DISCLOSURE

REDACTED STATISTICAL ANALYSIS PLAN

MEDI4736-MM-002

A PHASE 1/2 MULTICENTER, OPEN-LABEL STUDY TO DETERMINE THE RECOMMENDED DOSE AND REGIMEN OF DURVALUMAB (MEDI4736) IN COMBINATION WITH LENALIDOMIDE (LEN) WITH AND WITHOUT DEXAMETHASONE (DEX) IN SUBJECTS WITH NEWLY DIAGNOSED MULTIPLE MYELOMA (NDMM)

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STATISTICAL ANALYSIS PLAN

A PHASE 1/2 MULTICENTER, OPEN-LABEL STUDY TO DETERMINE THE RECOMMENDED DOSE AND REGIMEN OF DURVALUMAB (MEDI4736) IN COMBINATION WITH LENALIDOMIDE (LEN) WITH AND WITHOUT DEXAMETHASONE (DEX) IN SUBJECTS WITH NEWLY DIAGNOSED MULTIPLE MYELOMA (NDMM)

STUDY DRUG: MEDI4736 (durvalumab)

PROTOCOL NUMBER: MEDI4736-MM-002

DATE FINAL: 12th March 2018

Prepared by:

PPD

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SIGNATURE PAGE

STATISTICAL ANALYSIS PLAN (SAP) AND SAP AMENDMENT APPROVAL SIGNATURE PAGE	
SAP TITLE	MEDI4736-MM-002 Statistical Analysis Plan
SAP VERSION, DATE	Version 1.0 12th March 2018
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INVESTIGATIONAL PRODUCT	Durvalumab (MEDI4736)
PROTOCOL NUMBER	MEDI4736-MM-002
PROTOCOL VERSION, DATE	Version Amendment 2, 06 Apr 2017
SIGNATURE STATEMENT	By my signature, I indicate I have reviewed this SAP and find its contents to be acceptable.
Statistical Therapeutic Area Head Signature PPD Printed Name PPD Date PPD	
Lead Clinical Research Physician / Clinical Research Physician Signature PPD Printed Name Date PPD	
Lead Product Safety Physician	

Signature	PPD		
Printed Name		Date	PPD

1. LIST OF ABBREVIATIONS

Table 1: Abbreviations and Specialist Terms

AE	Adverse event
AESI	Adverse event of special interest
AUC	Area under the curve
BMI	Body mass index
CI	Confidence interval
CL/F	Clearance
C_{max}	Maximum plasma concentration of drug
CR	Complete response
CrCl	Creatinine clearance
CRO	Contract research organization
CRF	Case report form
CTCAE	Common terminology criteria for adverse events
Dex	Dexamethasone
DLT	Dose-limiting toxicity
DOR	Duration of response
DRT	Dose Review Team
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EE	Efficacy evaluable
EOT	End of treatment
FDA	Food and Drug Administration
HRQoL	Health-related quality of life
ICF	Informed consent form
IMWG	International Myeloma Working Group
IPD	Important protocol deviation
IRT	Interactive response technology
IV	Intravenous

KM	Kaplan-Meier
LEN	Lenalidomide
Max	Maximum
MDS	Myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
MR	Minimal response
MRD	Minimal residual disease
MTD	Maximum tolerated dose
NCI	National Cancer Institute
NDMM	Newly diagnosed multiple myeloma
ORR	Overall response rate
OS	Overall survival
Pd	Pharmacodynamics
PD	Progressive disease
PD-1	Programmed cell death 1
PD-L1	Programmed cell death ligand 1
PD-L2	Programmed cell death ligand 2
PE	Pulmonary embolism
PFS	Progression-free survival
PK	Pharmacokinetics
PR	Partial response
PT	Preferred Term
RD	Recommended dose
RIR	Response improvement rate
SAP	Statistical analysis plan
SAS®	Statistical Analysis System
SD	Stable disease
SOC	System Organ Class

SPM	Second primary malignancy
STD	Standard deviation
$t_{1/2}$	Terminal elimination half-life
TEAE	Treatment-emergent adverse event
T_{max}	Time to maximum concentration
TTR	Time to response
VAS	Visual analogue scale
VGPR	Very good partial response
VTE	Venous thromboembolism
V_z/F	Volume of distribution
WHO	World Health Organization

2. INTRODUCTION

The statistical analysis plan (SAP) describes the analyses and data presentations for Celgene's protocol MEDI4736-MM-002 "A Phase 1/2, multicenter, open-label study to determine the recommended dose (RD) and regimen of durvalumab (MEDI4736) in combination with lenalidomide (LEN) with and without dexamethasone (dex) in subjects with newly diagnosed multiple myeloma (NDMM)." The SAP contains definitions of analysis populations, derived variables and statistical methods for the analysis of efficacy and safety.

Throughout this SAP, the treatment arms will be referred to as Arms A, B and C. The purpose of the SAP is to ensure the credibility of the study findings by pre-specifying the statistical approaches to the analysis of study data prior to database lock for the final analysis. This SAP will be finalized and signed prior to the clinical database lock for the final analysis. All statistical analyses detailed in this SAP will be conducted using Statistical Analysis System (SAS)® Version 9.1 or higher.

Due to the full clinical hold placed by the Food and Drug Administration (FDA), the study will prematurely terminate and data collected up to 15th December 2017 (ie date of the last follow-up data point required per protocol) will be included in the final analysis. An additional analysis focused on overall survival and second primary malignancies will be also performed up to 5 years after the last subject is enrolled into the study, as required per protocol.

3. STUDY OBJECTIVES

3.1. Primary Objective

The primary objective of the study is to determine the RD of durvalumab in combination with LEN with and without dex in subjects with NDMM.

3.2. Secondary Objectives

The secondary objectives are to

- evaluate the safety and preliminary efficacy of durvalumab in combination with LEN with and without dex in subjects with NDMM.
- evaluate the pharmacokinetic(s) (PK) of durvalumab and LEN with and without dex in subjects with NDMM.

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4. INVESTIGATIONAL PLAN

4.1. Overall Study Design and Plan

This is a multicenter, open-label, Phase 1/2 study to determine the RD and regimen of durvalumab in combination with LEN with or without dex in subjects with NDMM. The study will consist of a Dose-finding Phase and a Dose-expansion Phase to determine the optimal regimen.

Dose-finding Phase

The Dose-finding Phase will determine the RD and regimen of durvalumab in combination with LEN with or without dex in a 28-day treatment cycle.

Three treatment cohorts (A, B and C) will be enrolled in parallel:

Treatment Cohort A (for high risk transplant non-eligible [TNE] NDMM subjects)

- Intravenous (IV) durvalumab at 1500 mg on Day 1 of a 28-day cycle,
- Oral LEN 25 mg/day (adjust per the creatinine clearance [CrCl] value, see details in Section 7.2.1.2 and Table 4 of the protocol) on Days 1 to 21 of each 28-day treatment cycle,
- Oral dex 40 mg/day (≤ 75 years old) or 20 mg/day (> 75 years old) on Days 1, 8, 15, and 22 of each 28-day cycle.

Treatment Cohort B (for ≥ 65 years old TNE NDMM subjects who are not high risk)

- Intravenous durvalumab at 1500 mg on Day 1 of a 28-day cycle,
- Oral LEN 25 mg/day (adjust per the creatinine clearance [CrCl] value, see details in Section 7.2.1.2 and Table 4 of the protocol) on Days 1 to 21 of each 28-day treatment cycle,
- Oral dex 40 mg/day (≤ 75 years old) or 20 mg/day (> 75 years old) on Days 1, 8, 15, and 22 of each 28-day cycle (for up to 12 cycles).

Treatment Cohort C (for high risk post-transplant NDMM subjects as maintenance)

- Intravenous durvalumab at 1500 mg on Day 1 of a 28-day cycle,
- Oral LEN 10 mg/day on Days 1 to 21 of each 28-day treatment cycle.

All subjects on these 3 treatment cohorts will continue study treatment until progressive disease (PD) or unacceptable toxicity occurs, or withdrawal of consent.

Based on experience with durvalumab in other indications (solid tumors and myelodysplastic syndrome [MDS]), the initial dose of durvalumab will be at 1500 mg every treatment cycle for each cohort. In the event of dose-limiting toxicities (DLTs), the dose of durvalumab would be de-escalated to a 750 mg dose level.

The Dose Review Team (DRT) are responsible for dosing decisions. The DRT members will consist of the following: Celgene medical monitor, Celgene lead safety physician, Celgene

biostatistician, other Celgene functional area representatives as appropriate, and site investigator and/or designees.

Initially, 6 subjects will be enrolled into each cohort for DLT evaluation and will receive 1500 mg durvalumab. The DLT evaluation period will be the first treatment cycle.

- If ≤ 1 of the 6 initial subjects experience a DLT within the first cycle, then the Dose-expansion Phase may be initiated with durvalumab 1500 mg as the RD;
- If 2 or more of the 6 initial subjects experienced a DLT within the first cycle, then the maximum tolerated dose (MTD) has been exceeded and de-escalation to the durvalumab 750 mg dose level after review of safety and PK/Pd of the initial 6 subjects by the DRT.

Any of the cohorts may be removed from the study based on emerging PK, Pd, efficacy or safety data.

Dose de-escalation will only occur after review of safety data (DLT), and possibly PK/Pd data by the DRT.

Dose-expansion Phase

All dose-expansion decisions will be determined by the DRT after review of all safety, and if applicable PK/Pd, and/or biomarker, and/or preliminary efficacy data.

After all 6 subjects enrolled in the Dose-finding Phase have completed the Cycle 1 treatment; and all data are obtained and reviewed, additional eligible subjects (see detailed eligibility criteria on Sections 4.2 and 4.3 of the protocol) for each respective cohort may be enrolled. The total of subjects for each cohort can be expanded up to 40 (including the 6 subjects enrolled in the Dose-finding Phase and 34 in the expansion phase).

The expansion for each study cohort can occur independently.

Study Population

The study population is to include NDMM subjects who have measurable myeloma protein (M-protein) by protein electrophoresis analyses (in serum [SPEP] and/or urine [UPEP]) per International Myeloma Working Group (IMWG) criteria.

Length of Study

The screening period will be within 28 days prior to start of Cycle 1. Eligible subjects will be treated in 28-day cycles and may continue study treatment until PD or unacceptable toxicity occurs. All subjects will have an end of treatment visit (EOT) within 7 days after discontinuation of all study treatment. Subjects are to return to the study site 28 + 3 days after the EOT visit and 90 (+ 3) days after the last dose of durvalumab for safety follow-up visits. Occurrence of second primary malignancies (SPM) will continue to be monitored at the above required 90-day visit and then every 6 months up to 5 years after the last subject enrolled into the study.

The End of Trial is defined as either the date of the last visit of the last subject to complete the post-treatment follow-up, or the date of receipt of the last data point from the last subject that is required for primary, secondary and/or exploratory analysis, as pre-specified in the protocol, whichever is the later date.

Study Treatments

Subjects will be assigned into different treatment cohorts based on the eligibility criteria.

For subjects in Cohort C, the study treatment is to be initiated at 100 days (± 14 days) after transplant.

The initial dose of durvalumab will be at 1500 mg on Day 1 of a 28-day treatment cycle for all treatment cohorts.

The dose of LEN will be 25 mg (adjustable per the CrCl value, see details in Section 7.2.1.2 of the protocol) on Days 1 to 21 of each 28-day treatment cycle for treatment Cohort A and Cohort B.

The dose of LEN will be 10 mg on Days 1 to 21 of each 28-day treatment cycle for treatment Cohort C.

The dose of dex will be 40 mg/day (≤ 75 years old) or 20 mg/day (> 75 years old) on Days 1, 8, 15, and 22 of a 28-day cycle for treatment Cohort A and Cohort B (for up to 12 cycles).

4.2. Study Endpoints

Table 2: Study Endpoints

Endpoint	Name	Description
Primary	Recommend dose	Review safety (including DLTs), and if applicable, PK/Pd, and/or biomarker, and/or preliminary efficacy data by DRT
Secondary	Safety	Type, frequency, seriousness and severity of adverse events (AEs) (included SPMs), and relationship of AEs to study treatment
	Overall Response Rate (ORR) (for Cohorts A and B)	Proportion of subjects who achieved partial response (PR) or better according to the IMWG Uniform Response Criteria (Rajkumar, 2011)
	Response Improvement Rate (RIR) (for Cohort C)	Proportion of subjects who achieve a response improvement from baseline according to the IMWG Uniform Response Criteria. (Pre-autologous stem cell transplantation [ASCT] diseases measurement will be used as baseline for response assessment)
	Time to Response (TTR) (for Cohorts A and B)	Time from the first date of dosing of study medication to the first date of documented response (PR or better).
	Duration of Response (DoR) (for Cohorts A and B)	Time from the first response (PR or better) to the first documentation of disease progression or death, whichever is earlier, based on the investigator assessments according to the IMWG Uniform Response Criteria

Endpoint	Name	Description
	Pharmacokinetics	Typical serum/plasma PK parameters for durvalumab and LEN, such as maximum observed concentration (C_{max}), area under the concentration-time curve (AUC), time to maximum concentration (T_{max}), terminal elimination half-life ($t_{1/2}$), clearance (CL/F), and volume of distribution (V_z/F)
	CCI [redacted]	[redacted]
	Progression-free Survival (PFS)	Time from first dose to disease progression, as determined by the investigator using the IMWG Uniform Response Criteria, or death during study treatment, whichever occurred earlier
	Overall Survival (OS)	Time from first dose to death due to any cause
CCI [redacted]	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]

Source: Table 2 of the protocol MEDI4736-MM-002.

4.3. Stratification, Randomization, and Blinding

Subjects will be assigned to either Cohort A, B, or C based on the eligibility criteria and current available slots. Slots will be assigned on a first come-first serve basis and will be valid for 48 hours following assignment. Unconfirmed eligibility following 48 hours from slot assignment may result in forfeiture and subsequent reassignment of the slot.

Celgene trial staff will review specific eligibility criteria for all screened subjects prior to enrollment of subjects via the interactive response technology (IRT).

An IRT will be used to track subject assignments to the treatment cohorts and dose levels.

4.4. Sample Size Determination

Up to 138 subjects are planned to be enrolled in the study, of which up to 36 in the 3 cohorts for dose finding and up to 102 in the 3 cohorts for expansion. The actual number of subjects for the study will depend on the number of dose levels being tested.

Phase I expansion dose sample size estimation for Cohort A and Cohort B

Table 3 shows the probability of observing an ORR ≥ 75% under different assumptions about the true ORR in this population. With a sample size of 40 subjects, this study has reasonable operating characteristics of observing an ORR ≥ 75% if the true ORR is 85% or higher.

Table 3: Decision Operating Characteristics of Overall Response Rate with 40 Subjects in the Expansion Dose for Cohort A and Cohort B

True ORR	Probability of observing an ORR ≥ 75% with 40 subjects (≥ 30 out of 40 subjects)
60%	3.5%
65%	12.1%
70%	30.9%
75%	50.4%
80%	83.9%
85%	97.0%
90%	99.9%

ORR = overall response rate.

Table 4 shows probability of observing a RIR ≥ 15% under different assumptions about the true RIR in this population. With a sample size of 40 subjects, this study has reasonable operating characteristics of observing an RIR ≥ 15% if the true RIR is 25% or higher.

Phase I expansion dose sample size estimation for Cohort C

Table 4: Decision Operating Characteristics of Response Improvement Rate with 40 Subjects in the Expansion Dose for Cohort C

True ORR	Probability of observing a RIR ≥ 15% with 40 subjects (≥ 6 out of 40 subjects)
5%	1.4%
10%	20.6%
15%	56.7%
20%	83.9%
25%	95.7%
30%	99.1%
35%	99.9%

ORR = overall response rate; RIR = response improvement rate.

5. GENERAL STATISTICAL CONSIDERATIONS

5.1. Reporting Conventions

Summary tables, listings, and any supportive SAS output will include a "footer" of explanatory notes that will indicate, at a minimum, the program name and the data extraction date (eg, 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 table and figure.

In addition:

- P-values will be rounded to 4 decimal places. P-values that round to 0.0000 will be presented as '<0.0001' and p-values that round to 1.000 will be presented as '>0.9999';
- Confidence intervals (CIs) will be presented as 2-sided 80% CIs unless specified differently in specific analysis;
- All listings will be sorted for presentation in order of cohort, dose level, study center, subject, and date of procedure or event;
- All analysis and summary tables will have the analysis population sample size (ie, number of subjects);
- The day of the first dose of any study drug will be defined as Day 1;
- For handling of dates please refer to 16.1.

5.1.1. Descriptive Statistics

By default, descriptive statistics for continuous variable include: n, mean, standard deviation (STD), Q1 and Q3, median, minimum (Min), and maximum (Max). Unless specified in the actual table shells, the mean, median, Q1 and Q3 should be displayed to the one more decimal place than the original data (derived analysis data). Standard deviation should be displayed to the two more decimal places than the original data (derived analysis data). The minimum and maximum should be displayed to the same number of decimal places as the original data.

5.2. Analysis Populations

5.2.1. Full Analysis Population

The Full Analysis Population (FAS) is defined as all subjects who are enrolled (subjects that sign the inform consent form and meet all eligibility criteria) in the study. Subjects will be analyzed according to the initial cohort actually assigned.

5.2.2. Safety Population

The Safety Population is defined as all enrolled subjects who receive at least 1 dose of the study medications. Subjects will be classified according to the initial durvalumab dose level received.

Drug exposure and all safety analyses (including AEs, labs and deaths) will be based on the Safety Population. Efficacy will also be analyzed based on the Safety Population. Subjects will be analyzed according to the initial cohort assigned.

5.2.3. Efficacy Evaluable Population

The Efficacy Evaluable (EE) Population is defined as all enrolled subjects who receive at least 1 dose of the study medications, and have at least 1 evaluable postbaseline response assessment. Efficacy endpoints including ORR, RIR, TTR, and DoR will be analyzed using the EE Population. Subjects will be analyzed according to the initial cohort assigned.

5.2.4. Dose-determining Population

The Dose-determining Population consists of all subjects from the Safety Population who meet the minimum exposure criterion and have sufficient safety evaluations, or experience a DLT during the first treatment cycle.

Dose-limiting toxicities will be evaluated during the DLT evaluation period for the subjects in the dose-finding portion of the study. The DLT evaluation period will be defined as the first treatment cycle for each subject. Subjects are considered evaluable for assessment of DLT if they receive 1 dose of durvalumab.

5.2.5. Pharmacokinetic Population

The PK Population includes all subjects who receive at least 1 dose of study treatment and have at least 1 measurable PK assessment. If any subjects are found to be noncompliant with respect to dosing, have incomplete data, or encounter other circumstances that would affect the evaluation of the PK, a decision will be made on a case-by-case basis as to the inclusion of his PK data in the statistical analysis.

5.2.6. Grouping of Dose Level

For all analyses by treatment cohort and dose level, subjects in the dose-finding portion will be combined with the corresponding dose level in the expansion phase as 1 single dose cohort. Subjects will be analyzed according to the initial dose level assigned.

5.3. Definitions

5.3.1. Date of First Administration of Study Treatment

The date of first administration of study treatment is derived as the first date when a nonzero dose of any of the study drug (durvalumab, LEN, or dex) was administered.

For simplicity, the date of first administration of study treatment will also be referred as the start date of study treatment.

5.3.2. Date of Last Administration of Study Treatment

The date of last administration of study treatment is the last date when a nonzero dose of any of the study drugs (durvalumab, LEN, or dex) was administered.

5.3.3. Study Day

The study day for safety assessments (eg, AE onset, laboratory abnormality occurrence, vital sign measurement, dose administration) will be calculated as the difference between the date of the assessment and the start date of study treatment plus 1.

The study day for time to event assessments (eg, response assessment, OS, PFS) will be calculated as the difference between the date of the event and the date of first dose plus 1.

5.3.4. Baseline

Baseline value will be defined as the last value on or before the first dose of study drug is administered; if multiple values are present for the same date, the average of these values will be used as the baseline. For subjects who were not treated, the baseline will be the assessment value taken on the visit of Cycle 1 Day 1 if available; otherwise, the value on or prior to enrollment date will be used.

6. SUBJECT DISPOSITION

The total number of subjects with screen failure will be summarized and listed for all screened subjects. Enrollment by country and center will be presented for each treatment cohort for the FAS.

A summary of subject disposition, cohort, and dose level for the FAS will be provided.

Reasons for discontinuing study treatment will be collected on the case report form (CRF) and will be summarized for all enrolled subjects with the following categories:

- Completed
- Death
- Adverse event
- Progressive disease
- Subject withdrew consent
- Lost to follow-up
- Protocol violation
- Other

Reasons for discontinuing/completing the study (ie, no more follow-up visit and no longer participating the study) will be collected on the CRF and will be summarized for all enrolled subjects with the following categories:

- Completed
- Death
- Adverse event
- Progressive disease
- Subject withdrew consent
- Lost to follow-up
- Protocol violation
- Other

7. PROTOCOL DEVIATIONS/ IMPORTANT PROTOCOL DEVIATIONS

Protocol deviations/ Important protocol deviations (PD/IPDs) will be reported and monitored throughout the study. PD/IPDs will be identified and assessed by the clinical research physician or designee following company standard operational procedure. Data of PD/IPDs will be finalized prior to database lock and summarized by cohort and dose level for the FAS.

The following by-subject listing of subjects with demographic information will be provided:.

- Subject listing of discontinuation.
- Subject listing of screen failures.
- Subject listing of PD/IPD.
- Subject listing of being excluded from Safety, DLT, EE, or PK Population.

8. DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Demographics and baseline characteristics will be summarized for the FAS. Individual subject listings will be provided to support the summary tables.

8.1. Demographics

Age (years), height (cm), weight (kg), body mass index (BMI) (weight (kg) / height (m^2)) at baseline will be summarized descriptively. Age category (< 65 versus ≥ 65 and < 75 versus ≥ 75 years), sex, race, and ethnicity will be summarized by frequency counts.

Age will be calculated as follows: age = Integer ≤ [(Date of consent – Date of birth + 1) / 365.25].

Subjects that have an International Staging System (ISS) Stage III, high-risk cytogenetic abnormalities (with t(4:14), or/and, t(14;16), or/and 17p13 deletions abnormality), or/and 1q amplification), or LDL (in U/L) > 2 Upper Limit of Normal (ULN) will be considered as high rick subjects. In addition to fulfilling the high-risk criteria, subjects in Cohort C would also have a post-transplant response of PR or better at the time of enrollment into this study and Minimal Residual Disease (MRD) positive (defined as more than 1 malignant cells in 10^5 cells) measured by ClonoSIGHT™ NGS assay of a BMA sample)..

8.2. Baseline Characteristics

The number and percentage of subjects in each of the following categories will be presented.

1. Eastern Cooperative Oncology Group (ECOG) performance status at baseline;
2. Electrocardiogram (ECG) at baseline;
3. ISS stage and sub category at diagnosis;
4. Serum and Urine M-protein;
5. High-risk cytogenetic abnormalities at baseline for Cohort A, cytogenetic abnormalities at diagnosis for Cohort C.

Time from diagnosis to enrollment, vital signs (temperature, systolic blood pressure, diastolic blood pressure and pulse rate), serum and urine M-protein, light chain (kappa, lambda, kappa/lambda ratio), laboratory data at baseline will be summarized descriptively by cohort.

8.3. Baseline Symptoms

The number and percentage of subjects presenting the following symptoms at baseline will be summarized descriptively along with the grade of the symptoms: motor neuropathy, sensory neuropathy, other neuropathy, neutropenia, thrombocytopenia, leukopenia, anemia, chronic kidney disease, hypercalcaemia, hypertension, arrhythmia, atrial fibrillation, diabetes mellitus and chronic obstructive pulmonary disease.

8.4. Medical History

Medical history will be coded using the Medical Dictionary for Drug Regulatory Activities (MedDRA) Version 20.0, or higher. System organ class (SOC) and preferred term (PT) will be summarized by frequency and percentage. Tables will be provided for subjects in the FAS.

8.5. Prior Radiation and/or Antimyeloma Therapy

Prior radiation therapies (all cohorts) and/or prior antimyeloma therapies (Cohort C only) will be summarized with frequency counts and percentages for the FAS. Prior radiation therapies will be summarized by type and location whereas prior antimyeloma therapies will be presented by World Health Organization (WHO) (March 2017 version, or higher) drug preferred name.

For Cohort C, last prior antimyeloma therapies will be also presented by drug class and drug preferred name.

8.6. Prior and Concomitant Medications

Medications initiated prior to the start of study treatment and continued after the start of study treatment will be counted as both prior and concomitant medications for the FAS.

8.6.1. Prior Medications

Prior medications are defined as medications that were started before the start of the study treatment and either ended before the start of the study treatment or continued after study treatment.

The Anatomical Therapeutical Chemical (ATC) coding scheme of the WHO (March 2017 version, or higher) will be used to group medications into relevant categories.

All prior medications will be summarized by ATC level 1 and drug preferred name in frequency tabulations for the FAS.

8.6.2. Concomitant Medications

Concomitant medications are defined as medications that were either initiated before the first dose of study drug and continued during the study treatment, or initiated on / after the date of the first dose of study drug till the end of the last dose of study drug plus 90 days.

The Anatomical Therapeutical Chemical (ATC) coding scheme of the WHO (March 2017 version, or higher) will be used to group medications into relevant categories.

All concomitant medications will be summarized by ATC level 1 and drug preferred name in frequency tabulations for the FAS.

8.7. Concomitant Procedures

The eCRF page records procedure, date, and indication. These procedures will be coded using MedDRA Version 20.0 or higher. A frequency summary of subjects by concomitant procedures summarized in frequency tabulations by SOC and PT by disease cohort for the FAS.

Concomitant procedures will be identified as procedures or surgeries that occurred after or on the date of first dose of study drug and continued during the study treatment, or initiated on / after the date of the first dose of study drug till the end of the last dose of study drug plus 90 days.

9. STUDY TREATMENTS AND EXTENT OF EXPOSURE

9.1. Treatment Duration

Treatment duration will be summarized by treatment arm and dose cohort for the Safety Population.

The treatment duration (in weeks) for each individual study drug is defined as follows:

[(Treatment duration end date for individual study drug) – (1st dose of individual study drug) +1]/7

Treatment duration end date is defined as Min [(last non-zero/non-missing dose date + days to be covered by the last dose), death date].

The treatment duration for the overall study (in weeks) is defined as follows:

[(Treatment duration end date for the overall study – first date when subject receives any dose of study drug + 1) / 7 (in weeks)

Treatment duration end date is defined as Min [(last non-zero/non-missing dose date of all study drugs + days to be covered by the last dose), death date].

In addition to treatment duration, the number of cycles received will also be summarized (Refer to 16.1.2 for the definition of cycle length).

The number of days to be covered by the last dose is defined in Table 5.

Table 5: Number of Days to be Covered by the Last Dose

Arm	Schedule	n = days to be covered by the actual last dose*
Cohort A		
durvalumab	CxD1	n=27
LEN	CxD1 to CxD20 CxD21	n=0 n=7
dex	CxD1 CxD8 CxD15 CxD22	n=6 n=6 n=6 n=6
Cohort B		
durvalumab	CxD1	n=27
LEN	CxD1 to CxD20 CxD21	n=0 n=7
dex	CxD1 CxD8 CxD15 CxD22	n=6 n=6 n=6 n=6
Cohort C		
durvalumab	CxD1	n=27
LEN	CxD1 to CxD20 CxD21	n=0 n=7
dex	N/A	

* if schedule is not respected the number of days to be covered by the actual last dose will be adapted accordingly so that the last dose date + n corresponds to the study day 28 of the cycle.

9.2. Cumulative Dose

Cumulative dose is defined as the sum of all doses taken across the treatment period in milligrams (mg). Cumulative dose will be calculated separately for each drug by treatment cohort and dose level.

Cumulative dose for (durvalumab/LEN/dex) = Sum of (administered dose of each cycle [mg])

9.3. Dose Exposure

Dose exposure is defined as the total number of days on the study drug during the treatment phase (excluding the periods of dose break per protocol or dose interruptions). Dose exposure will be calculated separately for each drug by treatment cohort and dose level.

9.4. Average Daily Dose

Average daily dose is defined as the cumulative dose divided by dose exposure (mg/day). Average dose will be calculated separately for each drug by treatment cohort and dose level.

9.5. Dose Intensity

Dose intensity during the treatment is defined as the cumulative dose divided by treatment duration, ie, dose intensity (mg/day) = cumulative dose (mg) / treatment duration (day). Dose intensity will be calculated for each drug separately by treatment cohort and dose level.

9.6. Relative Dose Intensity

Relative dose intensity is defined as the dose intensity divided by the planned dose intensity:

- For durvalumab the planned dose intensity is (dose level) / per 28 days, with dose level of 750 or 1500 mg.
- For LEN the planned dose intensity is (dose level)*21 / per 28 days, with an adjustable dose level based on renal function on the first day of cycle 1 and 10 mg for Cohort C.
- For dex, the planned dose intensity is 40*4 = 160 mg / per 28 days for subjects ≤ 75 years old, or 20*4 = 80 mg / per 28 days for subjects > 75 years old.

The dose of lenalidomide must be adjusted for renal function on the first day of Cycle on Days 1 to 21 of each 28-day treatment cycle based on Table 6.

Table 6: Lenalidomide Dosing Guideline for Renal Insufficiency for Cohort A and Cohort B

Renal Function (CrCl)	Dosing
Normal to Mild RI (CrCl ≥ 50 mL/min)	25 mg once daily on Days 1 to 21 of each 28-day cycle
Moderate RI (30 ≤ CrCl < 50 mL/min)	10 mg[a] once daily on Days 1 to 21 of each 28-day cycle
Severe RI (CrCl < 30 mL/ min)	15 mg once every other day from Day 1 to 21 of each 28-day cycle

CrCl = creatinine clearance; RI = renal insufficiency.
[a] This dose may be escalated to 15 mg after 2 Cycles at the discretion of the treating physician if the subject tolerates the 10 mg dose of lenalidomide without dose-limiting toxicity.

In Cohorts A and B for LEN, if the CrCl ≥ 50 mL/min at the first day of Cycle 1, the planned dose intensity is (dose level)*21 / per 28 days, with dose level of 25 mg.

In Cohorts A and B for LEN, if 30 ≤ CrCl < 50 mL/min at the first day of Cycle 1, the planned dose intensity is (dose level)*21 / per 28 days, with dose level of 10 mg.

In Cohorts A and B for LEN, if CrCl < 30 mL / min at the first day of Cycle 1, the planned dose intensity is (dose level)*11 / per 28 days, with dose level of 15 mg.

9.7. Dose Modifications

Dose reduction / interruption will be summarized separately for each drug, as applicable. Durvalumab will be summarized according to dose delay / infusion interruption while lenalidomide and dexamethasone will be summarized according to dose reduction or interruption, as appropriate. The number of subjects who have at least 1 dose reduction / interruption, number of dose reductions / interruptions per subject, reason for dose reduction / interruption and time to first dose reduction / interruption will be summarized by drug, assigned cohort, and dose level.

10. EFFICACY ANALYSIS

Efficacy analyses pertaining to the response (eg, ORR, RIR, TTR and DoR) will be carried out on the EE Population. Supportive efficacy analyses for ORR and RIR will be also performed on the Safety Population.

Additional time-to-event analyses for PFS and OS will be based on the Safety and FAS Populations. All analyses will use descriptive statistics. Subjects treated with the recommended dose in the expansion portion will be combined with the corresponding dose level in the dose-finding portion as one single dose level for efficacy and safety analysis. No formal statistical comparison / testing will be performed.

Response Using the IMWG Uniform Response Criteria

Tumor response, including PD, will be assessed by the investigators.

The preliminary efficacy endpoint for Cohorts A and B is the ORR, calculated as the proportion of subjects achieving a PR or better as assessed by the investigators using the IMWG uniform response criteria. PR or better is defined as PR, very good partial response [VGPR], complete response [CR], or stringent complete response [sCR]. The ORR will be summarized together with the two-sided 80% exact confidence interval (CI).

The best overall clinical response categories (sCR, CR, VGPR, PR, Minimal Response [MR], stable disease [SD] and PD) will be also tabulated for Cohort A and B and dose level.

Response Improvement Rate Using the IMWG Uniform Response Criteria

The preliminary efficacy endpoint for Cohort C is the proportion of subjects achieving a RIR from Cycle 1 Day 1 as assessed by the investigators using the IMWG Uniform Response Criteria. The RIR will be summarized together with the two-sided 80% exact CI.

Shift table from baseline will also be generated.

Time to Response (TTR)

Time to response (for responders only, per IMWG Uniform Response Criteria) is calculated as the time from the first date of dosing of study medication to the first date of documented response (PR or better). Subjects who do not achieve any defined response during the treatment period will be censored at the date of last adequate response assessment, disease progression, or death, whichever occurs first.

TTR will be summarized using descriptive statistics or listed by treatment cohort and dose level for Cohorts A and B using the EE Population.

Duration of Response (DoR)

Duration of response (for responders only, per IMWG Uniform Response Criteria) is defined as time from the earliest date of documented response (PR or better) to the earliest date of disease progression as determined by the investigator per IMWG Uniform Response Criteria or death during the study treatment by treatment cohort for Cohorts A and B, whichever occurs first.

DoR will be summarized using descriptive statistics or listed by treatment cohort and dose level for Cohorts A and B using EE Population. Median duration of response and associated two-sided 80% CI will be also estimated using the Kaplan-Meier (KM) method.

Censoring rules are defined in Table 7.

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Overall Survival (OS)

OS is calculated as the time from first dose to death due to any cause. Subjects who died will be considered as having events on the date of death. Subjects who are alive at the time of clinical data cut-off date will be censored at the earlier between last assessment at which the subject was known to be alive and cut-off date will be used. All subjects who were lost to follow-up prior to the clinical data cut-off date will also be censored at the time of last contact. Overall survival will be summarized using KM estimates by treatment cohort and dose level for the Safety Population and the FAS.

Progression-free Survival (PFS)

Progression free survival will be calculated as the time between first dose and disease progression, as determined by the investigator using the IMWG Uniform Response Criteria, or death during study treatment, whichever occurs earlier.

Median PFS along with the two-sided 80% CI will be summarized using KM estimates by treatment cohort and dose level for the Safety Population and FAS.

Censoring rules are defined in Table 7.

Table 7: Censoring Rules for PFS and DoR

Situation	Date of Progression or Censoring	Situation Outcome
Death within the first two scheduled assessments without disease progression	Date of death	Event
Progression	If the first PD is a scheduled assessment then Date of first PD; If the first PD is an unscheduled assessment and no previous assessment, then Date of PD; If the first PD is an unscheduled assessment and has previous assessment, then Date of previous assessment (regardless of the response type)	Event
Death between scheduled assessments	Date of death	Event
No progression	Date of last adequate assessment with evidence of no progression	Censored
Death or progression after two or more missed scheduled assessments	Date of last adequate assessment with evidence of no progression	Censored
New antimyeloma / nonprotocol treatment started prior to progression or death due to any reason	Date of last adequate assessment with evidence of no progression before the start of new treatment	Censored

PD = progressive disease.
Source: United States Food and Drug Administration (US FDA) guidance for cancer trial endpoints for the approval of cancer drugs and biologics (FDA Guidance, 2007).

11. SAFETY ANALYSIS

The purpose of this section is to define the safety parameters for the study. All summaries of safety data will be conducted using the Safety Population.

11.1. Dose-limiting Toxicity

A DLT will be defined as below:

Hematologic DLT

a. Grade 4 neutropenia observed for greater than 5 days duration.
b. Grade 3 neutropenia associated with fever (≥ 38.5°C / 101.3°F) of any duration.
c. Grade 4 thrombocytopenia or Grade 3 thrombocytopenia with bleeding, or any requirement for platelets transfusion.
d. Any other Grade 4 hematologic toxicity that does not resolve to subject's pre-treatment baseline level within 72 hours.
e. Grade 4 anemia, unexplained by underlying disease.

Nonhematologic DLT

a. Any nonhematologic toxicity Grade ≥ 3 except for alopecia and nausea controlled by medical management.
b. Any treatment interruption greater than 2 weeks due to AE.

While the rules for adjudicating DLTs in the context of dose decision are specified above, an AE not listed above may be defined as a DLT after consultation with the sponsor and investigators, based on the emerging safety profile.

Dose-limiting toxicity will be listed by treatment cohort and dose level using the Dose-determining Population.

11.2. Adverse Events

Adverse events will be analyzed in terms of treatment-emergent adverse events (TEAEs). All AEs will be coded using the MedDRA Version 20.0 or higher. The intensity of AEs will be graded according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03 or higher.

TEAEs include AEs between the earliest of the first dose date of either study drug and the maximum of the following 2 points below.

Maximum of:

(a) 28 days after the last dose of LEN or dex

(b) 90 days after the last dose of durvalumab

A treatment-related TEAE is defined as a TEAE which is suspected to be related by the investigator to the study drug.

If a subject experience the same AE more than once with different toxicity grade, then the event with the highest grade will be tabulated in "by grade" tables. If a subject experiences multiple AEs under the same PT (SOC), then the subject will be counted only once for that PT (SOC). In addition, AEs with a missing intensity will be presented in the summary table as an intensity category of "Missing."

The incidence of TEAEs will be summarized by MedDRA SOC and PT. The intensity of AEs will be graded 1 to 5 according to the CTCAE Version 4.03 or higher. For all other AEs not described in the CTCAE criteria, the intensity will be assessed by the investigator as mild (Grade 1), moderate (Grade 2), severe (Grade 3), life-threatening (Grade 4) or death (Grade 5). Tables summarizing the incidence of TEAEs will be generated, including but not limited to the following:

- All TEAEs;
- TEAEs by cycle;
- All TEAEs with Grade ≥ 3;
- TEAEs with Grade 1 or 2;
- TEAEs by maximum Grade;
- TEAEs reported as treatment-related;
- Treatment-related Grade 3 or higher TEAEs;
- Serious TEAE;
- Treatment-related serious TEAEs;
- TEAEs with action of study drug permanently discontinued;
- Treatment-related TEAEs with action of study drug permanently discontinued;
- TEAEs with action of study drug dose delayed/reduced;
- Treatment-related TEAEs with action of study drug dose delayed/reduced;
- TEAEs with action of study drug dose/infusion interrupted;
- Treatment-related TEAEs with action of study drug dose/infusion interrupted;
- TEAEs with action of study drug dose/infusion delayed/reduced or interrupted;
- Treatment-related TEAEs with action of study drug dose infusion delayed/reduced or interrupted;
- TEAEs that led to death.

Listings for the corresponding summary tables will be presented separately. A listing for non-treatment-emergent AEs will also be provided.

All deaths and reasons for death will be summarized for the Safety Population. Deaths within 28 and 90 days after the last dose of any drug component will be summarized separately. Death information will come from the death eCRF page

11.3. Adverse Events of Special Interest

The adverse events of special interest (AESIs) refer to a group of PTs from one or more SOCs relating to a defined medical condition or area of interest. Unless an AESI is defined by a single PT, the AESI generally refers to a group of PTs.

AESIs will be summarized separately for durvalumab and LEN. The AESI summary for each study treatment will be summarized by AESIs, which will be referred as AESI categories in tables and listings, and by PT.

The following AESIs for durvalumab, as identified by MedImmune, will be summarized for regulatory purposes:

- Diarrhea
- Colitis
- Intestinal perforations
- Pneumonitis including ILD
- Hepatitis/ Hepatic events
- Hepatic laboratory parameters reported as AEs
- Adrenal insufficiency
- Type 1 diabetes mellitus
- Hypophysitis
- Thyroiditis
- Hyperthyroid events
- Thyroid laboratory parameters reported as AEs (increased thyroid activity))
- Hypothyroid events
- Thyroid laboratory parameters reported as AEs (decreased thyroid activity))
- Rash / Dermatitis
- Nephritis/ Renal events
- Renal laboratory investigations reported as AEs
- Pancreatitis

- Pancreatic laboratory investigations reported as AEs
- Myocarditis
- Myositis / Polymyositis
- Myasthenia gravis
- Guillain-Barré syndrome
- Other rare/miscellaneous (other inflammatory responses that are rare / less frequent with a potential immune-mediated aetiology)
- Infusion/hypersensitivity reactions

The following AESIs for LEN, based on risk definitions (search criteria) as outlined in the Revlimid risk management plan (RMP) approved at the time of data cut-off, will be summarized:

- Hepatic disorders
- Diarrhea
- Constipation
- Interstitial lung disease (interstitial pneumonitis)
- Renal failure
- Cutaneous reactions
- Peripheral neuropathy
- Hypersensitivity and angioedema
- Neutropenia and infections
- Teratogenicity
- Thrombocytopenia and bleeding
- Thromboembolic events
- Tumor lysis syndrome
- Cardiac failure
- Cardiac arrhythmias
- Ischemic heart disease (including myocardial infarction)
- AML
- B-cell malignancies
- NMSC
- Other hematologic malignancies

- Solid tumors

After review of the data, there may be other AESIs identified. In addition, the following summaries will be generated for TEAEs included in the above-mentioned AESIs:

- All TEAEs of special interest;
- TEAEs of special interest of Grade 3 or 4;
- TEAEs of special interest by maximum Grade;
- TEAEs of special interest by cycle (at first onset and any onset)
- TEAEs of interest leading to study drug permanently discontinued;
- TEAEs of interest leading to death

The list of AE PTs for each AESI can be based on the Standard MedDRA Query (SMQ) search and/or the clinical/medical considerations.

SPMs, occurring at any time from the time of signing the informed consent up to and including the long-term follow-up period, will be summarized as events of interest. SPMs occurring before and after the first dose will be presented separately. SPMs are collected in the Serious Adverse Event for Second Primary Malignancies eCRF form.

Graphical displays will be provided where useful to assist in the interpretation of results.

Listings for the corresponding summary tables will be presented separately.

11.4. Clinical Laboratory Evaluations

Clinical laboratory values from the central laboratories (hematology, chemistry) will be graded according to NCI CTCAE Version 4.03 or higher for applicable tests. The worst grade during the treatment period will be summarized by assigned cohort, and dose level. Frequency distributions for shift from baseline to the worst grade during treatment period will be presented by treatment arm.

Clinical laboratory values will be also summarized descriptively.

Listings of clinical laboratory data from central laboratory (hematology, chemistry, coagulation, thyroid function tests) with abnormal flags will be provided by subjects and tests. Listings will also be provided for the local laboratory data.

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11.6. Vital Sign Measurements

For vital signs, with shifts from baseline to worst during treatment (below, within, and above the normal ranges) will be displayed in cross–tabulations for each treatment. Summary statistics of observed values and change from baseline values will be presented.

11.7. Electrocardiograms

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' by treatment. The shift from baseline to worst during treatment in the overall ECG interpretation will be displayed in cross–tabulations for each treatment.

11.8. Eastern Cooperative Oncology Group Performance Status

Shift table from baseline to worst post-baseline in ECOG performance score will be displayed by cohort and dose level for the Safety Population.

11.9. Pharmacokinetic Analysis

Pharmacokinetic analysis will be based on the PK Population. Typical serum / plasma PK parameters for durvalumab and LEN, such as maximum observed concentration (C_{max}), area under the concentration-time curve (AUC), time to maximum concentration (T_{max}), terminal elimination half-life ($t_{1/2}$), clearance (CL/F), and volume of distribution (V_z/F) will be summarized descriptively by cohort and dose level using the PK Population. CCI [redacted]

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13. INTERIM ANALYSIS

No formal interim analyses are planned. However, during the study, data will be analyzed and reviewed on an ongoing basis to allow for DRT to review and make decisions about dosing decisions

14. CHANGES TO THE STATISTICAL ANALYSES SECTION OF THE PROTOCOL

PFS and OS will be derived from first dose date rather than from date of enrollment. This update is required to ensure consistency across time-to-event analyses.

15. REFERENCES

Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, FDA/CDER/CBER May 2007.

Rajkumar SV, Harousseau JL, Durie B, Anderson KC, Dimopoulos M, Kyle R, et al. Consensus recommendations for the uniform reporting of clinical trials: report of the International Myeloma Workshop Consensus Panel 1. Blood. 2011;117(18):4691-5.

16. APPENDICES

16.1. Handling of Dates

Dates will be stored as numeric variables in the SAS analysis files and reported in DDMMMYYYY format (ie, 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 are present and should only be missing when a procedure are marked as NOT DONE in the database. Procedure dates will not be imputed.
- **Log Dates** are dates recorded in CRF data logs. Specifically, they are the start and end dates for adverse events 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 16.2 (eg, 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, study drug start date, study drug termination date, study closure date, 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, progression, etc. In most cases they are derived either from a milestone (eg, the survival date is derived from the death date), or a procedure date (eg, 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 did not occur, but are not otherwise subject to imputation.
- **Special Dates** cannot be classified in any of the above categories and they include the date of birth. They may be subject to variable-specific censoring and imputation rules.

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

16.1.1. Calculation Using Dates

Calculations using dates (*eg*, subject's age or relative day after the first dose of study drug) 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 study drug (eg, durvalumab) plus 1 day. The generalized calculation algorithm for relative day is the following:

- If TARGET DATE >= DSTART then STUDY DAY = (TARGET DATE – DSTART) + 1;
- Else use STUDY DAY = TARGET DATE – DSTART.

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

- Age (expressed in days) is calculated: AGE = CONSENT – DATE of BIRTH + 1. In practice, age will be transformed to years by dividing the difference by 365.25 days, then truncating. If date of birth is missing in the CRF then use the age recorded in the CRF.Intervals that are presented in weeks will be transformed from days to weeks by using (without truncation) the following conversion formula:

  WEEKS = DAYS / 7

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

  MONTHS = DAYS / 30.4167

16.1.2. 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 dose of study drug.

Once the start dates, eg, 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, ie, $E_i = S_{i+1} - 1$. For the last cycle, the end date will be calculated as the start date plus prescribed cycle length, or the treatment discontinuation date, or the death date, whichever is earlier. If a date is on or after S_i and before S_{i+1}, the corresponding cycle number will be i.

16.2. Date Imputation Guideline

16.2.1. Impute Missing Adverse Events/Prior or Concomitant Medications

Incomplete Start Date:

Missing day and month

- If the year is the **same** as the year of the first dosing date, then the day and month of the first doing date will be assigned to the missing fields.
- If the year is **prior to** the year of first dosing date, then 31 Dec will be assigned to the missing fields.
- If the year is **after** the year of first dosing, then 1 Jan 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 dosing date, then the first doing date will be assigned to the missing day.
- If either the year of the partial date is **before** the year of the first dosing date or the years of the partial date and the first dosing date are the same but the month of partial date is **before** the month of the first dosing date, then the last day of the month will be assigned to the missing day.
- If either the year of the partial date is **after** the year of the first dosing date or the years of the partial date and the first dose date are the same but the month of partial date is **after** the month of the first dosing date, then the first day of the month will be assigned to the missing day.
- If the stop date is not missing, and the imputed start date is after the stop date, the start date will be imputed by the stop date.

Missing day, month, and year

- No imputation is needed, the corresponding AE will be included as TEAE.

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

- If the year of the incomplete stop date is the same as the year of the last dosing date, then the day and month of the last dosing date will be assigned to the missing fields.
- If the year of the incomplete stop date is prior to the year of the last dosing date or prior to the year of the first dosing date, then 31 Dec will be assigned to the missing fields.
- If the year of the incomplete stop date is prior to the year of the last dosing date but is the same as the year of the first dosing date, then the first dosing date will be assigned to the missing date.
- If the year of the incomplete stop date is after the year of the last dosing date, then 1 Jan 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 dosing date, then the day of the last dosing date will be assigned to the missing day.
- If either the year of the partial date is not equal to the year of the last dosing date or the years of the partial date and the last dosing date are the same but the month of partial date is not equal to the month of the last dosing date, then the last day of the month will be assigned to the missing day.

16.2.1. Adverse Events

Partially missing AE start dates will be imputed in the ADaM dataset for AEs. If the AE end date is complete with no missing year, month, or day, and the partially missing start date imputed by the rules above is after the AE end date, then the start date will be imputed by the AE end date.

16.2.2. Prior/Concomitant Medications/Procedures

Partially missing start/stop dates for prior/concomitant medications and partially missing start dates for prior/concomitant procedures will be imputed in the ADaM dataset for prior/concomitant medications/procedures. For prior/concomitant medications, if the stop date is complete with no missing year, month, or day, and the partially missing start date imputed by the rule below is after the stop date, then the start date will be imputed by the stop date.

Partially missing prior/concomitant medication/procedure start dates will be imputed by the earliest possible date given the non-missing field(s) of the date.

Partially missing prior/concomitant medication stop dates will be imputed by the latest possible date given the non-missing field(s) of the date.

16.2.3. 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.

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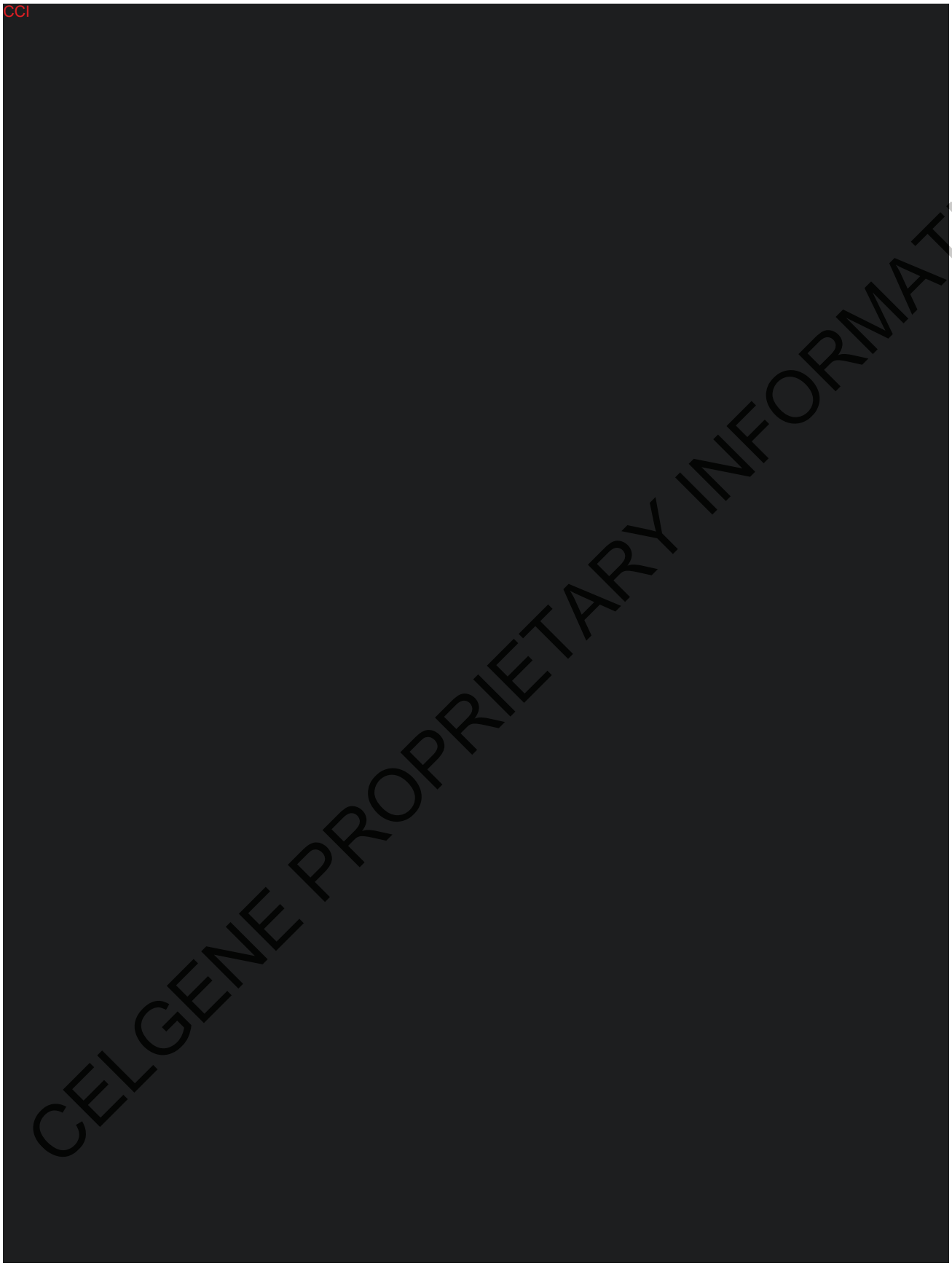

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