Statistical Analysis Plan	
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A Phase I/II Study of the Tolerability of Lenalidomide and Low Dose Dexamethasone in Previously Treated Multiple Myeloma Patients with Impaired Renal Function.

DOCUMENT:	Statistical Analysis Plan
PROTOCOL	
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1. LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
AE(s)	Adverse event(s)
BUN	Blood urea nitrogen
CBC	Complete blood count
CR	Complete response
CRF	Case report form
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
FDA	Food and Drug Administration
H	Hour(s)
HCG	Human Chorionic Gonadotropin
HepC	Hepatitis C antibody
HIPAA	Health Information Portability and Accountability Act
HIV	Human immunodeficiency virus antibody
ICF	Informed consent form
ICH	International Conference on Harmonization
IHC	Immunohistochemistry
IND	Investigational New Drug
IRB	Institutional Review Board
ITT	Intent-to-treat
LDH	Lactate dehydrogenase
Max	Maximum
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MID	Minimum intolerable dose
min	Minimum
MIP	Molecular inversion probe
MR	Modified Release

Abbreviation or special term	Explanation
N	Number of observations
NDA	New Drug Application
PaR	Partial response
pCR	Pathologic complete response
PD	Progressive disease
PK	Pharmacokinetic(s)
PR	PR wave complex
PT	Prothrombin time
PTH	Parathyroid hormone
QD	Once daily
QID	Four times daily
QDS	Quality Data Services, Inc.
QRS	QRS wave complex
RBC	Red blood cell
SAE	Serious adverse event
SAP	Statistical analysis plan
sCR	Stringent Complete response
SD	Standard deviation
SGOT	Serum glutamic-oxaloacetic transaminase (same as AST)
SGPT	Serum glutamic-pyruvic transaminase (same as ALT)
SOP	Standard Operating Procedure
SD	Standard deviation
SE	Standard error
TEAE	Treatment Emergent Adverse Event
TSH	Thyroid-stimulating hormone
US	United States
VGPR	Very good partial response
WBC	White blood cell
WHO-DD	World Health Organization Drug Dictionary

2. INTRODUCTION

2.1. Objective of the Statistical Analysis Plan

This statistical analysis plan (SAP) describes the planned analysis of the safety and efficacy data from this study. A detailed description of the planned tables, figures and listings (TFLs) to be presented in the Clinical Study Report (CSR) is provided in the accompanying TFL template document. The analyses for the lenalidomide pharmacokinetics (PK) of plasma samples collected during cycle 1 day 6 (phase II) will be reported in a separate report.

The intent of this document is to provide guidance for the analysis of data related to safety and efficacy to describe any applicable statistical procedures. In general, the analyses come directly from the protocol, unless they have been modified by agreement between the Sponsor and Quality Data Services, Inc. (QDS). A limited amount of information concerning this study (e.g., objectives, study design) is summarized to help the reader interpret the accompanying TFL templates. That information is not a synopsis of the study and does not require review or approval because it is simply extracted from the protocol. Attached signatures indicate approval of the statistical analysis sections of the SAP, as well as accompanying TFL templates. These sections must be agreed upon prior to database lock. When the SAP and TFL templates are agreed upon and finalized, they will serve as the template for a portion of this study's CSR.

This SAP supersedes the statistical considerations identified in the protocol; where considerations are substantially different, they will be so identified. If additional analyses are required to supplement the planned analyses described in this SAP, they may be performed and will be identified in the appropriate section of the CSR. Any substantial deviations from this SAP will be agreed upon between the sponsor and QDS. Deviations from this SAP, both substantial and non-substantial, will be documented in the CSR. Any updates to their respective analyses, study designs, and TFL presentations after this SAP is finalized and approved will be documented in a running Note to the SAP document.

Various outputs may be required during the conduct of this trial which will necessitate the production of some but not all of the Figures, Summary Tables and Key Data Tabulations detailed in this document. The SAP will not be updated to reflect these potential changes.

3. STUDY OBJECTIVES

3.1. Primary Objective

The primary objectives of this study are:

- **Phase I:** To establish the maximum tolerated dose of lenalidomide in each of three groups of myeloma patients with impaired renal function.

- **Phase II:** To assess the efficacy of lenalidomide and low dose dexamethasone given in combination across the three groups of myeloma patients with impaired renal function.

3.2. Secondary Objectives

The secondary objectives of this study are:

- To describe the overall survival, progression-free survival, duration of response, and time to treatment failure of myeloma patients with impaired renal function treated with lenalidomide and dexamethasone;

- To evaluate the safety profile of lenalidomide given in combination with weekly dexamethasone in myeloma patients with impaired renal function;

- To describe renal function over time and to evaluate the safety profile of a onetime increase in lenalidomide dose at least 2 cycles after start of treatment due to improved renal function; and

- To determine the pharmacokinetics of lenalidomide administration in myeloma patients with impaired renal function.

4. STUDY DESIGN

4.1. General Study Design and Plan

This phase I/II study involves three single arm phase I trials designed to determine the MTD and toxicity of lenalidomide in the treatment of multiple myeloma in three groups of patients defined by renal dysfunction. Once an MTD is determined within a group, an additional 15 patients will be accrued within the group and treated with the MTD as part of the phase II study to assess efficacy of lenalidomide and dexamethasone in the treatment of multiple myeloma. The 6 phase I patients treated at the MTD plus 15 additional patients accrued in each group will be combined (total = 63 patients) to assess efficacy using a one-stage design.

The first phase I study enrolls patients with moderate renal dysfunction (Group A); the second one enrolls patients with severe renal dysfunction (Group B); and the third one enrolls patients with ESRD renal dysfunction (Group C). Groups A, B, and C have a maximum of 3, 4, and 4 dose levels respectively. The MTD for each group will be determined concurrently.

4.2. Study Population

Sixty-three, 18 years or older, patients who meet all inclusion and exclusion criteria as stated in the Section 3 of the study protocol, will be eligible to participate in this study.

Upon determination that a patient meets eligibility criteria, the patient will be registered in the study.

4.3. Treatment Administration

Patients must not start protocol treatment prior to registration. Treatment should begin ≤ 7 working days of registration.

Dexamethasone will be given at a fixed dose of 40 mg by mouth once weekly on a 28 day treatment cycle. If a dose of dexamethasone is missed, it is up to the treating physician whether the dose should be made up. In addition, continuing dexamethasone if lenalidomide is stopped is also at the discretion of the treating physician.

5. EFFICACY MEASUREMENTS

Efficacy measurements include complete response (CR), stringent complete response (sCR), very good partial response (VGPR), and partial response (PR).

5.1. Response and Progression

Criteria for response and progression are listed in tables 11.2 (page 41) and 11.5 (pages 42 and 43) of the study protocol.

5.2. Other Efficacy Measurements

ECOG performance status will be assessed at pre-study and at day 1, end of cycle 4, day 1 of each additional cycle and at day 1 of cycle 9 or at the end of treatment.

6. SAFETY MEASUREMENTS

Safety will be evaluated by

- Clinical laboratory tests,
- Physical examination findings,
- Vital signs measurements, and
- By the documentation of concomitant medications and adverse events.

6.1. Adverse Events

Adverse Event (AE) is defined as any new untoward medical occurrence or worsening of a pre-existing medical condition in a patient administered a medicinal product in a clinical investigation and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (e.g., including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a product (investigational or marketed), whether or not considered related to the product (investigational or marketed). Following written consent to participate in the study, the collection of AEs/SAEs should begin at the initiation of therapy, unless related to a protocol related procedure.

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The categories and definitions of severity used for this clinical trial's AEs are defined in the NCI's Common Terminology Criteria (CTCAE) Version 4.0.

Categories 'Definite', 'probable' and 'possible' are considered study drug related. Categories 'not likely' and 'not related' are considered not study drug-related.

AEs should be followed to resolution or stabilization, and reported as SAEs if they become serious.

6.2. Physical Examination and Medical History

Physical examination findings will be collected at screening, day 1 of cycles 1 through 4, end of cycle 4, day 1 of each additional cycle, and at day 1 of cycle 9 or end of treatment.

All physical examination findings must be recorded in the patient's source documents and in the patient's CRF.

Medical history will also be collected prior to registration.

6.3. Electrocardiogram

12-lead ECG will be obtained within 21 days prior to registration.

6.4. Clinical Laboratory Assessments

Clinical laboratory tests will be collected at screening, day 1 of cycles 1 through 4, end of cycle 4, day 1 of each additional cycle and day 1 of cycle 9 or end of treatment.

7. LENALIDOMIDE PHARMACOKINETIC MEASUREMENTS

The pharmacokinetic sampling will only apply to selected Mayo Clinic patients who are registered in the Phase II portion of this clinical investigation. 5cc of blood will be drawn on Day 6 of Cycle 1: 0 (pre-dose), 0.5, 1, 1.5, 2, 3, 4, 6, 8, 24 hour at all dose groups and at 48 and 72 hour for patients in Group B with severe renal impairment or in Group C on dialysis.

8. GENERAL STATISTICAL CONSIDERATIONS

This section will go into detail about the statistical approaches and methodology for this study analysis. Statistical analysis and programming of tables and listings will be conducted by QDS, using SAS® Release 9.2 (SAS Institute Inc., Cary, North Carolina, USA). After the TFLs are approved as final, SAS programs used to perform statistical analyses and generate analysis datasets and TFLs will be archived in 3 formats (ASCII, .PDF, and .SAS); the analysis SAS Datasets will archived in XPT format created using SAS PROC COPY.

Analyses for the pharmacokinetic parameters are not included in the statistical analysis plan.

8.1. Determination of Sample Size

Phase I: For Group A, the study may involve a maximum of 18 patients (6 for each of the 3 dose levels) but would likely require 15 patients (3 at the first dose level, 6 for the dose level prior to the MTD, and 6 at the MTD). For Group B, the study may involve a maximum of 24 patients (6 for each of the 4 dose levels) but would likely require 18 patients (3 at the first 2 dose levels, 6 for the dose level prior to the MTD, and 6 at the MTD). For Group C, the study may involve a maximum of 24 patients (6 for each of the 4 dose levels) but would likely require 18 patients (3 at the first 2 dose levels, 6 for the dose level prior to the MTD, and 6 at the MTD).

Phase II: Each group will accrue an additional 15 patients at the MTD.

Overall: The study needs a maximum of 111 patients, and an expected number of 96 patients.

In addition, the protocol allows replacement of patients in phase I who withdraw before completing cycle 1 for reasons other than toxicity.

8.2. Methodology

Continuous data will be summarized with the following descriptive statistics: number of observations (n), mean, standard deviation (SD), median, minimum (min), and maximum (max). Categorical data will be summarized with frequencies and percentages.

In general, listings will be presented by patient. Tables will be presented by renal impairment group relative to specific patient populations.

8.3. Handling of Dropouts or Missing Data

All attempts will be made to prevent any missing values. Missing or invalid data will be treated as missing, not imputed.

No data imputation will be done for safety parameters except for the adverse events (AEs) with missing starting date. If the AE onset date is unknown, then the date of first study treatment will be used for classification of AEs that were experienced following administration of study drug.

8.4. Endpoints

8.4.1. Primary Endpoint

The primary endpoint is the proportion of patients who have at least a partial response to treatment. A partial response or better will be considered synonymous with "success", unless specified otherwise. The 6 patients treated at the recommended dose level (MTD) within each group will be included in the analysis for this portion of the study. The efficacy population will include the 63 patients across groups and include all patients meeting eligibility criteria who signed a consent form and began treatment.

8.4.2. Secondary Endpoints

In this section:

- Survival time is defined as the time from registration to death due to any cause.

- Progression-free survival time is defined as the time from registration to the earliest date of documentation of disease progression. If a patient dies without a documentation of disease progression the patient will be considered to have had disease progression at the time of their death. If the patient is declared to be a major treatment violation, the patient will be censored on the date the treatment violation was declared to have occurred. In the case of a patient starting treatment and then never returning for any evaluations, the patient will be censored for progression on day 1 post-registration.

- Duration of response is defined for all eligible, treated patients who have achieved a partial response or better as the date at which the patient's earliest objective status is first noted to be either a partial response or better to the earliest date progression is documented.

- Time to treatment failure is defined to be the time from registration to the date at which the patient is removed from treatment due to progression, adverse events, or refusal. If the patient is considered to be a major treatment violation or is taken off study as a nonprotocol failure, the patient will be censored on the date they are removed from treatment.

The failure time distributions for the secondary endpoints defined above will be estimated using Kaplan-Meier methods.

8.5. Analysis Populations

This section is designed to identify the characteristics that are necessary for inclusion in particular populations defined for the purpose of analysis.

8.5.1. Intent-to-Treat (ITT) Population

The intention-to-treat (ITT) population is defined to include all patients as randomized.

8.5.2. Safety Population

The safety population is defined as all patients treated with at least one dose of trial therapy. All safety data collected up to the end of the study (i.e., through the last follow-up evaluation) are included in the safety analysis.

8.5.3. Efficacy Population

The efficacy population is defined as all eligible patients who received at least one dose of trial therapy. Patients who do not have an efficacy evaluation will be included and will be classified as unevaluable.

8.6. Efficacy Analysis

8.6.1. Primary Efficacy Analysis

The proportion of successes will be estimated by the number of successes divided by the total number of patients in the efficacy population. Eligible, treated patients who are unevaluable for response will be included in the denominator when estimating the proportion of successes. 95% Confidence intervals for the true success proportion will be calculated according to exact two-stage binomial confidence intervals. (Atkinson and Brown, 1985) Secondary analyses include estimation of the proportion of successes with 95% confidence intervals for each group.

8.7. Safety Analysis

The safety evaluations include AEs, clinical laboratory assessments, vital signs with weight, and physical examination.

The results of this study will be reported using summary tables, figures, and data listings. Continuous variables will be summarized using mean, SD, median, minimum, and maximum. Categorical variables will be summarized by presenting the number (frequency) and percentage in each category.

If any screening safety data is repeated, the measurement taken closest to dosing will be used in the analysis as pre-study baseline. If any post-dose safety data is repeated the measurement taken first at the particular visit in question will be used in the analysis.

8.7.1. Demographics and Baseline Characteristics

Demographic data (e.g. age, gender, race, height, screening body weight, etc.) will be listed for the ITT population. Data will be summarized descriptively (number of patients, mean, SD, median, minimum, and maximum within the efficacy population, overall and by renal impairment group).

Pre-study (i.e., screening and Baseline) data will be listed for the ITT population. When appropriate, tabular summaries of incidence (frequencies) of events/abnormalities or descriptive statistical

summaries (number of patients, mean, SD, median, minimum, and maximum) will be presented within the efficacy population, overall and by renal impairment group.

8.7.2. Prior and Concomitant Medications

The use of prior and concomitant medications taken will be recorded on the CRFs. Prior and concomitant therapies will be coded to a World Health Organization Drug Dictionary (WHO-DD) term. A by-patient listing of prior and concomitant medication use will be included in the CSR.

Prior medications are all doses taken prior to the first dose of study medication. Concomitant medications are all doses taken after the first dose of study medication. If any medications were started prior to dosing and were continued after dosing they will be shown in the listings as prior but will be included in the concomitant summary table.

The use of concomitant medications will be summarized by renal impairment group for the safety population. In each of these summary tables, the number and percentage of patients taking each medication will be presented by ATC Classification.

8.7.3. Adverse Events

Adverse events will be assessed in the safety population.

TEAEs are those that occur after administration of the first study dose until completion of the follow up evaluations. In the case where the start date of the AE is unknown, it will be assumed to be treatment-emergent. Treatment-emergent AEs (TEAEs) will be summarized by system-organ-class (SOC) and preferred term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA®). The frequency of patients who experience TEAEs will be summarized overall cycle. Patients, having the same AE more than once per group, will be counted once for each PT and once within each SOC.

All AEs are listed by patient, including non-treatment-emergent (i.e., pre-dosing or post-dosing) AEs, if applicable. Separate patient data listings are provided for patients who experience treatment-emergent SAEs, TEAEs leading to early termination from the study, or fatal TEAEs.

Additional summary tables will display the number of patients with treatment-emergent AEs by maximum intensity, treatment-emergent AEs by strongest relationship to study drug, and treatment-emergent AEs that led to premature discontinuation of study classified by renal impairment group, system organ class and preferred term. The total number of all treatment-emergent AEs, serious TEAEs, TEAEs by maximum severity, treatment-related TEAEs, TEAEs leading to discontinuations, and TEAEs leading to death will also be summarized by renal impairment group.

CTC Version 4.0 will be used.

8.7.4. Physical Examination and Medical History

Physical examination data will be summarized using frequencies for each visit, Body System, and result by baseline, day 1, end of cycle 4, day 1 of each additional cycle and day 1 of cycle 9 or end of treatment for the safety population. The incidence of abnormalities at each visit for each Body System will be

summarized by frequency counts. A by-patient listing of all physical examination data will be displayed. Unscheduled visits will only be displayed in the listings.

Medical history data will be presented with a by-patient listing.

8.7.5. Electrocardiogram data

A by-patient listing of all ECG data at pre-study will be displayed.

8.7.6. Clinical Laboratory Data

Numeric clinical laboratory data will be summarized using descriptive statistics. Non-numeric laboratory tests will be summarized separately using frequency counts on unique responses. Individual change from baseline in lab values will be calculated and summarized descriptively. The incidence of treatment-emergent graded abnormalities (shown as High, Low, or Abnormal depending on the test) at each visit for each laboratory test will be summarized by frequency counts. Listings of abnormal laboratory results will be produced, showing normal ranges, out-of-range flags, and toxicity grades.

All clinical laboratory data with normal ranges, out-of-range flags, and toxicity grades will be listed by patient. Unscheduled visits will only be displayed in the listings.

9. SUMMARY OF CHANGES FROM PROTOCOL-SPECIFIED ANALYSES

No changes are planned.

10. REPORTING CONVENTIONS

The mean and median will be displayed to one decimal place greater than the original value and the standard deviation will be displayed to two decimal places greater than the original value. All statistical programming and analyses will be performed using SAS® Release 9.2 (SAS Institute Inc., Cary, North Carolina, USA).

The following standards will be used in the data presentation:

- Section 14 tables should be in landscape format. Output should adhere to US / International Conference on Harmonization (ICH) margins and should not require changes for European page size. For item 14 tables, a blank row will separate the header from the content of the table listing. For tables that have “n (%)”, the placement should be centered below “N=xx” in the column header. Frequency tables will be center justified. Descriptive statistics will be decimal aligned.

- Percentages presented in in-text tables should be rounded to one decimal using the SAS rounding function. If “%” is part of the column heading, do not repeat the “%” sign in the body of the table. Unless specified otherwise, “%” should reflect the total population of the treatment groups. Any deviation from that should be part of the footnote. For 0 counts, leave the corresponding percentage blank.

- The format for minimum and maximum should be “Min, Max”. SD should be the default for representing scale, unless standard error has been specified. Standard deviation should be

abbreviated as “SD”, and presented next to the mean value, without any +/- sign. The SD should have one additional decimal place beyond that of the mean (e.g. mean has one decimal place, SD should have two).

- “N” will represent the entire treatment group for the population group being analyzed, while “n” will represent a subset of the treatment group. For tables with population designated as a row heading, “N” should be used (i.e. tables where all participant data is not available for every variable within a treatment group). As a guideline, if the number is used in a denominator it should be presented as “N”. If the number is used in the numerator, it should be presented as an “n”.

- The heading should consist of four lines. Line 1: Sponsor identifier. Line 2: Protocol identifier. Line 3: blank line. Line 4: Table/Appendix number Table Title – Population. The title for in-text tables should begin with the Table/Appendix number.

- All data listings will be sorted by Patient Number and time point (if applicable).

- The date format for all dates is DDMMMYYYY.

A solid line should appear both above and below the column headings of a table. A solid line should appear at the end of the table or at the bottom of each page if the table extends to more than one page. Footnotes should start after the bottom solid line.

11. REFERENCES

References are provided in the protocol.

Atkinson, E. N., and Brown, B. W. (1985). Confidence limits for probability of response in multistage phase II clinical trials. *Biometrics,* 41, 741-744.

12. TABLES, FIGURES, AND LISTINGS

See separate template document.

DOCUMENT HISTORY

Version Date	[redacted] By	Summary of Changes
26JAN2017		Updated names of signatories

Amendment for PrE1003 SAP (20130507 PRECOG10003 SAP V0.3.pdf)

July 13, 2015

Per communication with PrE1003 study statistician [redacted] confirmed that "the efficacy analysis was to be done among 63 patients who were treated at the MTD (Maximum Tolerated Dose) across all groups."

[redacted] confirmation email comes through PrECOG study contact [redacted] sending to QDS on July 09, 2015 5:04pm (with subject PrE1003 SAP and Mocks).

As an amendment, the following sentences (underline) are added to further clarify the "eligible patients" in the definition of Efficacy Population at SAP 8.5.3:

The efficacy population is defined as all eligible patients who received at least one dose of trial therapy. Patients who do not have an efficacy evaluation will be included and will be classified as unevaluable.

<u>Once patients reached their Maximum Tolerated Dose (MTD), they are eligible patients for efficacy population.</u>