, the end date of each cycle is calculated as the day before the start date of the following cycle, i.e., $E_i = S_{i+1} - 1$. For the last cycle, the end date (if missing or less than 28 days after start of cycle) will be calculated as the start date plus the prescribed cycle length (28) - 1, or the death date, or the discontinuation date, whichever is earlier.

The cycle number for each date of interest, e.g., AE or lab, will be calculated based on the cycle window set by their start and end dates. If a date is on or after S_i and before S_{i+1}, the corresponding cycle number will be cycle i.

Once the cycles are derived, they can be used to attribute adverse events to a specific cycle based upon the following rules: the start date of the adverse event should be included in a given cycle or if the start date does not fit in any defined cycle, the adverse event will be attributed to the previous cycle if the AE has started within 28 days after the end of the cycle.

4.1.4. P value reporting

Although formal hypothesis testing is not planned for the analysis, should any testing be undertaken (e.g., a paired t-test for change in vital signs measurements), p values will be reported per the American Medical Association (AMA) Style Guide. Specifically, in tables, column headers for p values will be referred to as "*P* value." Actual p values will contain no leading zeros. All p values will be reported as exact numbers to 2 decimal places, regardless of significance, unless they are lower than 0.01, in which case they should be presented to 3 decimal places. Furthermore, in the event a p value is between 0.045 and < 0.050, three decimal places will be reported. For p values lower than 0.001 will be expressed as "< .001."

4.1.5. Duplicate Subject Identification Number

Subjects entered twice with two different subject identification numbers will have the inactive identification number allocated to a dummy site to avoid duplicate information appearing in tables and listings.

5. ANALYSIS POPULATIONS

5.1. Safety Population

The safety population includes all enrolled subjects who received at least one dose of the IP and shall be used for analysis of all safety endpoints (e.g. the incidence of AEs and SPMs).

5.2. Intention-to-Treat Population

The intention-to-treat (ITT) population is defined as all enrolled subjects (subjects receiving an IVRS enrollment date) regardless of whether they received any IP or not. The ITT population shall be used for the analysis of all efficacy endpoints (i.e. ORR, TTR, DoR, PFS, TTP and OS).

5.3. Efficacy Evaluable Population

The efficacy evaluable (EE) population is defined as all ITT subjects who take at least one dose of IP, who have baseline disease measurement and at least one post-baseline disease measurement or PFS event. The EE population should be used for analyses of the following endpoints: ORR, TTR, DoR, TTP, PFS and OS.

For the purpose of the clinical study report (CSR) deliverables, the EE population substitutes the Per-protocol population outlined in the study protocol.

6. SUBJECT DISPOSITION

A summary of subject disposition (analysis population allocation, subjects entered, subjects discontinued, along with primary reason for both IP and study discontinuation) will be presented for each of the analysis populations (ITT Population and Safety Population) and will be summarized using frequency and corresponding percentage.

Reasons for discontinuing the IP will be collected on the CRF and will be summarised for all subjects with the following categories possible:

- Death
- Adverse event
- Pregnancy
- Progressive disease
- Lack of efficacy
- Recovery
- Withdrew consent
- Non-compliance with the study drug
- Lost to follow-up
- Study terminated by sponsor
- Transition to commercially available treatment
- Protocol violation (specify)
- Other (specified)

Among those who discontinue the IP, the number of subjects who then discontinue from the study versus those that enter follow-up will be summarised.

Reasons for discontinuing the study will be collected on the CRF and will be summarized for all subjects with the following categories possible:

- Screen failure
- Death
- Adverse event
- Pregnancy
- Progressive disease

- Lack of efficacy
- Recovery
- Withdrew consent
- Non-compliance with the study drug
- Lost to follow-up
- Study terminated by sponsor
- Transition to commercially available treatment
- Protocol violation (specify)
- Other (specified)

A summary tabulation will be provided for subjects enrolled by study center. Duration of study participation, defined as the time from IVRS enrollment date to IP discontinuation date (or the date of last visit for subjects still receiving the IP at the time of study close), will be summarized.

A separate listing will be provided for subjects who have signed consent but are not enrolled because of not meeting all inclusion/exclusion criteria (i.e., screen failure subjects). The reasons for screen failure will be tabulated.

Protocol deviations and violations will be presented in a data listing and summarized by categories in summary tables per deviation/violation type using frequency and corresponding percentage of occurrence.

7. DEMOGRAPHICS, BASELINE CLINICAL CHARACTERISTICS, AND MEDICAL AND TREATMENT HISTORIES

Summaries for the demographics and baseline characteristics will be produced for the safety and ITT populations individually. Summaries of medical history and prior therapies and medications will be produced for subjects in the ITT population. Individual subject listings will be provided to support summary tables.

7.1. Demographic and Baseline Clinical Characteristics

Subjects' age, height, weight and other baseline continuous characteristics (e.g., vital signs, laboratory data) will be summarized with summary statistics (n, mean, standard deviation, median, minimum and maximum), while gender, ethnicity, race, and other baseline categorical characteristics [e.g., age category (<65 vs. ≥ 65), electrocardiogram (ECG) interpretation, Eastern Cooperative Oncology Group (ECOG) performance status] will be reported using frequency tabulations showing frequency and corresponding percentages. Baseline is defined as the last measurement before the first dose of the IP (or the last measurement before enrollment in case the first dose date is missing). When there are retested values, the retest values will be used for the analysis.

Stage of MM and duration in years of MM will be summarized descriptively. Serum and urine heavy chain type, light chain type, and type of light chain disease from immunofixation will be tabulated descriptively. Presence of bone lesions, presence of plasmacytoma, development of hypercalcemia, increasing Myeloma paraprotein will be tabulated descriptively.

7.2. Medical History

Medical and surgical history will be coded using the Medical Dictionary for Drug Regulatory Activities (MedDRA) Version 15.0 or higher. System organ class and preferred term will be summarized by frequency and percentage. Prior Anti-myeloma Therapies, Radiotherapy, and Surgeries.

Prior anti-myeloma drugs will be summarized using frequency tabulations by preferred term [World Health Organization (WHO) dictionary term version in use at the time of analysis]. A summary of last prior anti-MM drugs (i.e., drugs included in the last anti-MM regimen prior to study entry) will also be produced.

Exposure (Y/N) to selected prior anti-MM therapies and regimens and refractory (Y/N) to selected prior anti-MM drugs and regimens will also be summarized using frequency tabulations.

Prior anti-MM drugs will also be classified to one of the following drug classes and tabulated: Immunomodulatory compounds, Proteasome inhibitors, Corticsteroids, Alkylators, Anthracyclines, Nitrosourreas, Alkaloids, Platinum, and other novel agents.

Evidence of disease progression on the last lenalidomide-containing regimen, evidence of disease progression the last Bortezomib-containing regimen and evidence of the most recent disease progression (i.e., progression on the last treatment if it did not include lenalidomide and/or Bortezomib).

7.3. Prior Medications

Prior medications are defined as medications that were started before the start of the study treatment (regardless whether or not ended before the start of the study treatment). Prior medications that continue into study treatment period will also be reported as concomitant therapy.

All prior medications will be summarized in frequency tabulations. The Anatomical Therapeutic Chemical (ATC) coding scheme of the WHO dictionary term (according to the version in use at the time of analysis) will be used to group medications into relevant categories for these tabulations.

7.4. Other Medical History related to Refractory or Relapsed and Refractory Multiple Myeloma

Prior venous thromboembolic events, prior cancer history and corresponding treatments will be summarized with summary statistics or frequency distributions, as appropriate.

7.5. Cytogenetic Analysis

Subjects will be considered as having a ‘modified high risk’ cytogenetic profile if having either a 17 p Deletion or t(t;14) translation abnormality based on adequate cytogenetic sample(s).

Subjects will be considered as having a ‘standard risk’ cytogenetic profile if having neither a 17 p Deletion nor a t(t;14) translation abnormality based on adequate cytogenetic sample(s).

The cytogenetic sub-group analysis will be provided in a separate report.

8. STUDY TREATMENTS AND EXTENT OF EXPOSURE

Treatment duration, cumulative dose, dose exposure, average daily dose, relative dose intensity, and dose modification will be assessed separately for POM and LD-DEX as well as combined. Summary statistics will be reported for treatment duration, cumulative dose, dose exposure, average daily dose, dose intensity, relative dose intensity, and dose modification/interruption.

8.1. Treatment Duration

The treatment duration (weeks) is defined as:

[(last cycle end date) – (date of the first study drug administration) + 1] / 7

where 'last cycle end date' is defined in section 4.1.3: Calculation of Cycles, in this document. Summary statistics will be provided for treatment duration for overall treatment (i.e., either pomalidomide or dexamethasome, whichever is earliest for the 'date of the first study drug administration' and whichever is later for the 'last cycle end date'), as well as for pomalidomide and dexamethasone separately.

Additional summaries will be created for all treated subjects, displaying number of subjects treated by the number of cycles administered.

8.2. Cumulative Dose

Cumulative dose is defined as the sum of all doses taken across the treatment period (in milligrams) and will be calculated for pomalidomide and dexamethasone separately.

8.3. Dose Exposure

Dose exposure in days is defined as the total number of actual days on drug during the treatment period and will be calculated for pomalidomide and dexamethasone separately.

8.4. Average Daily Dose

Average daily dose will be calculated as the cumulative dose divided by dose exposure and will be calculated for pomalidomide and dexamethasone separately.

8.5. Dose Intensity

The delivered dose intensity (DDI) is defined as the cumulative dose delivered divided by the treatment duration and will be calculated for pomalidomide and dexamethasone separately.

8.6. Relative Dose Intensity

The relative dose intensity (RDI) is calculated as the DDI divided by the planned dose intensity (PDI) whereby the DDI is calculated as the total dose delivered divided by the total time to complete the delivery:

- For POM, the PDI is (4*21)/28 = 3 mg per day.
- For LD-DEX, the PDI is (40*4)/28 = 160/28 mg per day for subjects ≤ 75 years old and (20*4)/28 = 80/28 mg per day for subjects > 75 years old.

The RDI will be calculated for pomalidomide and dexamethasone separately

8.7. Dose Modifications

Dose reductions and interruptions will be summarized for subjects who had at least one dose reduction or interruption. In addition, summary statistics (frequency of patients and median number of days) will be produced for time to first dose reduction/interruption as well as the number of reduction/interruptions per subject.

10. STATISTICAL ANALYSIS OF EFFICACY ENDPOINTS

All efficacy analyses will be performed using the ITT population and the EE population. The ITT population shall form the primary analysis while the EE population shall form the sensitivity analysis of the endpoints.

10.1.1. Overall Response Rate

Under the IMWG uniform response criteria, a response is defined as being either a stringent complete response (sCR), complete response (CR), very good partial response (VGPR) or a partial response (PR). Investigator's assessment of response will be used for the response analysis. The overall response rate (ORR) is defined as the percentage of subjects with a confirmed disease response (sCR, CR, VGPR, or PR) according to the International Myeloma Working Group International Myeloma Working Group International Myeloma Working Group(IMWG) uniform response criteria, over the number of subjects included in the analysis. For the response to be confirmed, a consecutive disease assessment must achieve the same response or better. Confirmed responses that are documented after the initiation of another anti-myeloma treatment will not be counted as responses. Subjects without a disease assessment will be considered a non-responder for the purpose of the ORR. The ORR shall be presented along with the corresponding Clopper-Pearson 95% confidence interval (CI).

The proportion of subjects in each response category [i.e. sCR, CR, VGPR, PR, stable disease (SD), PD, relapse, relapse from CR, and Not Evaluable] as well as the proportion of subjects without any disease assessment will be calculated.

10.1.2. Time to Response

TTR is calculated as the time from study enrollment, defined as the IVRS enrollment date, until a documented disease response (either SCR, CR, VGPR or PR). Subjects not observed with a response will not be included in the analysis. The analysis will consist of presenting the number of subjects available for analysis of TTR, the mean and median time as well as the minimum and maximum time to reach a response.

10.1.3. Time to Event Analyses

Four time to event endpoints (DoR, TTP, PFS, and OS) will be analysed for this study. Response values (as determined by the site investigator based on the IMWG uniform response criteria) categorised as PD, relapse and relapse after CR indicate that the subject had a disease progression, while other response values (i.e. sCR, CR, VGPR, PR and SD) indicate that the subject did not have a disease progression.

For each time to event endpoint, the Kaplan-Meier method will be used to estimate the survival distribution function. The median, 25 and 75 percentile of the survival distribution along with

the two-sided 95% CI for the median will be estimated. In addition, the event rates at 6, 12 and 24 month time-points will be computed, along with the standard errors. The plots of survival curves using Kaplan-Meier estimates will be presented as appropriate.

10.1.3.1. Duration of Response

Duration of response is defined as the time from the first documented disease response to the IP (either SCR, CR, VGPR or PR) until the first recorded disease progression on the IMWG assessment of response CRF or LTFU CRF, whichever occurs first, or death if no disease progression recorded (refer to PFS for complete event details) for responders.

Censoring of subjects not experiencing an event are similar to PFS outlined in Table 1 with the following exceptions:

- If a subject is still on therapy and therefore has no LTFU CRFs, then censor at time of last response assessment, otherwise,
- If the subject did not have a disease progression during therapy but has entered into long term follow-up and still no disease progression is indicated, then censor at the time of the last completed LTFU CRF.

10.1.3.2. Progression-Free Survival

Progression Free Survival is calculated as the time from study enrollment, defined as the IVRS enrollment date, until either PD or death (any cause). Subjects without an event (either a documented PD or death) at the time of study end will be censored at the time of their last documented disease assessment or at the IVRS enrollment date if no disease assessment was conducted. A subject with a documented PD directly following a missing assessment, if not having previously had a documented PD, will be censored at the time of the assessment directly preceding the missing assessment.

Missing assessments are defined as 2 or more consecutive missing assessments, considered as > 66 days (during the treatment period) or > 192 days (during the long-term follow-up phase) between the last adequate assessment and the date of the event, or, >94 days if there is no assessment after enrollment and the subject having an event.

Table 1 below includes the event and censoring rules for PFS.

Table 1: Event and Censoring Rules for Progression Free Survival

Scenario	Date Subject has Event or is Censored	Comment
Progression documented at scheduled assessment	EMA and FDA Guidelines: Event date = first disease assessment date where a PD is documented	A subject with a documented PD directly following a missing assessment, if having not

Scenario	Date Subject has Event or is Censored	Comment
		had a PD observed previously, shall be censored at the time of the last documented assessment or the IVRS enrollment date if there is no prior response assessment.
Progression documented between scheduled assessment	EMA Guidelines: Event = date of documented progression. FDA Guidelines: Event data = last scheduled adequate assessment prior to the unscheduled assessment; if no adequate assessment at scheduled visits existed prior to the unscheduled assessment, then event date = date of unscheduled assessment.	
Subject did not progress nor die	EMA and FDA Guidelines: Censored date: date of last adequate assessment without PD; if no adequate assessment existed then censored at date of enrollment.	
Subject died without initial documented progression	EMA and FDA Guidelines: Event date = date of death.	Per FDA Guidelines if the death date is after AMT then the patient is censored at the last assessment date.
For events during the treatment period: Death or progression from the follow-up within 2 cycles (2 x 28 +10-day window = 66 days) after the latest of: treatment period discontinuation date, last cycle end date of study drug, and last adequate assessment date during treatment period For events during the long-term follow-up phase: Death or progression within 6 months (6 x 30.25 + 10-day window = 192 days) after the last assessment	EMA and FDA Guidelines: Event date = date of death or documented progression if occurring before death.	

Scenario	Date Subject has Event or is Censored	Comment
For treatment period: Death or progression from the follow-up more than 2 assessment cycles (2 x 28 +10-day window = 66 days) after the latest of: treatment period discontinuation date, last cycle end date of study drug, and last adequate assessment date during treatment period For long-term follow-up phase: Death or progression from the follow-up more than 2 assessment cycles, i.e. 6 months (6 x 30.25 + 10-day window = 192 days) after the last assessment	EMA and FDA Guidelines: Censor date = date of last adequate assessment with evidence of no progression; if no adequate assessment existed then censor at date of enrollment.	
New anti-myeloma/non-protocol treatment started prior to progression/death	EMA Guidelines: Event date = date of documented progression/death. FDA Guidelines: Censor date = date of last adequate assessment with evidence of no progression; if no adequate assessment exits then censor at the date of enrollment.	
Death or progression during the treatment period after an extended lost-to-follow-up time (two or more missed scheduled assessments)	EMA Guidelines: Event date = date of documented progression or death. FDA Guidelines: Censor date = date of last adequate assessment with evidence of no progression; if no adequate assessment exits then censor at the date of enrollment.	

Abbreviations: CR = complete response; DoR = Duration of response; OS = overall survival; PD = Disease progression; PFS = Progression free survival; PR = Partial response; sCR = stringent complete response; TTP = Time to progression; VGPR = very good partial response.

10.1.3.3. Time to Progression

Time to progression is calculated as the time from study enrollment, defined as the IVRS enrollment date, until the first recorded disease progression on the IMWG assessment of response CRF or LTFU CRF, whichever occurs first, or death due to PD (refer to PFS for complete event details).

Censoring of subjects not experiencing an event are similar to PFS outlined in Table 1 with the following exceptions:

- If a subject is still on therapy and therefore has no LTFU CRFs, then censor at time of last response assessment, otherwise,

- If the subject did not have a disease progression during therapy but has entered into long term follow-up and still no disease progression is indicated, then censor at the time of the last completed LTFU CRF.

10.1.3.4. Overall Survival

Overall survival is calculated as the time from study enrollment, defined as the IVRS enrollment date, until death due to any cause. Subjects who do not have death data at the time of study end/analysis will be censored at the time they were last known to be alive.

11. STATISTICAL ANALYSIS OF SAFETY ENDPOINTS

All safety analyses will be performed on the safety population.

11.1.1. Adverse Events

Adverse Events will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA) version 15 or higher. The severity of AEs will be graded according to the NCIs CTCAE version 4.0. Summaries will be by system organ class and preferred term.

Treatment-emergent AEs (TEAEs) are defined as any AE occurring or worsening on or after the first treatment of the IP and within 28 days after the last dose. If a subject experiences the same preferred term multiple times then the event will be counted only once and by the greatest severity.

All TEAEs, TEAEs leading to IP discontinuation, TEAEs leading to dose reduction/interruption, TEAEs related to the IP, serious TEAEs, serious TEAEs related to study medication, and serious TEAEs leading to study medication discontinuation will be summarized by system organ class and preferred term. Summary of TEAEs with NCI-CTCAE grade 3 or 4 and with NCI-CTCAE grade 5 will also be provided. Summary of TEAEs by dosing cycle will also be provided. Where necessary, adverse events will be categorized by using specified MedDRA hierarchy terms (i.e., SOC, HLGT, HLT, and PT), and/or by Standardized MedDRA Queries (SMQs); the number and percentage of subjects with adverse events alone and/or with concurrent events, medical history, medications, laboratory values, etc., may be tabulated, and where possible, may be organized or displayed by specific parameters (e.g., time to occurrence, other demographics, exposure/duration/cycle, therapy period(s), etc.) . Where necessary, and as the data allow, incidence rates will be calculated, summarized and displayed.

If a subject experiences the same preferred term multiple times then the subject will be counted only once by the greatest severity of that term when presented in tabulations.

An AE listing will be presented separately for individual subjects.

Adverse Events of Special Interest

Analysis of AEs of special interest will be presented with tabulations for: TEAEs of interest, NCI-CTCAE grade 3 or 4 TEAEs of interest, TEAEs of interest related to study medication, serious TEAEs of interest and TEAEs of interest leading to study medication discontinuation. The following AE of interest categories and preferred terms include but are not limited to:

- neutropenia
- febrile neutropenia
- infection
- thrombocytopenia
- hemorrhage and bleeding
- neuropathy
- DVT (deep vein thrombosis)
- PE (pulmonary embolism)

- SPM (second primary malignancies)
- muscular weakness
- glucose intolerance
- mood alteration
- cataract
- cardiovascular events/dysrhythmia
- fluid retention/edema
- hematopoietic cytopenias

In addition the following tables will be presented to further investigate the corresponding AEs of interest:

- treatment emergent neutropenia and febrile neutropenia by GCSF usage on study
- treatment emergent arterial thrombotic events with and without prophylaxis medications (where prophylaxis medication is defined as low-dose aspirin, low molecular weight heparin, or other equivalent antithrombotic or anticoagulant within one week of prior to onset of event)
- treatment emergent venous thrombotic events with and without prophylaxis medications (where prophylaxis medication is defined as low-dose aspirin, low molecular weight heparin, or other equivalent antithrombotic or anticoagulant within one week of prior to onset of event)
- treatment emergent DVT with and without concurrent PE (where concurrent PE is defined as PE onset within +/- two weeks of onset of DVT, and before resolution of DVT)
- treatment emergent neuropathy by baseline neuropathy status
- time to onset of neuropathy from enrollment
- time to improvement/resolution of neuropathy from enrollment
- time to worsening/new incidence of neuropathy from enrollment
- neuropathy still ongoing at treatment discontinuation
- treatment emergent grade 3 or higher infections and infestations and concurrent neutropenia (where concurrent grade 3 or 4 neutropenia is defined as grade 3 or 4 neutropenia onset within +/- two weeks of onset of infection and infestation, and before resolution of infection and infestation)
- treatment emergent grade 3 or higher neutropenia and concurrent infections and infestations (where concurrent grade 3 or 4 infections and infestations is defined as grade 3 or 4 infections and infestations onset within +/- two weeks of onset of neutropenia, and before resolution of neutropenia)
- treatment emergent (grade 3 or higher) thrombocytopenia with concurrent haemorrhage and bleeding (where concurrent bleeding is defined as bleeding onset within +/- two weeks of onset of thrombocytopenia, and before resolution of thrombocytopenia)

- treatment emergent (grade 3 or higher) haemorrhage and bleeding with concurrent thrombocytopenia (where concurrent grade 4 thrombocytopenia is defined as grade 4 thrombocytopenia onset within +/- two weeks of onset of bleeding, and before resolution of bleeding)
- summary and incidence of second primary malignancy (SPM)

11.1.2. Second Primary Malignancies

Second primary malignancies include any regardless of the causal relationship to the IP (POM with or without DEX).

11.1.3. Deaths

Deaths during treatment period (i.e. after the first treatment of the IP and within 28 days after the last actual dose of study drug received) will be tabulated for the safety population. Deaths during the first 60 days of treatment and after 28 days after the last actual dose of study drug received will also be tabulated.

11.1.4. Clinical Laboratory Evaluations

Clinical laboratory values will be graded according to NCI CTC version 4.0 for applicable tests. Baseline grade and worst severity grade (both high and low, as appropriate) observed during the treatment period for selected laboratory results will be summarized. Furthermore, the shift from baseline to the worst grade observed during the treatment period for selected laboratory results will also be presented. Normal ranges will be used to determine the categories if High, Low and Normal for lab tests with no assigned severity grade. Listings of clinical laboratory data with abnormal flags will be provided by subject and test.

11.1.5. Vital Signs

For vital signs, a shift during treatment from baseline to worse for below-, within-, and above-normal range categories will be displayed in cross–tabulations. Normal ranges are defined as follows:

- Systolic blood pressure (BP) → Normal (90 – 119 mmHg, inclusive)
- Diastolic BP → Normal (60 – 79 mmHg, inclusive)
- Body Temperature → Normal (36.1 – 37.8 degrees centigrade, inclusive)

Descriptive statistics (N, Mean, Standard Deviation, Median, Minimum and Maximum) of observed and change from baseline values will be presented.

11.1.6. Electrocardiogram

The overall ECG interpretation will be summarized by presenting the number and percentage of subjects with “Normal” “Abnormal, not clinically significant and “Abnormal, clinically significant”. Shift from baseline to worst during study, as well as shift from baseline by cycle in the overall ECG interpretation will be displayed in cross–tabulations tabulations.

Other ECG measurements such as QTc will be tabulated with summary statistics (N, Mean, Standard Deviation, Median, Minimum and Maximum) of observed and change from baseline values presented.

11.1.7. ECOG Performance Status

Shift from baseline to worst during study, shift from baseline to best during study, as well as shift from baseline by cycle in ECOG performance status will be displayed in cross-tabulations.

12. PHARMACOKINETIC ANALYSIS

All PK and PD related table, figures and listings will be provided in a separate delivery document.

12.1. Software for Analysis

The software to be used in the pharmacokinetic data analysis and data presentation includes:

- SAS Version 9.1.3 or higher (SAS Institute, Inc., Cary, NC)
- SigmaPlot Version 10.0 or higher (Systat Software, Inc., Point Richmond, CA)

12.2. Analysis population

As a data cut-off date of May 4th 2015, all subjects who receive POM and have PK data will be included. If any subjects are found to be noncompliant with respect to dosing, or encounter other circumstances that could affect the evaluation of PK, a decision will be made on a case-by-case basis as to their inclusion in the PK analysis. Data excluded from PK analysis and/or statistical analysis will be included in the data listings, but not in the summaries.

12.3. Pharmacokinetic Analysis

12.3.1. Data handling

Pre-dose concentrations that are below the limit of quantification (BLQ) or missing will be assigned a number value of zero.

12.3.2. Statistical Analysis

POM plasma concentrations will be listed and summarized by cycle using descriptive statistics (N, mean, SD, coefficient of variation [CV%], geometric mean, geometric CV%, median, Min, and Max). Box-Whisker plot of POM plasma concentrations will be generated.

[redacted]

13. EXPOSURE-RESPONSE ANALYSIS

All analyses related to PK/PD data will be reported separately from the clinical study report.

[redacted]

The key exposure data are serum drug concentration, Cmax, Cmin and AUC derived from the population PK analysis. The key efficacy and safety endpoints include AEs, ORR, time to response, DoR, PFS, TTP, and OS. Other efficacy and safety endpoints may also be explored, as appropriate.

[redacted]

APPENDICES

Appendix A: Date Imputation Guideline

Impute Missing AE / Prior or Concomitant Medications Start Dates:

If the stop date is non-missing and the imputed start date is after the stop date, the stop date will be imputed by the stop date.

Missing day and month with non-missing year

- If the year is the **same** as the year of first day on the IP, then the day and month of the start date of the IP will be assigned to the missing fields
- If the year is **prior to** the year of first day on the IP, then December 31 will be assigned to the missing fields.
- If the year is **after** the year of first day on the IP, then January 1 will be assigned to the missing fields.

Missing day only

- If the month and year are the **same** as the year and month of first day on the IP, then the start date of the IP will be assigned to the missing day.
- If the month and year are **before** the year and month of first day on the IP, then the last day of the month will be assigned to the missing day.
- If the month and year are **after** the year and month of first day on the IP, then the first day of the month will be assigned to the missing day.
- If the stop date is non-missing and the imputed start date is after the stop date, the start date will be imputed by the stop date.

Missing year

- Not imputed. Included as TEAE.

Impute Missing AE / Prior or Concomitant Medications Incomplete Stop Date:

If the imputed stop date is before the start date then the imputed stop date will be equal to the start date.

Missing day and month with non-missing year

- If the year of the incomplete stop date is the **same** as the year of the last dose date of the IP, then the day and month of the last dose date will be assigned to the missing fields.

- If the year of the incomplete stop date is **prior to** the year of the last dose date of the IP, then December 31 will be assigned to the missing fields.
- If the year of the incomplete stop date is **after** the year of the last dose date of the IP, then January 1 will be assigned to the missing fields.

Missing day only

- If the month and year of the incomplete stop date are the **same** as the month and year of the last dose date of the IP, then the day of the last dose date will be assigned to the missing day.
- If the month and year of the incomplete stop date are **before** the month and year of the last dose date of the IP, then the last day of the month will be assigned to the missing day.
- If the month and year of the incomplete stop date are **after** the month and year of the last dose date of the IP, then the first day of the month will be assigned to the missing day.

Missing year

- Not imputed. Included as TEAE.

Impute Missing Disease Diagnosis Dates:

For partial diagnosis dates, January will be assigned to the missing month; and the first day of the month will be assigned to the missing day.

Impute Incomplete Prior Evidence of Disease Progression Dates:

For partial prior disease progression dates, the first day of the month shall be imputed.

Impute Missing Dates in Prior Anti-myeloma Regimen:

For each prior anti-myeloma regimens, the regimen start/stop date, disease progression date, best response date, and date of first response for RR or better, will be collected. If the day of any date is missing, then the first day of the non-missing month will be assigned to the missing day; if month or year of the missing date is missing, then the date will not be imputed and treated as missing.

Impute Missing Dates in Subsequent Anti-myeloma Therapy:

Subjects will be allowed to take other anti-myeloma therapy after discontinuation from the study. The anti-myeloma therapy start/stop date will be collected. If the day of any date is

missing, then the last day of the non-missing month will be assigned to the missing day; if day and month are both missing, the December 31 of the non-missing year will be assigned to the missing day.

Appendix B: Tables Graphs and Listings

Tables Section 14.

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14.1.2.2	Subject Disposition – Long-term Follow-up Phase: All Populations
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[redacted]	[redacted]
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[redacted]	[redacted]

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14.3.2.5.1	Treatment Emergent CTCAE Grade 3 or 4 Adverse Events Related to Any Study Drug: Safety Population

14.3.2.5.2	Treatment Emergent CTCAE Grade 3 or 4 Adverse Events Related to Pomalidomide: Safety Population
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14.3.2.16.5.1	Treatment Emergent CTCAE Grade 3 or 4 Adverse Events of Interest Related to Any Study Drug: Safety Population

14.3.2.16.5.2	Treatment Emergent CTCAE Grade 3 or 4 Adverse Events of Interest Related to Pomalidomide: Safety Population
14.3.2.16.5.3	Treatment Emergent CTCAE Grade 3 or 4 Adverse Events of Interest Related to Low-Dose Dexamethasone: Safety Population
14.3.2.16.6	Treatment Emergent Serious Adverse Events of Interest: Safety Population
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14.3.2.16.7.2	Treatment Emergent Serious Adverse Events of Interest Related to Pomalidomide: Safety Population
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Figures Section 14.

Figure Number	Figure Title
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16.2.4.8	Prior Bisphosphonate Therapy for Bone Lesions
16.2.4.9.1	Evidence of Most Recent Disease Progression
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[redacted]	[redacted]
16.2.4.13	Cytogenetic Assessment
16.2.4.14	Skeletal Survey
16.2.4.15	Bone Marrow Assessment
16.2.4.16	Venous Thromboembolic Event
16.2.4.17	Pregnancy Status and Test Results
16.2.4.18	Subject Eligibility
16.2.4.19	Prior Cancer History

16.2.4.20	Prior Cancer History II – Diagnostic Exams for Cancer Within 6 months Prior to Screening
16.2.4.21	Prior Procedures for Cancer Not Under Study
16.2.4.22	Prior Radiation Treatment for Cancers not Under Study
16.2.4.23	Prior Regimen Treatment for Cancers not Under Study
16.2.5	Study Drug Record: Pomalidomide and Low-Dose Dexamethasone
16.2.6.1	Investigator Assessment of Response (IMWG Criteria)
16.2.6.2	Variables for Determination of Myeloma Response
16.2.6.3	Clinical Plasmacytomas Assessment
16.2.6.4	Radiological Plasmacytomas Assessment
16.2.6.5.1	Subsequent Anti-myeloma Therapy
16.2.6.5.2	Subsequent Stem Cell Transplant for Myeloma
16.2.6.5.3	Subsequent Therapies for Stem Cell Transplant Conditioning
16.2.6.6	Follow-up Therapies
16.2.6.7	Long-term Progression Follow-up
16.2.6.8	Survival Follow-up
[redacted]	[redacted]
16.2.6.10	Individual CC-4047 Plasma Concentrations (ng/mL): Pharmacokinetic Population
16.2.7.1.1	Treatment Emergent Adverse Events
16.2.7.1.2	Pre-treatment and Post-treatment Adverse Events
16.2.7.1.3	Treatment Emergent Adverse Events Leading to Pomalidomide Discontinuation
16.2.7.1.4	Treatment Emergent Adverse Events Leading to Low-Dose Dexamethasone Discontinuation
16.2.7.1.5	Treatment Emergent CTCAE Grade 3 or 4 Adverse Events
16.2.7.1.6	Grade 5 Treatment Emergent Adverse Events
16.2.7.1.7	Treatment Emergent CTCAE Grade 2 or Higher Infections and Concomitant Antibiotic Medication
16.2.7.2	Serious Adverse Events
16.2.7.3.1	Deaths During Treatment Period
16.2.7.3.2	Deaths During First 60 Days of Treatment
16.2.7.3.3	Deaths After 28 Days of End of Treatment
16.2.7.3.4	Deaths for Enrolled Subjects
16.2.7.3.5	Deaths During Screening Period: Non-enrolled Subjects

16.2.7.4	Adverse Events of Clinical Interest
16.2.8.1.1	Local Laboratory - Chemistry
16.2.8.1.2	Local Laboratory - Hematology
16.2.8.1.3	Local Laboratory – Urinalysis
16.2.8.1.4	Local Laboratory - Renal Function Assessment
16.2.8.1.5	Local Laboratory – Immunoglobulins
16.2.8.2	Local Serum Free Light Chain Assessment
16.2.8.3	Vital Signs
16.2.8.4	ECG
16.2.8.5	ECOG Performance Status
16.2.8.6	Healthcare Resource Utilisation
16.2.8.7	Second Primary Malignancies
16.2.8.8	Second Primary Malignancies Procedures
16.2.8.9	Second Primary Malignancy Regimen Therapy
16.2.8.10	Second Primary Malignancy Radiation Therapy