Integrated Analysis Plan

Clinical Study Protocol Identification No.	MS201814-0010
Title	A Phase I Open Label First in Human Dose Escalation of the Immunoproteasome Inhibitor M3258 as a Single Agent and Expansion Study of M3258 in Combination with Dexamethasone in Participants with Relapsed Refractory Multiple Myeloma
Study Phase	Phase I (dose escalation and expansion)
Investigational Medicinal Product(s)	M3258
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Integrated Analysis Plan Reviewers	

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Approval Page

Integrated Analysis Plan: MS201814-0010

A Phase I Open Label First in Human Dose Escalation of the Immunoproteasome Inhibitor M3258 as a Single Agent and Expansion Study of M3258 in Combination with Dexamethasone in Participants with Relapsed Refractory Multiple Myeloma

Approval of the IAP by all Merck Data Analysis Responsibles has to be documented within ELDORADO via eSignature. With the approval, the Merck responsible for each of the analysis also takes responsibility that all reviewers' comments are addressed adequately.

By using eSignature, all signatures will appear at the end of the document.

1 Table of Contents

2 List of Abbreviations and Definition of Terms

AE	Adverse Event
AESI	Adverse Event of Special Interest
ATC	Anatomical Therapeutic Chemical classification
CDISC	Clinical Data Interchange Standards Consortium
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CR	Complete Response
(e)CRF	(electronic) Case Report Form
CSR	Clinical Study Report
DLT	Dose Limiting Toxicity
DOR	Duration of Reponse
ECG	Electrocardiogram
ECOG	Eastern Co-operative Oncology Group
FLC	Free Light Chain
ICH	International Conference on Harmonization
IAP	Integrated Analysis Plan
IMWG	International Myeloma Working Group
MedDRA	Medical Dictionary for Regulatory Activities
M-protein	M-protein Monoclonal Paraprotein
MRD	Minimal Residual Disease
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
NA	Not Applicable
NCI-CTCAE	National Cancer Institute – Common Terminology Criteria for Adverse Events
NLME	Non-linear Mixed Effects
OR	Overall Response
ORR	Overall Response Rate
PD	Progressive Disease

Pd	Pharmacodynamics
PR	Partial response
PT	Preferred Term
PK	Pharmacokinetics
PP	Per Protocol
QD	Once Daily
PR	Partial Response
RDE	Recommended Dose for Expansion
RRMM	Relapsed Refractory Multiple Myeloma
SAE	Serious Adverse Event
SAF	Safety
sCR	Stringent Complete Response
SCR	Screening analysis population
SD	Stable Disease or Standard Deviation
SDTM	Study Data Tabulation Model
SMC	Safety Monitoring Committee
SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Event
TRAE	Treatment-Related Adverse Event
TLF	Tables, Listings, and Figures
TTR	Time to Response
VGPR	Very Good Partial Response
WHO-DD	World Health Organization Drug Dictionary

3 Modification History

Unique Identifier for Version	Date of IAP Version	Author	Changes from the Previous Version
0.1	06DEC2019	PPD	Initial draft
1.0	07MAY2020	PPD	Final version
2.0	16May2021	PPD	Added additional analysis needed for primary analysis Adapted iAP to the premature stop of the trial without expansion cohort, e.g. removed analyses that are no longer needed

4 Purpose of the Integrated Analysis Plan

The purpose of this Integrated Analysis Plan (IAP) is to document technical and detailed specifications for the primary analysis and other analyses of protocol MS201814-0010.

The current version specifies the analyses that will be performed at the end of the trial (primary analysis).

Results of the analyses described in this IAP will be included in the Clinical Study Report (CSR), except for

- citrulline results analysis,
- Bayesian modelling considering toxicity and pharmacodynamics (section 16.2.1)).

Citrulline analysis and Bayesian modelling considering toxicity and Pharmacodynamics may be performed internally at Merck at a later point in time. The results of these analyses are not reported in the CSR.

Additionally, the planned analyses identified in this IAP may be included in regulatory submissions or future manuscripts. Any post-hoc, or unplanned analyses performed to provide results for inclusion in the CSR but not identified in this prospective IAP will be clearly identified in the CSR.
The IAP is based upon section 9 (Statistical considerations) of the study protocol and protocol amendments and is prepared in compliance with ICH E9. It describes analyses planned in the protocol and protocol amendments. Details of the Safety Monitoring Committee (SMC) analyses for regular review of the participants' safety are provided in appendix.

5 Objectives and Endpoints

Part A

Objectives	Endpoints (Outcome Measures)	IAP section
Primary		
• To determine safety, tolerability and the MTD (if observed) of M3258 as a single agent in participants with RRMM	• Occurrence of DLTs in participants with RRMM receiving M3258 as a single agent during the first 28-day treatment cycle • Occurrence of any AEs reported (serious or nonserious) will be considered TEAEs and TRAEs (including TEAEs leading to death or discontinuation of treatment) in participants receiving M3258 as a single agent from start of study intervention to 30 days after end of study intervention • Occurrence of TEAEs outside of the DLT period that SMC deems relevant for determination of the MTD • Study treatment-emergent changes in clinical laboratory measures from Baseline, safety Electrocardiograms (ECGs) measures, vital signs, ECOG performance status in participants receiving M3258 as a single agent from start of study intervention to 30 days after end of study intervention	• Section 15 Safety Analyses
Secondary		
• To investigate the PK profile of M3258 (single and multiple dose exposure) in participants with RRMM	• PK profile of M3258 in terms of C_{max}, AUC_{0-t}, AUC_{0-24} at Day 1, Cycle 1, (single dose): predose, 1, 2, 3, 4, 5, 6, 8 and 24 h after administration • PK profile of M3258 in terms of C_{max}, AUC_{0-24} at Day 15 Cycle 1, (multiple dose): predose, 1, 2, 3, 4, 5, 6, and 8 h after administration	• Section 16.1 Pharmacokinetics
• To investigate the RDE in participants with RRMM	• In addition to safety, tolerability and PK, for selection of RDE, changes in Pd (LMP7 activity) in pre and post study intervention samples on Day 1 Cycle 1 pre and postdose, Day 2 Cycle 1 predose and Day 15 Cycle 1 pre and postdose • Changes from Baseline in serum M-protein, urine M-protein, or free light chain protein levels (for free light chain disease) on Day 1 of every cycle	•
• To evaluate preliminary clinical activity using IMWG criteria	• Overall Response (OR), Duration of Response (DOR), Time to Response until Complete Response (CR), stringent Complete Response (sCR), Very Good	• Section 14 Efficacy Analyses

Objectives	Endpoints (Outcome Measures)	IAP section
	Partial Response (VGPR) or Partial Response (PR) according to IMWG	

Exploratory		
• To investigate the changes in the Pd marker of M3258 as a single agent in participants with RRMM	• Changes in Pd (LMP7 activity) in pre and post study intervention samples on Day 1 Cycle 1 pre and postdose, Day 2 Cycle 1 predose and Day 15 Cycle 1 pre and postdose	• Section 16.2 Pharmacodynamics • Section 16.3.2.1 LMP7 Residual Activity
• To investigate further PK parameters of M3258 (single and multiple dose exposure) in participants with RRMM	• PK profile of M3258 in terms of t_{max}, t_{lag}, $t_{1/2}$, CL/F, V_z/F at Day 1 Cycle 1, (single dose): predose, 1, 2, 3, 4, 5, 6, 8 and 24 h after administration • PK profile of M3258 in terms of $AUC_{0\rightarrow\infty}$ (if calculable), t_{max}, t_{lag}, $t_{1/2}$, CL_{ss}/F, at Day 15 Cycle 1, (multiple dose): predose, 1, 2, 3, 4, 5, 6 and 8 h after administration • PK profile of M3258 in terms of C_{trough} at Day 8 and Day 22: predose, Cycle 1 and predose, Day 1 Cycle 2 • PK profile of M3258 in terms of $R_{acc\ (AUC)}$ and $R_{acc\ (Cmax)}$ after Day 1 (single dose) and Day 15 (multiple dose), Cycle 1 and dose-normalized C_{max}, AUC_{0-t}, AUC_{0-24} for single and multiple dose	• Section 16.1 Pharmacokinetics
• To investigate the relationship between exposure of M3258 as a single agent and QTc in participants with RRMM	• Relative changes from Baseline in ECG parameter QTc in relation to M3258 plasma concentration: all times after single and multiple dosing with concurrent QTc and plasma concentration assessments	• Not in scope of the CTR, will be reported separately.
• To investigate genetic variations that may affect PK of M3258 as a single agent	• Assessment of genetic variations that affect drug metabolism and drug transport of M3258 and other potential genes that may account for differences in the PK profile	• Not in scope of the CTR, will be reported separately.
• To explore potential metabolites of M3258 in plasma in participants with RRMM	• Assessment of potential metabolites of M3258 in plasma	• Not in scope of the CTR, will be reported separately.
• To explore L-citrulline as an exploratory biomarker	• Changes in the L-citrulline blood levels during the study at Day 1 predose and Day 15 predose, Cycle 1, and Day 1 predose, Cycles 2 – 6 predose and every third cycle after Cycle 6 predose, and at End of Study Visit	• Section 16.2

• To investigate relationship of drug treatment and Minimal Residual Disease (MRD) in participants with RRMM	• Assessment of MRD upon CR or sCR	• Section 16.7 MRD

Part B (will not be done due to stop of study)

Objectives	Endpoints	IAP section
Primary		
• To determine safety and tolerability of M3258 at RDE when co-administered with dexamethasone in participants with RRMM	• Occurrence of dose-limiting toxicities (DLTs) in participants receiving M3258 in combination with dexamethasone during the first 28-day treatment cycle) • Occurrence of study treatment-emergent SAEs including deaths from first dose of study intervention to 30 days after end of study intervention • Occurrence of TEAEs and TRAEs (including deaths) from start of study intervention up to 30 days after end of study intervention • Study treatment-emergent clinically relevant abnormal changes in clinical laboratory measures from Baseline, ECGs measures, vital signs, ECOG performance status from start of study intervention to 30 days after end of study intervention	• Tbd in later version
• To determine recommended Phase II dose of M3258 when co-administered with dexamethasone in participants with RRMM based on early signs of safety and efficacy in the expansion phase	• Occurrence of TEAEs and TRAEs (including deaths) in participants receiving M3258 when given in combination with dexamethasone from start of study intervention to 30 days after end of study intervention • OR, DOR. Time to Response until CR, sCR, VGPR, or PR according to IMWG	• Tbd in later version
Secondary		
• To collect preliminary efficacy data in participants with RRMM under treatment with M3258, when co-administered with dexamethasone	• OR, DOR. Time to Response until CR, sCR, VGPR, or PR according to IMWG • Progression-Free Survival (PFS) per Investigator • Overall Survival (OS) censored at End of Study	• Tbd in later version

Objectives	Endpoints	IAP section
• To investigate the PK profile of M3258 (single and multiple dose exposure) when co-administered with dexamethasone in participants with RRMM	• PK profile of M3258 in terms of C_{max}, AUC_{0-t} at Day 1 Cycle 1, (single dose): predose, 1, 2, 3, 4, 5, and 6h after administration • PK profile of M3258 in terms of C_{max}, AUC_{0-24} at Day 15 Cycle 1, (multiple dose): predose, 2, 4, and 6h after administration	• Tbd in later version
Exploratory		
• To investigate the changes in the pharmacodynamic marker of M3258 when co-administered with dexamethasone in participants with RRMM	• Changes in LMP7 activity on Day 1 Cycle 1 pre and postdose and Day 15 Cycle 1 pre and postdose	• Tbd in later version
• To investigate further PK parameters of M3258 (single and multiple dose exposure) when co-administered with dexamethasone in participants with RRMM	• PK profile of M3258 in terms of t_{max}, t_{lag}, $t_{1/2}$, CL/F, V_z/F at Day 1 Cycle 1, (single dose): predose, 1, 2, 3, 4, 5, and 6 h after administration • PK profile of M3258 in terms of $AUC_{0\rightarrow\infty}$, t_{max}, t_{lag}, $t_{1/2}$, CL_{ss}/F, at Day 15 Cycle 1, (multiple dose): predose, 2, 4, and 6 h after administration • PK profile of M3258 in terms of dose-normalized C_{max}, AUC_{0-t}, AUC_{0-24} for single and multiple dose	• Tbd in later version
• To investigate the food effect on the PK of M3258 when co-administered with dexamethasone in participants with RRMM	• Area under the plasma concentration-time curve (AUC_{0-8h}) with and without food from time zero (= dosing time) to 8 h and C_{max} of M3258 observed on Day 1 Cycle 2: predose, 1, 2, 3, 4, 5, 6 and 8 h postdose	• Tbd in later version
• To investigate the relationship between exposure with M3258 and QTc, when co-administered with dexamethasone in participants with RRMM	• Relative changes from Baseline in ECG parameters (QTc) in relation to M3258 plasma concentration: all times after single and multiple dosing with concurrent QTc and plasma concentration assessments	• Not in scope of the CTR, will be reported separately.
• To investigate genetic variations that may affect PK of M3258, when co-administered with dexamethasone in participants with RRMM	• Assessment of genetic variations that affect drug metabolism and drug transport of M3258 and other potential genes that may account for differences in the PK profile	• Not in scope of the CTR, will be reported separately.
• To explore potential metabolites of M3258 in plasma, when co-administered with dexamethasone in participants with RRMM	• Assessment of potential metabolites of M3258	• Not in scope of the CTR, will be reported separately.

Objectives	Endpoints	IAP section
• To investigate the PK profile of dexamethasone when co-administered with M3258 in participants with RRMM	• Area under the plasma concentration-time curve (AUC_{0-8h}) from time zero (= dosing time) to 8 h and C_{max} of dexamethasone observed on Day 1, Cycle 2: predose, 1, 2, 3, 4, and 6 h postdose	• Tbd in later version
• To explore L-citrulline as an exploratory biomarker	• Changes in the L-citrulline blood levels during the study at Day 1 predose and Day 15 predose, Cycle 1, and Day 1 predose, Cycles 2 – 6 predose and every third cycle after Cycle 6 predose, and at End of Study Visit	• Tbd in later version
• To investigate change β5c activity after M3258, when co-administered with dexamethasone in participants with RRMM	• Changes in β5c activity on Day 1 Cycle 1 pre and postdose and Day 15 Cycle 1 pre and postdose	• Tbd in later version
• To investigate relationship of drug treatment and MRD, when M3258 is co-administered with dexamethasone in participants with RRMM	• Assessment of MRD upon CR or sCR	• Tbd in later version

6 Overview of Planned Analyses

The following analyses are planned for this trial:

- SMC analyses (See IAP for SMC in Appendix 18.1)
- Primary analysis of trial

Statistical analyses (except for SMCs) will be performed on the basis of CDISC SDTM data. These SDTM data contain as clean as possible eCRF data as well as external data for central laboratory and DLT decisions from SMC.

A data review meeting will be held prior to any database lock. In addition, no database can be locked until this IAP has been approved (except for emergency).

6.1 Analyses for SMC meetings

Details of analyses for SMC meetings are specified in a separate IAP, provided in Appendix 18.1.

7 Changes to the Planned Analyses in the Clinical Study Protocol

The study was stopped due to lack of enrollment before part B was started and before part A reached its primary objective. Therefore, additional to the SMC analyses there is only one primary analysis (this includes the end of dose escalation analysis).

There is one change in the definition of the DLT analysis set compared to the protocol. The following is added:

"Additionally, participants that did not receive at least 80% of the planned total dose of study treatment, but at least 80% dosing of a different (lower) dose level, did not miss more than 20% of planned administrations, and finished the DLT period are eligible for the DLT analysis set to be analyzed in the highest dose level they received 80% of dosing."

The protocol only mentioned β5c as an endpoint for part B, however, data analyses for this marker are planned for the dose escalation part A, too.

In case the received cumulative dose is higher than planned dose (and all other criteria for inclusion in DLT analysis set are fulfilled) the participant will still be analyzed in the planned dose level For analysis of pharmacodynamic markers and efficacy analysis the participant will be shown in listings and figures showing data on individual level. A footnote will explain the cumulative dosing the subject received. In summary analysis of pharmacodynamic markers and efficacy analysis the participant's data will not be included.

8 Analysis Populations and Subgroups

8.1 Definition of Analysis Populations

The analysis populations are specified below. The final decision to exclude participants from any analysis population will be made during a data review meeting prior to database lock except for the DLT analysis populations. For the DLT analysis populations, decisions for DLTs are taken by the SMC.

Screening Analysis Population (SCR)

The Screening analysis population includes all participants who signed the informed consent.

Safety Analysis Population (SAF)

The Safety analysis set will include all participants who were administered any dose of any study intervention. Analyses will consider participants as treated, meaning that participants will be classified according to the study intervention actually received (regarding dose level, see section 9 General Specifications for Data Analyses including explanation on how to deal with participants that did receive a dose different to the planned dose).

Dose Limiting Toxicity Analysis Population (DLT)

The Dose Limiting Toxicity analysis population (DLT) will include all participants who received at least one dose of study intervention and meet at least one of the following criteria:

- Experienced at least one DLT during the DLT period, regardless of the administered number of doses of study intervention/completion of the DLT period
- Received at least 80% of the planned cumulative dose and at least 80% of planned administrations (eg.: 4 administrations by cycle, 2 administrations by week…etc.) of each treatment during the DLT period and completed the DLT period.
- Additionally,participants that did not receive at least 80% of the planned total dose of study treatment, but at least 80% dosing of a different (lower) dose level, did not miss more than 20% of dosing, and finished the DLT period are eligible for the DLT analysis set to be analyzed in the highest dose level they received 80% of dosing of.

In case the received cumulative dose is higher than planned dose (and all other criteria for inclusion in DLT analysis set are fulfilled) the participant will still be analyzed in the planned dose level

Pharmacokinetics Population (PK)

The pharmacokinetics population (PK) will include all participants, who received at least one dose of study intervention, have no clinically important protocol deviations or important events affecting PK, and provide at least one measurable postdose concentration. Participants will be analyzed per the actual study intervention they received.

Pharmacodynamics Population (Pd)

The pharmacodynamics population (Pd) will include all, who received at least one dose of study intervention, have no clinically important protocol deviations or important events affecting Pd, and provide at least one measurable Pd endpoint postdose. In case the received cumulative dose of a participant is higher than the planned dose, the participant's data will be included in listings and figures showing data on individual level. A footnote will explain the cumulative dose the subject received. In summary analysis of pharmacodynamic markers the participant's data will not be included.

Analyses per Analysis Population

The following table summarizes the use of the analysis sets in the different analyses.

	Analysis Population			
Analyses	SAF	DLT	PK	Pd
DLT		✓		
Safety and Tolerability	✓			
PK			✓	
Pd				✓
Efficacy	✓			
Exploratory biomarkers (MRD)	✓			
Baseline Characteristics	✓			
Previous and Concomitant Therapies	✓			
Compliance and Exposure	✓			

Note:

Safety, PK, will be described by actual dose.

Baseline characteristics and compliance and exposure will be described for both (by planned dose and actual dose) if different.

All other analyses will be described by planned dose, according to Intention To Treat principle.

For more details see section 9 General Specifications for Data Analyses including.

9 General Specifications for Data Analyses

This section describes any general specifications not included in subsequent sections.

Study intervention is defined and labelled as "M3258".

Analyses will be displayed separately by regimen (ordered by dose intensity starting from most intensive regimen (QD)), dose (in increasing order and not evaluable at the final) and summarized.

The planned regimen and dose level will be taken from the CRF "Cohort Assignment".

General rule for actual dose if actual dose differs from planned dose (determined during the DLT period):

- Planned dose > dose received
    - If the participant receives at least 80% of his cumulative planned dose or has DLT during DLT period, then his actual dose will be his planned dose

- If the participant receives less than 80% of his cumulative planned dose and has no DLT during DLT period but received at least 80% of a cumulative lower tested dose, then his actual dose will be the lower dose level he received at least 80% of cumulative dose for safety analyses and the planned dose is used for all other analyses.

- If the participant receives less than 80% of the cumulative of any tested dose or less than 80% of the planned administrations or did not finish the DLT period the participant is not evaluable for the DLT analysis set (this category will be presented in the tables for DLT analysis set), but for other safety analyses. For other safety analyses in this case the participant will be analyzed with the

    - planned dose in case he did receive less than 80% cumulative dose of any tested dose

    - Cumulative dose he received 80% of (in case he missed too many dosings or did not finish the DLT period)

- Planned dose < dose received:

    - Actual dose will be the planned dose (in DLT analysis set)

    - For analysis of pharmacodynamic markers and efficacy analysis the data of such a participant will be shown in listings and figures showing data on individual level. A footnote will explain the cumulative dosing the subject received. In summary analysis of pharmacodynamic markers and efficacy analysis the data of such a participant will not be included.

The "start date" for this study is the date of first study drug administration (M3258).

All analyses will be performed using SAS® Software version 9.2 or higher, and otherwise as specified (e.g. for Bayes modeling)

Significance level:

There is no formal significance level for this study, and all analyses are considered descriptive.

There will be no statistical tests performed. If confidence or credibility intervals are mentioned, the level will be 95% unless otherwise specified.

Presentation of continuous and qualitative variables:

Continuous variables will be summarized using descriptive statistics, i.e.

- number of participants with non-missing values (n)
- mean, standard deviation (SD)

- median, 25th Percentile - 75th Percentile (Q1-Q3)
- minimum, maximum

If there are fewer than 5 observations summarized, only the number of participants with non-missing values, the mean, and the minimum and maximum will be given.

Qualitative variables will be summarized by counts and percentages.

Unless otherwise stated the calculation of proportions will be based on the number of participants in the analysis set of interest. Therefore, counts of missing observations will be included in the denominator and presented as a separate category.

Deviations from this definition might apply to the PK analysis (see section 16.1 for definitions).

Descriptive statistics will be computed by treatment day (C1D1, C1D2, C1D8, …, EOT). Unscheduled visits will be included in the derivation of baseline (if occurred within the allowed screening period) or worst on-treatment values and in any analysis using treatment day (e.g. plots of lab data).

9.1 Definition of baseline and change from baseline

In general, the last non-missing measurement prior to the first study drug administration will be used as the baseline measurement.

If an assessment that is planned to be performed before treatment per protocol is performed on the same day as the start of treatment, respectively, but the assessment time is not available, it will be assumed that it was performed prior and will be considered as baseline.

If a scheduled pre-dose measurement actually occurred post-dose, then the corresponding measurement will be analyzed similar to an unscheduled post-dose measurement.

Absolute and percent changes from baseline are defined as

absolute change = post baseline value – baseline value

percent change = 100 * (post baseline value – baseline value) / baseline value

9.2 Definition of Duration and 'time since' Variables

If not otherwise specified, duration will be calculated by the difference of start and stop date + 1 (e.g. survival time (days) = date of death – date of first study drug administration + 1).

The time since an event (e.g. time since first diagnosis) will be calculated as reference date minus date of event.

9.3 Conversion factors

The following conversion factors will be used to convert days into months or years: 1 month = 30.4375 days, 1 year = 365.25 days.

9.4 Definition of On-treatment Period

The on-treatment period is defined as the time from first dose of study intervention to 30 days after end of study intervention, or the cut-off date, whichever occurs first.

9.5 Imputation of missing data

Unless otherwise specified all data will be evaluated as observed, and no imputation method for missing values will be used.

In all participant data listings, imputed values will be presented and imputed information will be flagged, if imputation was done.

Missing statistics, e.g. when they cannot be calculated, should be presented as "nd".

Where tables are presented over different time points, the total of missing and non-missing observations at each time-point should reflect the population still in the trial at that time. This does not apply when imputations are made beyond trial withdrawal. For example, if a participant is still in the trial at the time-point but with missing data, they should be counted in the number of missing observations.

The following table for imputation rules will be considered:

Adverse events	Incomplete AE-related dates will be imputed as follows: • If the onset date is missing completely or missing partially – but the onset month and year, or year, are equal to that of the study treatment start – then the onset date will be replaced by the minimum of the start of study treatment and the AE resolution date. • In all other cases, the missing onset day or month will be replaced by 1. • Incomplete stop dates will be replaced by the last day of the month (if day is missing only), if not resulting in a date later than the date of participant's death. In the latter case, the date of death will be used to impute the incomplete stop date.

	• In all other cases the incomplete stop date will not be imputed. If the stop date of an AE is after the date of cut-off, the outcome of the AE is ongoing at cut-off. • Further information after cut-off (such as fatal outcome) might be taken from the Safety database and reported separately.
Previous and concomitant medication	For identification of previous or concomitant medications/procedures, no formal imputation will be performed on missing or incomplete dates. Rules presented in Table 2 will be used to define if a medication/procedure is considered as a previous, concomitant or both previous and concomitant medication/procedure.

Table 1 Imputation rules for medication/procedure end dates

End date of medication/procedure			imputation rule
Day	Month	Year	
UNK	UNK	UNK	After treatment start (ongoing)
UNK	UNK	< Treatment start (year)	Before treatment start
UNK	UNK	>= Treatment start (year)	After treatment start
UNK	< Treatment start (month and year)		Before treatment start
UNK	>= Treatment start (month and year)		After treatment start
< Treatment start (complete date)			Before treatment start
>= Treatment start (complete date)			After treatment start

UNK = Unknown

Table 2 Rules to define previous and/or concomitant medication

Start date of medication/procedure			imputatio rule (see Table 1)	Medication/procedure
Day	Month	Year		
UNK	UNK	UNK	Before treatment start	Previous
UNK	UNK	UNK	After treatment start	Previous and concomitant
UNK	UNK	<= Treatment start (year)	Before treatment start	Previous
UNK	UNK	<= Treatment start (year)	After treatment start	Previous and concomitant

Start date of medication/procedure			imputatio rule (see Table 1)	Medication/procedure
Day	Month	Year		
UNK	UNK	> Treatment start (year) and <= Treatment end + 30 days (year)	After treatment start	Concomitant
UNK	<= Treatment start (month and year)		Before treatment start	Previous
UNK	<= Treatment start (month and year)		After treatment start	Previous and concomitant
UNK	> Treatment start (month and year) and <= Treatment end + 30 days (month and year)		After treatment start	Concomitant
<= Treatment start (date)			Before treatment start	Previous
<= Treatment start (date)			After treatment start	Previous and concomitant
> Treatment start (date) and <= Treatment end + 30 days (date)			After treatment start	Concomitant

UNK = Unknown

Death date Note: For participants who died and for whom no complete death date is available usually the death date is not imputed. Just for survival analyses imputation rules are applied, in death listings non-imputed data will be presented.	For the purpose of survival analyses partially missing death dates will be imputed as follows: If only the day is missing, the death date will be imputed to the maximum of the (non-imputed) day after the date of last contact and the 15th day of the month. Otherwise it will not be imputed.

9.6 Study Day / Study Treatment Day definition

Treatment day is defined relative to the date of first study drug administration (M3258). Treatment Day 1 is treatment start date of first administration of the study drug; the day before is defined as Treatment Day -1 (no Treatment Day 0 is defined).

10 Study Participants

The subsections in this section include specifications for reporting participant disposition and study intervention/study discontinuations. Additionally, procedures for reporting protocol deviations are provided.

10.1 Disposition of Participants and Discontinuations

A table will display the following (per regimen and dose level and overall):

- Number of participants in each analysis population (SCR, SAF, DLT, PK, Pd)
- Number of participants who discontinued from the study prior to treatment overall and grouped by the main reason (participants did not meet eligibility criteria, withdrew consent, other)

This table will be produced twice if there are participants with differing planned dose and actual dose, one by planned dose (including SCR, SAF, Pd, PK) and one by actual dose (including SCR, SAF, DLT, PK).

This table will additionally be displayed by site.

Another table of disposition will provide the following, among participants in SAF:

- Number and percentage of participants still in trial
- Number and percentage of participants withdrawn from trial
- Number of participants by reason for withdrawal

Additionally a listing will display all discontinued patients including planned regimen and dose, the reason for discontinuation from treatment and reason for discontinuation from study and treatment start and end date.

10.2 Protocol Deviations / Exclusion from Analysis Population

10.2.1 Important Protocol Deviations

Important protocol deviations (IPDs) are protocol deviations that might significantly affect the completeness, accuracy, and/or reliability of the study data or that might significantly affect a participant's rights, safety, or well-being.

The IPDs will be identified for all participants by either site monitoring, medical review processes or programming and confirmed prior to or at the Data Review Meeting at the latest.

All important protocol deviations are documented in SDTM datasets whether identified through site monitoring, medical review or programming.

A full list of potential protocol deviations including definition and categorization is maintained by Covance in the "Study Specific Protocol Deviation List" attached to the Protocol Deviation Management Plan.

A frequency table for important, separated for such pre-/post inclusion deviations, as well as a listing (by participant) of important protocol deviations, will be provided based on the Safety analysis set.

Referring to FDA, a listing of all participants affected by the COVID-19 related study disruption will be produce by unique subject number identifier and by investigational site, and a description of how the individual's participation was altered.

The protocol deviations are detailed in the document MS201814-0010 Protocol Deviation Listing_14Nov2019_v1.0.xlsx or an updated version.

10.2.2 Reasons Leading to the Exclusion from an Analysis Population

A listing of reasons for exclusion from DLT analysis population will be provided.

Additionally a listing of subjects excluded from analysis sets (DLT, SAF, PK,Pd) with reason for exclusion will be provided (for section 9.2.3).

Of note, participants who did not receive at least 80% of the planned dose are excluded from the DLT analysis set unless they can be considered in another dose level as described in Sections 8 and 10.2.1.

11 Demographics and Other Baseline Characteristics

If not stated otherwise, the following analyses will be performed based on the SAF, by regimen and dose, and overall.

11.1 Demographics

Demographic characteristics and physical measurements will be summarized descriptively using the following information from the Screening/Cycle 1 Day 1 eCRF pages.

The following demographic characteristics will be included:

Sex: Male, Female

Race: White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Not collected at this site, Other

Ethnic origin: Hispanic or Latino/Not Hispanic or Latino

Age (years)

Age categories :< 65 years, ≥ 65 years

Pooled Region: North America, Europe, Asia, Rest of the World)

Geographic Region: North America, Latin America, Western Europe, Eastern Europe, Middle East, Australia, Asia

Weight (kg)

BMI (kg/m²) at Baseline

Eastern Cooperative Oncology Group (ECOG) Performance status (0,1,2,3,4)

Specifications for computation:

- Age [years]: (date of given informed consent – 01JANYYYY + 1) / 365.25, where YYYY is the year of birth as collected in eCRF. The integer part of the calculated age will be used for reporting purposes.
- BMI [kg/m²] = $\frac{weight\ [kg]}{height[cm]^2} \times 10000$
- Site codes will be used for the determination of the participant's geographic region.

Additionally demographic data will be presented in a listing.

11.2 Medical History

The medical history will be summarized from the "Medical History" eCRF page, using the most recent MedDRA version at time of database lock, preferred term as event category and system organ class (SOC) body term as Body System category. Each participant will be counted only once within each PT or SOC.

Medical history will be displayed in terms of frequency tables: ordered by primary SOC and PT in alphabetical order.

Additionally medical history data will be presented in a listing.

11.3 Other Baseline Characteristics

Information on disease characteristics collected at baseline will be summarized. Summary statistics will be presented for (as applicable)

- Prior transplant:
    - Stem cell transplant (Yes, No)
    - Stem cell type (Bone marrow, Peripheral blood stem cell)
    - Single or Tandem transplant
    - Type of transplant (Autologous Stem Cell Transplant, Allogenic Stem Cell Transplant)
    - Chemotherapy (Yes, No)
    - Total Body Irradiation (Yes, No)
- History of disease under study:
    - Time since initial diagnosis
    - Type of myeloma at diagnosis (IgG, IgM, IgA, IgD, IgE)
    - Light chain of myeloma at diagnosis (Lambda, Kappa)
    - ISS stage at diagnosis (I, II, III)
- Disease characteristics at study entry:
    - Type of myeloma at (IgG, IgM, IgA, IgD, IgE)
    - Light chain of myeloma (Lambda, Kappa)
    - ISS stage (I, II, III)
- Presence of bone lesions at Cycle 1 Day 1 (based on page "Osteolytic bone lesion assessment")

All these other baseline characteristics along with substance usage (Drug, alcohol, nicotine and caffeine consumption) and family history of premature cardiovascular disease will be listed for primary analysis

Baseline characteristics with respect to vital signs and laboratory (including hematology/biochemistry) will be part of Section **Error! Reference source not found.** (Safety E valuation).

11.4 Prior Anti-cancer Therapy

The prior anti-cancer therapies are collected under the "Prior Anti-Cancer Drug Therapies Details", "Prior Anti-Cancer Radiotherapy Details" and "Prior Anti-Cancer Surgeries Details" eCRF pages.

The number and percentage of participants in each of the following anti-cancer therapy categories will be tabulated:

- Participants with at least one prior anti-cancer drug therapy
- Participants with at least one prior anti-cancer radiotherapy
- Participants with at least one prior anti-cancer surgery

This table will also tabulate the number of prior anticancer therapies, prior anticancer drug therapies, prior anti-cancer radiotherapies and number of prior anti-cancer surgeries.

The listing of prior anti-cancer treatments and procedures will also be provided as follows. These will include the participant identification number, and all the relevant collected data-fields on the corresponding eCRF pages (including if chemotherapy was associated to a stem cell transplant).

- Listing of prior anti-cancer drug therapies
- Listing of prior anti-cancer radiotherapy
- Listing of prior anti-cancer surgeries

12 Previous or concomitant medications/interventions

The following analyses will be performed based on the SAF analysis set, by regimen and by dose (in increasing order) and summarized

Concomitant treatments are medications, other than study treatment, which are taken by participants any time during the on-treatment period, see section 9.4.

Previous medications are medications, other than study treatment and pre-medications for study treatments, which started before first administration of study treatments.

A medication may be classified as both concomitant and previous. The respective flags will be derived based on start and end date.

Concomitant and previous treatment each will be summarized by number and percentage of participants from the "Relevant Previous medications" and "Concomitant medications" eCRF. ATC-2nd level and preferred term will be tabulated as given from the WHO-DD dictionary most current version. If any previous or concomitant medication is classified into multiple ATC classes, the medication will be summarized separately under each of these ATC classes. The summary tables will be sorted by decreasing frequency of drug class and decreasing frequency of drug name in a given drug class. In case of equal frequency regarding drug class (respectively drug name), alphabetical order will be used. In case any specific medication does not have an ATC classification level 2 coded term, it will be summarized under "Unavailable ATC classification"

category. Each participant will only be counted once, even if he/she received the same medication at different times.

All concomitant treatments, previous medications and **concomitant procedures**, which were undertaken during the on-treatment period will be listed. Concomitant procedures according to the CRF page "Concomitant Procedures".

13 Study intervention Compliance and Exposure

The following analyses will be performed based on the SAF analysis set, by regimen and dose (in increasing order) and summarized

All dosing calculations and summaries will be based on CRF "M3258 Administration Details", , in particular for first study drug administration.

The date of last study drug administration will be defined as the last date in the "M3258 Administration Details", with dose>0.

No imputation of missing start dates of study treatments will be done.

In case the last date of study drug is incomplete the date of last study drug administration will be taken from the End of Treatment page.

Interruption of treatment will be identified in the "M3258 Administration Details", with no dose.

Each study drug (M3258 and dexamethasone) will be analyzed separately.

.A dose is regarded to be administered, if the actual dose received ("Dose per administration") is > 0

For the end of dose escalation analysis, the summary of treatment exposure will include the following information:

- Exposure duration (in weeks) as defined by (date of last dose of study drug–date of first dose of study drug +1)/7
- Number of dosing days (in days) as defined by (date of last dose of study drug–date of first dose of study drug–sum of days with dose interruption +1)
- Total number of cycles received at least 80% of planned dose as defined sum of cycles with received dose >= 80% of planned dose
- Number and percentage of participants with at least one dose reduction will be presented.

A listing will be provided for all administrations of participants (date and dose of administration) including planned regimen and dose.

14 Efficacy Analyses

The following analyses will be performed based on the SAF analysis set, by regimen and dose (in increasing order) and summarized In case the received cumulative dose of a participant is higher than planned cumulative dose the participant will not be considered in efficacy analyses.

14.1 Overall Response

Overall response (OR) will be assessed based on reported overall responses at different evaluation time points from the treatment start date in accordance to IMWG response criteria, taking requirements for confirmation into account as detailed below.

OR is defined as a confirmed (2 consecutive assessments made at any time before the institution of any new therapy) Best Overall Response of sCR, CR, VGPR, or PR according to IMWG response criteria.

Participants will be considered evaluable for response in the analysis set if they have at least two on-treatment assessment of IMWG response criteria other than Not Evaluable (NE).

Except for participants who have at least one on-treatment assessment of IMWG response criteria and who receive anti-tumor treatments other than the study treatment, die, progress or withdraw for any reason prior to reaching confirmed sCR, CR, VGPR or PR. These will be considered as non-responders in the assessment of OR.

Each evaluable participant will have an objective response status (0: 'no OR'; 1: 'OR') The participants who are not evaluable will be considered Not Evaluyble (NE).

OR rate (ORR) is the proportion of participants with OR in the participants evaluable for response in the analysis set.

The ORR by regimen and dose and in summary will be calculated along with the two-sided 95% CI using the Clopper-Pearson method (exact CI for a binomial proportion as computed by default by the SAS FREQ procedure using the EXACT option).

A table will display the number and percentage of participants evaluable for response, the participants with overall response, including the confirmed IMWG response criteria

Moreover, this descriptive table will be include each category of Best Overall Response (sCR, CR, VGPR, PR, MR, SD, PD, NE) according the confirmed and not confirmed IMWG response criteria.

A listing will be also be provided with all IMWG assessments, specifying also the indicators for progressive disease and indicators for clinical relapse, as collected in the CRF.

14.2 Duration of treatment

A duration of treatment plot by actual time grouped by dose level will be plotted. The plot will be in increasing order of drug intensity (10mg QD at the bottom, the 10mg BIW in the middle and the 20mg BIW at the top) Tumor assessments will be displayed with outcome (e.g. PD or SD)

Molecular information on cytogenetic abnormality (if available) will be specified at the end of each bar.

An arrow at the end of the bar plot will identify the patient with treatment ongoing at the data cut off..

The sCR and CR will be grouped and NE not presented.

14.3 M-protein and FLC

Serum and urine M-protein (in g/dL and mg/24h respectively) and FLC ratio and FLC values (kappa and lambda) will be listed for all cycles. Changes from baseline will be added to the listing

In all further analysis the affected light chain only will be considered (as per "type of light chain" from eCRF, or if information not available, light chain type with > 10mg/L=1mg/dL at baseline)

The values for serum and urine mprotein, FLC ratio and affected light chain will be summarized using descriptive statistics of relative changes from baseline for each cycle. End of treatment visit will be summarized separately.

Figures

The following graphics will be plotted:

- A waterfall plot depicting the best % change from baseline between serum M-protein, urine M-protein and affected free light chain. Only the best change from the three different biomarkers will be depicted. Displays of serum M-protein will be identified by a circle, the urine M-protein by a triangle, the affected free light chain by a cross. The bar plot will be filled with different color depending of the dose level. If available, filled boxes below the waterfall plot will signify whether a high cytogenetic abnormality (del(17p), t (4;14) t (14;16)) was detected in the patient. Subject ID will be available below the bars.
- A spider plot by actual time for change from baseline for serum M-protein. The line will be drawn with different line types depending of the dose level. Color will be used to separate individual participants. The % change exceeding 100% will be identified with gray squares for actual values by treatment day
- A spider plot by actual time for change from baseline for affected free light chain. The line will be drawn with different line types depending of the dose level. Color will be used to separate

individual participants. The % change exceeding 100% will be identified with gray squares for actual values by treatment day

15 Safety Analyses

The subsections in this section include specifications for summarizing safety endpoints that are common across clinical studies such as adverse events, laboratory tests and vital signs.

The primary endpoint during dose escalation is the occurrence of DLTs, AEs and other safety related measurements.

The analysis population for the DLT analysis will be the DLT analysis set, for all other safety analyses it will be the SAF analysis set.

15.1 DLT analysis

Of Note, DLT as per SMC decision will be available in the table "Review of data" in the SMC minutes.

In case of new DLT appears after DLT period, the minutes will be updated.

A table of will display the following (per regimen and dose level and in total) for the DLT analysis set:

- Number and percentage of participants with a DLT per investigator's judgement as recorded in eCRF (using DLT flag from the AE CRF page)

  Number and percentage of participants with a DLT per SMC decision

A listing of DLTs (per investigator and/or per SMC) will be provided by dose level and participant, including whether it was judged to be a DLT by investigator and/or by SMC)

This listing will additionally contain age, sex, type of myeloma, SOC, PT, grade, SAE (yes/no), relatedness to M3258 (yes/no), start date (+treatment day), stop date (+treatment day), action taken with M3258, if treatment was stopped before start of AE: days since stop of treatment, and outcome.

In addition, the following will be presented:

- Quantiles (2.5%, 25%, 50%, 75% and 97.5%) for the posterior probability of a participant experiencing a DLT at each of the dose levels used in the study according to the same Bayesian Logistic Model (BLM) as described in the SMC IAP (see Appendix 18.1) or

SMC charter (if change occurred). For this analysis either SAS or R (using the package bcrm or crmPack) will be used.

MTD suggestion from the Bayesian logistic regression model

The MTD as suggested from the modeling will be derived as follows:

1) The BLRM will be updated with all DLT data (SMC decision) from the dose escalation.
2) The dose with targeted toxicity probability of 25% will be identified.
3) The next lower tested dose with the upper bound of the 95% credible interval of a potential MTD below or equal 40% and with estimated DLT probability above or equal to 17% will be selected.
4) The credibility interval will be provided.
5) If the MTD estimate of all tested doses is below 17%, there is no MTD suggestion from the model.

This information will be forwarded to the SMC that will decide on the determination of the MTD.

Additionally, the SMC will receive the estimated DLT probability and associated probability quantiles for all other doses tested.

For above analysis either SAS or R (using the package bcrm or crmPack) will be used.

Frequentist MTD suggestion

As second approach, the MTD as suggested by the frequentist estimation will also be derived:

1) All DLT data from the dose escalation will be included in a two-parameter logistic regression model (intercept and slop over log of the scaled dose, no prior; if the model does not converge, it will be reported as not calculable; the program code for this analysis can be found in the TLF shells).
2) The dose with targeted toxicity probability of 25% will be identified.
3) The next lower tested dose will be selected.

The two-sided confidence interval for the DLT probability will be provided.

15.2 Adverse Events

AEs will be analyzed among the SAF analysis set and presented by regimen and dose (in increasing order) and summarized. Only participants counts will be presented with frequency.

Treatment-emergent adverse events (TEAE) are those events with onset dates occurring within the on-treatment periods as defined in section 9.4.

- **Related Adverse Events**: AEs with relationship missing, unknown or yes. Relationship is judged separately for M3258, and dexamethasone.
- **SAEs**: Serious adverse events (as recorded on the AE eCRF page, Serious Adverse Event = 'Yes').
- **AEs Leading to Treatment Discontinuation**: AEs leading to permanent discontinuation of study treatment (as recorded on the AE eCRF page, Action taken with study treatment = 'Drug withdrawn'). Treatment discontinuation is recorded separately for M3258, and dexamethasone.
- **AEs Leading to Death**: AEs leading to death (as recorded on the AE eCRF page, Outcome = 'Fatal').

All analyses described in Section 15.2 will be based on TEAEs if not otherwise specified.

TEAEs will be summarized by number and percentage of participants with at least one TEAE in the category of interest, by primary MedDRA and PT (both sorted alphabetically), unless otherwise stated. Each participant will be counted only once within each SOC or PT. If a participant experiences more than one AE within a SOC or PT for the same summary period, only the AE with the strongest relationship or the worst severity, as appropriate, will be included in the summaries of relationship and severity.

The severity of adverse events will be graded using the NCI-CTCAE version 5.0, except where CTCAE grades are missing. No imputation of missing grades will be performed.

Adverse events will be coded according to the latest MedDRA version at the time of the data cut-off.

Incomplete AE-related dates will be handled as defined in section 9.5.

15.2.1 All Adverse Events

The overall summary of AEs table will include the frequency (number and percentage) of participants with each of the following, tabulated by dose level and overall:

- TEAEs
- TEAEs with NCI-CTCAE Grade ≥ 3
- TEAEs with NCI-CTCAE Grade ≥ 4
- Related with M3258 TEAEs
- Related with M3258 TEAEs with NCI-CTCAE Grade ≥ 3
- Related with M3258 TEAEs with NCI-CTCAE Grade ≥ 4
- TEAEs leading to permanent discontinuation of M3258
- Related with M3258 TEAEs leading to permanent discontinuation of M3258
- Serious TEAEs
- Related with M3258 Serious TEAEs
- TEAEs leading to death (AEs with Grade 5 or outcome "fatal" if grade 5 not applicable)
- Related with M3258 TEAEs leading to death

Tables by SOC and PT will be tabulated by regimen, dose level and overall in a table displaying in separate columns and showing the incidence of TEAEs, by SOC and PT (both sorted alphabetically). This type of table by SOC and PT will be done for:

- All TEAEs
- related TEAEs
- Grade ≥3 TEAEs
- Related Grade ≥3 TEAEs
- TEAEs excluding SAEs (Clinical trial.gov and EudraCT -requirement)
- Also, TEAEs will be summarized by worst toxicity (according to NCI-CTCAE version 5.0) per participant, using preferred term as event category and primary system organ class (SOC). Analysis by worst toxicity will be provided by regimen, dose level and overall.

If an adverse event is reported for a given participant more than once during study intervention, the worst toxicity and the worst relationship to study intervention will be tabulated. In case a

participant had events with missing and non-missing grades, the maximum of the non-missing grades will be displayed.

A listing of all AEs will be provided. This listing will be sorted by study part, regimen, dose level and participant. This listing will additionally contain age, sex, type of myeloma, SOC, PT, grade, SAE (yes/no), DLT per investigator (yes/no), DLT per SMC, relatedness to M3258 (yes/no), start date (+treatment day), stop date (+treatment day), duration (in days), action taken with M3258, if treatment was stopped before start of AE: days since stop of treatment, and outcome.

Similarly, listing of all adverse events grade >=3 (incl non TEAEs) and SAEs will be provided.

15.2.2 Adverse Events Leading to Study Intervention Discontinuation

A listing of TEAEs leading to treatment discontinuation, interruption, or dose reduction of each study drug will be provided . This listing, sorted by dose level and participant ID, will include: dose level, participant ID, age, sex, site of primary tumor, AE investigator term, SOC, PT, relationship to M3258 and dexamethasone (as applicable), seriousness, action taken with M3258 (displayed as: Disc/IR/DR), start date (+treatment day), stop date (+treatment day), duration (in days), if treatment was stopped before start of AE: days since stop of treatment, and outcome.

15.3 Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

15.3.1 Deaths

A listing of Deaths will be provided, defined as any AE with Grade 5, or outcome "fatal" if grade 5 not applicable. This will be sorted by study part, regimen, dose level and participant. This listing will additionally contain age, sex, type of myeloma, SOC, PT, grade, SAE (yes/no), DLT per investigator (yes/no), relatedness to M3258 (yes/no), start date (+treatment day), stop date (+treatment day), duration (in days), action taken with M3258, if treatment was stopped before start of AE: days since stop of treatment, and outcome.

15.3.2 Serious Adverse Events

The listing of SAEs will also be provided with the relevant information with a flag for SAEs with onset outside of the on-treatment period.

15.3.3 Other Significant Adverse Events

A listing of AEs of special interest (AESI) will be provided. This will be sorted by dose level and participant. This listing will additionally contain age, sex, , SOC, PT, grade, SAE (yes/no), DLT

per investigator/SMC (yes/no), relatedness to M3258 (yes/no),), start date (+treatment day), stop date (+treatment day), duration (in days), action taken with M3258, if treatment was stopped before start of AE: days since stop of treatment, and outcome.

15.4 Clinical Laboratory Evaluation

Laboratory values (including corresponding normal ranges) from the local laboratories will be used B for summary statistics and shift tables.

Laboratory results will be classified according to the NCI-CTCAE criteria version 5.0. Some of the toxicity gradings are based on laboratory measurements in conjunction with clinical findings. Non-numerical qualifiers (with the exception of fasting flags) will not be taken into consideration in the derivation of CTCAE criteria (e.g., hypokalemia Grade 1 and Grade 2 are only distinguished by a non-numerical qualifier and therefore Grade 2 will not be derived).

Additional laboratory results that are not part of NCI-CTCAE will be presented according to the categories: below normal limit, within normal limits and above normal limit (according to the laboratory normal ranges).

Parameters with NCI-CTC grades available:

Hematology:

Hemoglobin (HB), Leukocytes (white blood cell decreased), Lymphocytes (lymphocyte count increased/decreased), Neutrophils / Absolute Neutrophils Count (ANC) (neutrophil count decreased), Platelet Count (PLT) (platelet count decreased).

Serum Chemistry:

Albumin (hypoalbuminemia), Alkaline Phosphatase (alkaline phosphatase increased), Alanine Aminotransferase (ALT) (ALT increased), Aspartate Aminotransferase (AST) (AST increased), Total Bilirubin (blood bilirubin increased, Cholesterol (cholesterol high), Creatinine (creatinine increased), Potassium (hypokalemia/ hyperkalemia), Sodium (hyponatremia/ hypernatremia), Magnesium (hypomagnesemia/hypermagnesemia), Calcium (hypocalcemia/ hypercalcemia), Glucose (hypoglycemia/hyperglycemia), Gamma Glutamyl Transferase (GGT) (GGT increased), Lipase (lipase increased), Phosphates (hypophosphatemia)

Parameters with NCI-CTC grades not available:

Hematology:

Hematocrit, Red Blood Cell (RBC), Reticulocytes, Mean Corpuscular Hemoglobin (MCH), Mean Corpuscular Volume (MCV), Mean Corpuscular Hemoglobin Concentration (MCHC).

Serum Chemistry:

C-Reactive Protein, Lactate Dehydrogenase (LDH), Total Protein, Total Urea, Uric Acid.

Coagulation: activated partial thromboplastin time (aPTT), Prothrombin time (PT) and prothrombin time (INR).

Urinalysis and microscopic urinalysis: all urinalysis parameters

Pregnancy test (not needed for end of dose escalation analysis)

The last measurement before study treatment (including unscheduled measurements) will serve as the baseline measurement.

Values below the detection limit will be imputed by half of the detection limit.

In case just a text value with an "> x" is reported it will be analyzed as +1 significant digit, e.g. "> 7.2 mmol" will be analyzed as 7.3.

For **WBC differential counts** (total neutrophil, lymphocyte, monocyte, eosinophil, and basophil counts), the absolute value will be used when reported. When only percentages are available (this is mainly important for neutrophils and lymphocytes, because the CTCAE grading is based on the absolute counts), the absolute value is derived as follows:

Derived differential absolute count = (WBC count) * (Differential %value / 100)

If the range for the differential absolute count is not available (only range for value in % is available) then Grade 1 will be attributed to as follows:

- Lymphocyte count decreased:
  - derived absolute count does not meet Grade 2-4 criteria, and
  - % value < % LLN value, and
  - derived absolute count ≥ 800/mm3
- Neutrophil count decreased
  - derived absolute count does not meet Grade 2-4 criteria, and
  - % value < % LLN value, and
  - derived absolute count ≥ 1500/mm3

For **calcium**, CTCAE grading is based on Corrected Calcium and Ionized Calcium (CALCIO), if available. Corrected Calcium is calculated from Albumin and Calcium as follows

Corrected calcium (mmol/L) = measured total Calcium (mmol/L) + 0.02 (40 - serum albumin [g/L])

The time windows given in Table 4 will be applied to allocate measurements to treatment day. In case of multiple blood samples are collected in the same window, the value closest to the target day will be used for analysis. If there are two values with the same time before and after the target

day, the earlier value will be used for analysis. Windows only to be used for summary tables, not figures or listings

Table 4 Time windows for safety laboratory analysis

Treatment day	Window Definition
C1D1	No time window
C1D2	± 1 day
C1D8	
C1D15	
C1D22	
C1D1	
C1D8	
C1D15	
C1D22	
C3D1	
C3D15	
C4D1	± 3 days
C5D1	
C6D1	
CXD1 (after cycle 6)	± 7 days
End of Study Intervention (within 7 days after last intervention/intake)	± 3 days
Follow-up/Discontinuation (30 days after last dose)	± 7 days

Since the number of participants will decrease over time, time windows will not be applied for the complete treatment period (stopped after C6D1). For summaries by treatment day, the last available laboratory measurement will be presented in addition to the treatment day defined above.

Quantitative data will be summarized for actual values and absolute changes from baseline to each treatment day. The End of treatment visit will be summarized separately.

Qualitative data based on reference ranges will be described according to the categories (i.e. Low, Normal, and High). Abnormalities classified according to NCI-CTCAE toxicity grading version will be described using the worst on-treatment grade. For those parameters which are graded with two directions of toxicities such as potassium (hypokalemia/hyperkalemia), the toxicities will be summarized separately. Low direction toxicity (e.g., hypokalemia) grades at baseline and post baseline will be set to 0 when the variables are derived for summarizing high direction toxicity (e.g., hyperkalemia), and vice versa.

Parameters with NCI-CTC grades available:

The laboratory toxicities will be tabulated using descriptive statistics (number of participants and percentages) during the on-treatment period. The denominator to calculate percentages for each laboratory parameter is the number of participants evaluable for CTCAE grading (i.e. those participants for whom a Grade 0, 1, 2, 3 or 4 can be derived).
The summary of laboratory parameters by CTCAE grade table will include number and percentage of participants with Grade 1, 2, 3, 4, 3/4, and any grade (1 to 4), laboratory abnormalities during the on-treatment period.

The shift table will summarize baseline CTCAE grade versus the worst on-treatment CTCAE grade. The highest CTCAE grade during the on-treatment period is considered as the worst grade for the summary.

Parameters with NCI-CTC grades not available:

Hematology and chemistry evaluations which cannot be graded per CTCAE criteria will be summarized as frequency (number and row percentage) of participants with:

- shifts from baseline normal to at least one result above normal during on-treatment period
- shifts from baseline normal to at least one result below normal during on-treatment period

The coagulation parameters, urinalysis parameters, microscopic urinalysis parameters and pregnancy test will be listed in dedicated listings presenting all corresponding collected information on the eCRF.

The listings of laboratory results will be provided for all laboratory parameters,. The listings will be sorted by parameters and assessment dates or visits for each participant. Laboratory values that are outside the normal range will also be flagged in the data listings, along with corresponding normal ranges and CTCAE grades..

The lab abnormalities >= grade 3 will be also presented in a separate listing .

Line plots for Hematology

Graphical display (line plots) of neutrophils, platelets, lymphocytes and hemoglobin will be provided by actual time in days for all analyses. (with x-axis time, y-axis lab value), using different colors per regimen, dose level and different line types to identify participants

If available (and feasible due to potential differences between labs) reference lines for ULN and LLN should be added to the plots. Additionally treatment administration will be shown on the plot.

Hepatotoxicity assessment

A plot of peak ALT versus peak total bilirubin, both relative to the upper limit of normal (ULN) will be provided. This eDISH plot (evaluation of drug-induced serious hepatotoxicity) will have reference lines at 3×ULN for ALT and at 2×ULN for total bilirubin. Subjects outside the lower left box will be identified by subject-ID.

15.5 Vital Signs

Vital sign summaries will include vital sign assessments from the on-treatment period. All vital sign assessments will be listed and those collected outside the on-treatment period will be flagged in the listing.

All vital sign parameters will be summarized using descriptive statistics of the maximum change from baseline.

15.6 Other Safety or Tolerability Evaluations

ECOG

A frequency table will be provided with the number and percentage of participants in each ECOG status category and change of category from baseline by visit, by regimen, dose level and overall. Corresponding listing will be provided.

ECG results

The ECG parameters (HR, and QT, QTc, QRS, PR intervals) will be summarized by descriptive statistics per treatment day, with changes from Baseline, by regimen, dose level group and overall.

ECG summaries will include all ECG assessments from the on-treatment period as collected in the CRF.

Unscheduled ECG measurements will not be used in computing the descriptive statistics for change from baseline at each post-baseline time point. However, they will be used in the analysis of notable ECG changes.

Frequency (number and percentage) of participants with notable ECG values according to the following categories, by visit. The denominator to calculate percentages for each category is the number of participants evaluable for the category.

- QTcF increase from baseline >30 ms, >60 ms
- QTcF > 450 ms, > 480 ms, > 500 ms
- HR ≤ 50 bpm and decrease from baseline ≥ 20 bpm
- HR ≥ 120 bpm and increase from baseline ≥ 20 bpm
- PR ≥ 220 ms and increase from baseline ≥ 20 ms
- QRS ≥ 120 ms

Frequency (number and percentage) of participants with post-baseline qualitative ECG abnormalities (morphology) (ECG result=abnormal" in the ECG form of the eCRF) will be summarized.

All ECG assessments will be listed, and those collected outside the on-treatment period will be flagged in the listing as well as any abnormalities and values that fall into above specified categories.

Holter ECGs might be analyzed independently and at a later time by a central laboratory. Data are not planned to be part of this CTR and may be reported separately.

16 Analyses of Other Endpoints

16.1 Pharmacokinetics

16.1.1 Pharmacokinetic Analysis

Pharmacokinetic parameters for M3258 in Plasma will be calculated by Covance, using standard non-compartmental methods and the actual administered dose. PK parameters will be calculated using the actual elapsed time since dosing. In cases where the actual sampling time is missing, calculations will be performed using the scheduled time.

Non-compartmental computation of pharmacokinetic parameters will be performed using the computer program Phoenix® WinNonlin® version 6.4, or higher (Certara, L.P., 1699 S Hanley Road, St Louis, MO 63144, USA).

The following PK parameters will be calculated, where applicable:

Parameter	Definition

$AUC_{extra\%}$	percentage of AUC that is due to extrapolation from the last measurable concentration to infinity(single dose only)
AUC_{0-t}	area under the concentration-time curve from time 0 to the time of last quantifiable concentration (t_{last}) (single dose only)
AUC_{0-8}	area under the concentration-time curve from time 0 to 8h postdose
t_{lag}	time immediately prior to the first quantifiable concentration
C_{max}	maximum observed plasma concentration
t_{max}	time of maximum observed plasma concentration
t_{last}	time of last quantifiable plasma concentration
C_{trough}	The concentration observed immediately before next dosing (corresponding to predose or trough concentration for multiple dosing)
$t_{1/2}$	apparent plasma terminal elimination half-life
λ_z	apparent terminal elimination rate constant
$Racc_{(Cmax)}$	accumulation ratio based upon C_{max} (M3258 multiple dose only)
$Racc_{AUC0-8}$	accumulation ratio based upon AUC_{0-8} (M3258 multiple dose only)

Additional parameters may be calculated where appropriate

Dose normalized parameters, C_{max}/D, AUC_{0-t}/D, and AUC_{0-8}/D, will be calculated by dividing the original parameter by dose in mg.

C_{max} and t_{max} will be obtained directly from the plasma concentration-time profiles.

For multiple peaks, the highest postdose concentration will be reported as C_{max}. In the case that multiple peaks are of equal magnitude, the earliest T_{max} will be reported.

Accumulation ratios will be determined from single dose and multiple dose (at steady state) C_{max}, and $AUC0\text{-}8_{\tau}$ as follows

$$R_{acc(Cmax)} = \frac{C_{\max, multiple\ dose}}{C_{max, single\ dose}}$$

$$RaccAUC_{0-8} = \frac{AUC_{0-8, multiple\ dose}}{AUC_{0-8, single\ dose}}$$

The Phoenix WinNonlin NCA Core Output will be provided in a separate listing.

16.1.1.1 Criteria for Handling Concentrations Below the Limit of Quantification in Pharmacokinetic Analysis

Concentration values that are below the level of quantification (BLQ) will be set to zero.

16.1.1.2 Criteria for the Calculation of an Apparent Terminal Elimination Half-Life

At least 3 data points will be included in the regression analysis and should not include C_{max}. The last quantifiable concentration should be included.

When assessing terminal elimination phases, the coefficient of correlation for exponential fit (R^2) will be used as a measure of the goodness of fit of the data points to the determined line. Where the, R^2 value for the regression line is ≤ 0.8 the $t_{1/2}$ and $t_{1/2}$ dependent parameters will be calculated and flagged in the PK parameter output. Any flags will be included in the study specific SDTM and the exclusion of parameters agreed with the sponsor.

Time period used for the estimation of $t_{1/2}$, where possible, will be over at least 2 half-lives.

Where $t_{1/2}$ is estimated over a time period of less than 2 half-lives, it will be flagged in the data listings and the robustness of the value should be discussed in the CSR.

16.1.1.3 Calculation of Area Under the Concentration-time Curve

Area under the concentration – time curve (AUC) will be calculated using the mixed log-linear trapezoidal rule (linear up - log down).

The minimum requirement for the calculation of AUC will be the inclusion of at least 3 consecutive plasma concentrations above the lower limit of quantification (LLOQ), with at least one of these concentrations following C_{max}.

For any partial AUC determination (i.e. AUC over a dosing interval), nominal time will generally be used for the end of the interval. Actual times for partial AUC intervals may be used if the sample was taken within +/-10% of the protocol defined time.

AUC from time zero (dosing time) to extrapolated to infinity will be calculated based upon the predicted value for the concentration at t_{last}, as estimated using the linear regression from λ_z determination according to the equation below:

$$AUC_{0-\infty} = AUC_{0-t} + \frac{C_{last,\,predicted}}{\lambda_z}$$

Data will not be automatically excluded on the basis of percentage extrapolated. However, potentially unreliable values will be discussed with the sponsor.

If $AUC_{0-\infty}$ cannot be determined for all participants or all dose levels, an alternative AUC measure, such as AUC to a fixed time point, may be used in the assessment of dose proportionality.

16.1.1.4 Anomalous Values

Handling of anomalous values will be discussed with the sponsor. PK concentrations which are erroneous due to a protocol violation (as defined in the CTP), documented handling error or analytical error (as documented in the bioanalytical report) may be excluded from the PK analysis if agreed upon prior to performing a statistical analyses. In this case the rationale for exclusion must be provided in the Clinical Trial Report (CTR). Any other PK concentrations that appear implausible to the Pharmacokineticist/PKPD Data Analyst must not be excluded from the analysis. Any implausible data will be documented in the Clinical Trial Report (CTR).

Positive predose values at Day 1 >5% of C_{max} may be excluded from the PK analysis, summary statistics and statistical analysis at the discretion of the pharmacokineticist.

16.1.2 Presentation of Pharmacokinetic Data

Available individual M3258 plasma concentrations will be listed and summarized by regimen, dose, study day, analyte and scheduled collection time, including summary statistics where data allows, using: number of non-missing observations (N), arithmetic mean (Mean), standard deviation (SD), coefficient of variation (CV%), minimum (Min), median (Median) and maximum

(Max). Pharmacokinetic parameters will be summarized additionally, using the geometric mean (GeoMean), the geometric coefficient of variation (GeoCV) and the two-sided 95% confidence interval for the GeoMean (LCI 95% GM, UCI 95% GM). For time to reach maximum observed concentration (t_{max}), only n, Min, Median, and Max will be reported.

Descriptive statistics of PK concentration data will be calculated using values with the same precision as the source data and rounded for reporting purposes only. Descriptive statistics will only be calculated for N>2 in which a measurement of <LLOQ represents a valid measurement.

Descriptive statistics will be calculated for pharmacokinetic parameter where N>2. All no result (NR) and not done (nd) values will be set to missing.

PK parameters read directly from the measurements (i.e. C_{max}) will be reported with the same precision as the source data. All other PK parameters will be reported to 3 significant figures.

The following conventions will be applied when reporting descriptive statistics of PK data:

Mean, Min, Median, Max, GeoMean, two-sided 95% CI: 3 significant digits

SD 4 significant digits

CV%, GeoCV%: 1 decimal place

Individual M3258 plasma concentrations will be plotted by study day, analyte and scheduled collection time, including summary statistics where data allows.

Both individual and arithmetic mean concentration-time profiles, will be plotted on linear and semi-logarithmic scales as follows:

- Spaghetti plots showing M3258 plasma concentration vs actual time all individuals per regimen and dose group; Day1 Cycle 1 and Day 15 Cycle 1
- Individual per participant plots showing M3258 overlaying Day 1 Cycle 1 and Day 15, Cycle 1 concentration profiles
- Arithmetic mean concentration-time profile showing M3258 per regimen and dose group with Day 1, Cycle 1 and Day 15, Cycle 1 overlaid. On linear plots ±SD will be included.
- Arithmetic mean concentration-time profiles per Day, overlaying Single and Multiple Dose Day 1 and Day 15. On linear plots ±SD will be included.

The following plots will also be provided, for key PK parameters:

• Dose Normalized C_{max} , , AUC_{0-8} and AUC0-tlast for Day 1 versus Dose level as a scatter plot Any regression line should not be fixed through the origin.

For all linear PK plots, the x and y axes should both begin at (0,0).

16.2 Pharmacodynamics

The pharmacodynamic parameter analyzed are the results from the LMP7 β5i assay and b5c assay.

Sample collection for LMP7 is on Day1 (predose, 2h, 6h and 24h and on day15 (predose, 2h and 6h). If day 15 is no longer sampled, this will be day 8. On the plate for the assay there will two wells for each sample and blank wells (sample without substrate). Before using the data, the mean of the blank wells needs to be subtracted from the mean of the two wells per treatment day and timepoint. It is assumed that this correction will already be done at the lab and only corrected values will be delivered.

The preprocessed data will be analyzed as ratio to the preprocessed baseline value ("residual activity").

If the x-axes in line plots for PD data is time, all data will be used (with respective day of analysis), analysis is not visit based.

Line plots will show the individual residual activity over time (with x-axis time, y-axis LMP7 residual activity), using different colors per regimen and per dose level and different line types to identify participants. If possible (sufficient data in a dose level), LOESS lines per regimen and per dose level can be plotted.

Summary line plots will show the mean per regimen and per dose level

Dot plots will show data of individual participants at specific selected treatment day versus dose (x-axis dose, y-axis LMP7 residual activity). Selected treatment day are:

- Day 1 24h = C1D2 predose
- Day 15 predose (If day 15 is no longer sampled, this will be day 8)

The off-target β5c assay will be be handled in the same way as the LMP7 β5i assay, i.e. using the same plots. The expectation is to see only minimal inhibition in this assay (no changes from baseline activity to residual activity after dosing).

Citrulline data analysis will not be part of the CSR and will be performed for internal insight by Merck internally. Citrulline measurements will be plotted in subject line plots (time x-axis, y-axis: citrulline values, different shape for different dosing/regimen, different color for each participant). Parallel plot below will show the corresponding drug administrations and duration of AE in SOC: "gastrointestinal", using the same color code for participants.

Of note, citrulline is an exploratory biomarker and is being characterized in this clinical setting. Consequently, caution must be used in the interpretation of these data as their significance and implications are unclear.

16.2.1 Bayesian modeling considering toxicity and pharmacodynamics

Additional modeling may be performed by biostatistics to assess the feasibility of a dual modelling approach (Yeung, W. Y., Whitehead, J., Reigner, B., Beyer, U., Diack, C., & Jaki, T. (2015). Bayesian adaptive dose□escalation procedures for binary and continuous responses utilizing a gain function. *Pharmaceutical statistics*, 14(6), 479-487) utilizing DLT probabilities and early pharmacodynamics data for dose recommendations and RDE/RP2D recommendations in future dose escalation studies. In this study the results will usually only be used for internal information. The results will usually not be shown, distributed or discussed at/with the SMC, unless considered necessary by the team. This analysis will be performed internally at Merck and not be part of the CSR

In this dual modelling approach, two separate models will be used: the Bayesian 2-parameter logistic regression model (see protocol) to model toxicity, and a conditional linear model to model the relationship between efficacy and log-log dose levels. With this conditional linear model, the efficacy response y_i of participant i, for a trial with n participants, is modelled as

$$y_i = \theta_1 + \theta_2 \, log(log(d_{(i)})) + \epsilon_i$$

where $i = 1, \ldots, s$ for $s \leq n$, $d_{(i)}$ is the dose administered to participant i, and ϵ_i are independently normally distributed error terms with mean 0 and variance σ^2.

To obtain a dose recommendation for the next cohort using both models in a trial with dose levels $d_1 < \ldots < d_k$, a gain function for dose d_j will be used which takes into consideration the trade-off between safety and efficacy:

$$G_j = \frac{\theta_1 + \theta_2 \, log(log(d_j))}{1 + \ exp(\alpha + \ \beta \, log(d_j))}$$

The dose d_j that is recommended for the next cohort is chosen such that it maximizes G_j and that its posterior estimate of toxicity is below or equal to the target toxicity.

For this study, early efficacy will be assessed via residual LMP7 activity (in percent, compared to baseline). LMP7 residual activity will be used in a transformed version, such that the efficacy response for participant i is

$$y_i = -log\left(\frac{LMP7 \ activity \ at \ day \ x \ hour \ z}{LMP7 \ activity \ at \ baseline}\right)$$

Similar to the DLT model (Section 15.1), a prior distribution is used for the efficacy model to incorporate prior knowledge/expectations, e.g. from pre-clinical models. This prior knowledge is expressed in terms of pseudo data. For this study, the assumptions are: CCI [redacted] This pseudo data leads to the following prior parameters for the normal-gamma prior distribution for the efficacy model:

- $E(\theta_1) = -0.5566, \quad E(\theta_2) = 0.9349$

The prior precision of the pseudo data is assumed to be Gamma distributed with shape = 1 and rate = 0.025. Just as in Section 15.1, the prior distribution and likelihood are used to calculate the posterior probabilities based on Bayes theorem.

The modeling in this section will be performed in R with crmPack. For illustration purposes, Figure 1 shows a graphical representation of the dual modelling approach, including the gain function, based on the prior parameters. If the DLT model recommends a lower dose than the gain function, the recommendation of the DLT model will be followed.

Note that due to technical restrictions of crmPack, the prior for the DLT model is set up in a slightly different way as indescribed in the protocol. However, the underlying assumptions are the same for both models.

16.3 Pharmacometric modeling analysis

No PK/PD modelling will be implemented due to insufficient data.

17 References

1 R Core Team (2014). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL http://www.R-project.org/.

2 Sweeting M, Mander A, Sabin T. bcrm: Bayesian Continual Reassessment Method Designs for Phase I Dose-Finding Trials. J Statist Software 2013;54(13):1-26. http://www.jstatsoft.org/article/view/v054i13 URL

3 Sabanés Bové, D., Yeung, W., Palermo, G., & Jaki, T. (2019). Model-Based Dose Escalation Designs in R with crmPack. *Journal of Statistical Software, 89*(10), 1 - 22. doi: http://dx.doi.org/10.18637/jss.v089.i10

4 Yeung, W. Y., Whitehead, J., Reigner, B., Beyer, U., Diack, C., & Jaki, T. (2015). Bayesian adaptive dose□escalation procedures for binary and continuous responses utilizing a gain function. *Pharmaceutical statistics*, 14(6), 479-487.

5 Friberg L.E, Henningsson A, Maas H, Nguyen L & Karlsson M.O (2002). Model of chemotherapy-induced myelosuppression with parameter consistency across drugs. J Clin Oncol, 20 4713-4721.

6 Beal SL. (2001) Ways to fit a PK model with some data below the quantification limit. J *Pharmacokinet Pharmacodyn.* 28(5):481–50

18 Appendices

18.1 Integrated Analysis Plan for SMC

M3258 First in Human Dose Escalation of M3258 as a Single Agent and Expansion Study of M3258 in Combination with Dexamethasone
MS201814-0010 Version 2.0

Integrated Analysis Plan

Clinical Study Protocol Identification No.	MS201814-0010
Title	A Phase I Open Label First in Human Dose Escalation of the Immunoproteasome Inhibitor M3258 as a Single Agent and Expansion Study of M3258 in Combination with Dexamethasone in Participants with Relapsed Refractory Multiple Myeloma
Study Phase	Phase I (dose escalation and expansion)
Investigational Medicinal Product(s)	M3258
Clinical Study Protocol Version	12 September 2019/Version 3.0
Integrated Analysis Plan Author	Coordinating Author: PPD Merck; PPD Function / Author(s) / Data Analyst(s): PPD Merck PPD Merck PPD
Integrated Analysis Plan Date and Version	09 April 2020 / Version 2.0
Integrated Analysis Plan Reviewers	Function: PPD Name:

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Approval Page

Integrated Analysis Plan: MS201814-0010

A Phase I Open Label First in Human Dose Escalation of the Immunoproteasome Inhibitor M3258 as a Single Agent and Expansion Study of M3258 in Combination with Dexamethasone in Participants with Relapsed Refractory Multiple Myeloma

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1 Table of Contents

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2 List of Abbreviations and Definition of Terms

AE	Adverse Event
CDISC	Clinical Data Interchange Standards Consortium
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CR	Complete Response
(e)CRF	(electronic) Case Report Form
CSR	Clinical Study Report
DLT	Dose Limiting Toxicity
ECG	Electrocardiogram
ICH	International Conference on Harmonization
IAP	Integrated Analysis Plan
IMWG	International Myeloma Working Group
MTD	Maximum Tolerated Dose
NA	Not Applicable
NCI-CTCAE	National Cancer Institute – Common Terminology Criteria for Adverse Events
PD	Progressive Disease or Protocol Deviation
Pd	Pharmacodynamics
PR	Partial response
PT	Preferred Term
PK	Pharmacokinetics
MedDRA	Medical Dictionary for Regulatory Activities
PP	Per Protocol

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PR	Partial Response
SAE	Serious Adverse Event
SCR	Screening analysis population
SD	Stable Disease or Standard Deviation
SDTM	Study Data Tabulation Model
SMC	Safety Monitoring Committee
SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Event
TLF	Tables, Listings, and Figures
WHO-DD	World Health Organization Drug Dictionary

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3 Modification History

Unique Identifier for Version	Date of IAP Version	Author	Changes from the Previous Version
1.0	14 November 2019	PPD	
2.0	07 April 2020	PPD	Define handling and model for different dosing regimens. Additionally some changes to be flexible enough for upcoming amendment and minor corrections of earlier mistakes

4 Purpose of the Integrated Analysis Plan

The purpose of this Integrated Analysis Plan (iAP) is to document technical and detailed specifications for the analyses performed for the Safety Monitoring Committee (SMC) reviews of data collected for protocol MS201814-0010. Results of the analyses described in this iAP will be used (amongst other data) by the SMC to decide upon dose of future cohorts. This iAP describes the Bayesian two-parameter logistic regression model analysis methods used to make a recommendation to the SMC for dose escalation in part A (as in protocol) and later will also include the methods for the model to monitor safety of dose in part B. Additionally, this iAP will describe preliminary PK and Pd analyses for M3258, as well as patient profiles and Tables, Listings, and Figures (TLFs) summarizing safety data. TLFs will only be produced if a SMC is taking place and data of more than 6 subjects treated in the respective study part are available (for part A expected at SMC after cohort 3 and at the 3rd SMC for part B). The patient profiles and TLFs on safety and lab data will be produced on the raw data export available at cut-off. Biomarker analyses will be provided for SMC by biomarker representative, PK analyses by the Clin Pharm representative. If dose escalation is planned to continue beyond 50 mg, the materials produced for the SMC(s) for the 50 mg cohort may be submitted to FDA.

The SAP is based upon Section 9 (Statistics) of the trial protocol and protocol amendments and is prepared in compliance with ICH E9.

5 Objectives and Endpoints

Part A

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Objectives	Endpoints (Outcome Measures)	Endpoints (Outcome Measures) Timeframe	IAP section
Primary			
To determine safety, tolerability and the maximum tolerated dose (MTD) (if observed) of M3258 as a single agent in participants with RRMM	Occurrence of dose-limiting toxicities (DLTs) in participants receiving M3258 as a single agent during the first 28-day treatment cycle Occurrence of any adverse events (AEs) reported (serious or nonserious) will be considered study treatment-emergent adverse events (TEAEs) and study treatment-related adverse events (TRAEs) (including TEAEs leading to death or discontinuation of treatment) in participants receiving M3258 as a single agent from start of study intervention to 30 days after end of study intervention Occurrence of TEAEs outside of the DLT period that safety monitoring committee (SMC) deems relevant for determination of the MTD Study treatment-emergent changes in clinical laboratory measures from Baseline, safety electrocardiogram (ECG) measures, vital signs, Eastern Co-operative Oncology Group (ECOG) performance status in participants receiving M3258 as a single agent from start of study intervention to 30 days after end of study intervention	For DLTs: from first treatment to 28 days after first treatment. However, AEs occurring after the first 28 days that are considered relevant for dosing decisions can be defined as DLTs by the SMC. For TEAEs and changes in lab values, ECG values, vital signs: from first day of study treatment (before treatment: baseline measure) until 30 days after end of study intervention	Preliminary analysis for SMCs: tbd
Secondary			
To investigate the pharmacokinetic (PK) profile of M3258 (single and multiple dose exposure) in participants with RRMM	1. PK profile of M3258 in terms of C_{max}, AUC_{0-t}, AUC_{0-24} at Day 1 Cycle 1, (single dose): predose, 1, 2, 3, 4, 5, 6, 8 and 24 h after administration 2. PK profile of M3258 in terms of C_{max}, AUC_{0-24} at Day 15 Cycle 1, (multiple dose): predose, 1, 2, 3, 4, 5, 6, and 8 h after administration	Day 1: predose, 1,2,3,4,5, 6,8 and 24 h post dose Day 15: predose, 1,2,3,4,5, 6,8 and 24 h post dose AUC: predose to 24 h post dose on day 1 and day 15	Preliminary selected analysis for SMCs: tbd

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Objectives	Endpoints (Outcome Measures)	Endpoints (Outcome Measures) Timeframe	IAP section
To investigate the recommended dose for expansion (RDE) in participants with RRMM	In addition to safety, tolerability and PK, for selection of RDE, changes in pharmacodynamics (Pd) (LMP7 activity) in pre and post study intervention samples on Day 1 Cycle 1 pre and postdose, Day 2 Cycle 1 predose and Day 15 Cycle 1 pre and postdose Changes from Baseline in serum M-protein or urine M-protein or free light chain protein levels (for free light chain disease) on Day 1 of every cycle	LMP7 residual activity in scope of this iAP only LMP7 residual activity: Day 1 and day 15 post dose measurements compared to day 1 predose.	Preliminary analysis for SMCs of LMP7 residual activity only: tbd
To evaluate preliminary clinical activity using International Myeloma Working Group (IMWG) criteria	Overall response (OR), duration of response (DOR), time to response until complete response (CR), stringent complete response (sCR), very good partial response (VGPR), or partial response (PR) according to IMWG	Objective not in scope for this iAP	Not in scope of this iAP

Part B

Objectives	Endpoints (Outcome Measures)	Endpoints (Outcome Measures) Timeframe	IAP section
Primary			

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Objectives	Endpoints (Outcome Measures)	Endpoints (Outcome Measures) Timeframe	IAP section
To determine safety and tolerability of M3258 at RDE when co-administered with dexamethasone in participants with RRMM	Occurrence of DLTs in participants receiving M3258 in combination with dexamethasone during the first 28-day treatment cycle Occurrence of study treatment-emergent serious adverse events (SAEs) (including deaths) in participants receiving M3258 in combination with dexamethasone, from start of study intervention up to 30 days after end of study intervention Occurrence of TEAEs and TRAEs (including deaths) in participants receiving M3258 in combination with dexamethasone from start of study intervention up to 30 days after end of study intervention Study treatment-emergent clinically relevant abnormal changes in clinical laboratory measures from Baseline, ECGs measures, vital signs, ECOG performance status in participants receiving M3258 in combination with dexamethasone from start of study intervention to 30 days after end of study intervention	For DLTs: from first treatment to 28 days after first treatment. However, AEs occurring after the first 28 days that are considered relevant for dosing decisions can be defined as DLTs by the SMC. For TEAEs and changes in lab values, ECG values, vital signs: from first day of study treatment (before treatment: baseline measure) until 30 days after end of study intervention	Preliminary analysis for SMCs: tbd
To determine recommended Phase II dose of M3258 when co-administered with dexamethasone in participants with RRMM based on early signs of safety and efficacy in the expansion phase	Occurrence of TEAEs and TRAEs (including deaths) in participants receiving M3258 when given in combination with dexamethasone from start of study intervention to 30 days after end of study intervention OR, DOR, time to response until CR, sCR, VGPR, or PR according to the International myeloma working group (IMWG)	Objective not applicable for this iAP	Objective not applicable for this iAP
Secondary			

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Objectives	Endpoints (Outcome Measures)	Endpoints (Outcome Measures) Timeframe	IAP section
To collect preliminary efficacy data in participants with RRMM under treatment with M3258, when co-administered with dexamethasone	OR, DOR, time to response until CR, sCR, VGPR, or PR according to the IMWG Progression-Free Survival (PFS) per Investigator Overall Survival (OS) censored at End of Study	Objective not in scope for this iAP	Objective not in scope for this iAP
To investigate the PK profile of M3258 (single and multiple dose exposure) when co-administered with dexamethasone in participants with RRMM	PK profile of M3258 in terms of C_{max}, AUC_{0-t} at Day 1 Cycle 1, (single dose): predose, 1, 2, 3, 4, 5, and 6h after administration PK profile of M3258 in terms of C_{max}, AUC_{0-24} at Day 15 Cycle 1, (multiple dose): predose, 2, 4, and 6h after administration		Preliminary selected analysis for SMCs: tbd

6 Overview of Planned Analyses

The following analyses are planned for this trial:

- SMC analyses (this iAP, it will be added as an appendix of the main iAP, once available)
- End of monotherapy dose escalation analysis (part A) (part of main iAP)
- Interim analysis on OR in part B (part of main iAP)
- Primary analysis of trial (main iAP)

Cut-off date:

SMCs are usually planned after the last subject of each cohort has finished the DLT period or dropped out of the study. The usual cut-off is at the end of this day. In cases where enrollment of the last subject in a dosing cohort is delayed, the SMC may decide (based on available data) upon enrollment and dose for the next dosing cohort before all subjects in a cohort have completed the DLT period and thus set an earlier data cut-off.

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7 Changes to the Planned Analyses in the Clinical Study Protocol

There is one change in the definition of the DLT analysis set compared to the protocol. The following is added:

"Additionally, subjects that did not receive 80% of the planned total dose of study treatment, but at least 80% dosing of a different (lower) dose level, did not miss more than 5 days of dosing, and finished the DLT period are eligible for the DLT analysis set to be analyzed in the highest dose level they received 80% of dosing."

8 Analysis Populations and Subgroups

8.1 Definition of Analysis Populations

Important protocol deviations are protocol deviations that might significantly affect the completeness, accuracy, and/or reliability of the study data or that might significantly affect a subject's rights, safety, or well-being. These are coded as "Critical" or "Major" in the Clinical Trial Management System (CTMS) if identified via monitoring; they may also be identified from the database through medical review or programmatically.

All important protocol deviations are documented in SDTM datasets whether identified through site monitoring, medical review or programming.

For this iAP for SMCs the only protocol deviation that is considered in the analysis is deviation from planned dosing that leads to exclusion from the DLT analysis set, or leads to consideration in a different than planned dose level. See definition of DLT analysis set below.

8.2 Subgroup Definition and Parameterization

Analysis Set	Description
Screening (SCR)	All participants, who provided informed consent, regardless of the participant's randomization and study intervention status in the study.
Safety (SAF)	All participants, who were administered any dose of any study intervention. Analyses will consider participants as treated.
DLT	The DLT Set will include all participants who received at least one dose of study intervention and meet at least one of the following criteria: • Experienced at least one DLT during the DLT period, regardless of the administered number of doses of study intervention/completion of the DLT period

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	• Received at least 80% of the planned cumulative dose of each treatment during the DLT period and completed the DLT period. • Additionally, subjects that did not receive 80% of the planned total dose of study treatment, but at least 80% dosing of a different (lower) dose level, did not miss more than 5 days of dosing, and finished the DLT period are eligible for the DLT analysis set to be analyzed in the highest dose level they received 80% of dosing of.
PK	All participants, who received at least one dose of study intervention, have no clinically important protocol deviations or important events affecting PK, and provide at least one measurable postdose concentration. Participants will be analyzed per the actual study intervention they received.
Pd	All participants, who received at least one dose of study intervention, have no clinically important protocol deviations or important events affecting Pd, and provide at least one measurable Pd endpoint postdose.

9 General Specifications for Data Analyses

All analyses will be separate for each part (dose escalation (A) and expansion (B)), and so will decisions by the SMC.

Analyses will be displayed separately by regimen, dose and summarized by study part.

Significance level:

There will be no statistical tests performed in these SMC analyses. If confidence or credibility intervals are mentioned, the level will be 95% unless otherwise specified.

Presentation of continuous and qualitative variables:

Continuous variables will be summarized using descriptive statistics, i.e.

- number of participants, number of participants with non-missing values
- mean, standard deviation
- median, 25th Percentile - 75th Percentile (Q1-Q3)
- minimum, maximum

If there are fewer than 5 observations summarized, only the number of subjects (N), number of subjects with non-missing values, the mean, and the values themselves will be given.

Qualitative variables will be summarized by counts and percentages.

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Unless otherwise stated the calculation of proportions will be based on the number of subjects in the analysis set of interest. Therefore, counts of missing observations will be included in the denominator and presented as a separate category.

Deviations from this definition might apply to the PK analysis (see section **Error! Reference source not found.** for definitions)

Definition of baseline:

In general, the last non-missing measurement prior to the first study drug administration will be used as the baseline measurement.

Definition of change from baseline

Change from baseline = visit value – baseline value

Percent Change from Baseline = 100 * (visit value – baseline value) / baseline value

Definition of duration:

If not otherwise specified, duration will be calculated by the difference of start and stop date + 1 (e.g. survival time (days) = date of death – date of first study drug administration + 1).

The time since an event (e.g. time since first diagnosis) will be calculated as reference date minus date of event.

Conversion factors:

The following conversion factors will be used to convert days into months or years: 1 month = 30.4375 days, 1 year = 365.25 days.

Handling of missing data:

Unless otherwise specified (Section 15 and 16), missing data will not be replaced.

In all listings, imputed information will be flagged.

Missing statistics, e.g. when they cannot be calculated, should be presented as "nd".

Where tables are presented over different time points, the total of missing and non-missing observations at each time-point should reflect the population still in the trial at that time. This does not apply when imputations are made beyond trial withdrawal. For example, if a subject is still in the trial at the time-point but with missing data, they should be counted in the number of missing observations.

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Treatment day definition

Treatment day is defined relative to the date of first study drug administration (M3258 and in part B M3258 or dexamethasone). Treatment Day 1 is treatment start date of first administration of the study drug; the day before is defined as Treatment Day -1 (no Treatment Day 0 is defined).

Software

All analyses (except DLT plot, calculations of posterior distributions, recommended next dose and associated outputs) will be performed using SAS® Software version 9.2 or higher. For the outputs of the Bayesian two-parameter logistic model updates, R (version 3.5.1 or higher [1]) and the R packages bcrm [2] or crmpack [3], or SAS proc MCMC, or East® 6.5 or higher will be used. The computer program Phoenix® WinNonlin® version 6.4, or higher (Certara, L.P., 1699 S Hanley Road, St Louis, MO 63144, USA) will be used to derive PK parameters applying Non-compartmental analysis (NCA).

10 Study Participants

The subsections in this section include specifications for reporting participant disposition and study treatment/study discontinuations. Additionally, procedures for reporting protocol deviations are provided.

10.1 Disposition of Participants and Discontinuations

A table of disposition should display the following (per regimen, dose level and in total):

- Number of subjects screened
- Number of subjects who received at least one dose of study intervention (safety analysis set)
- Number of subjects who fulfill the dosing criterion (>=80% of a cohort's dose and at max 5 missed daily dosings) of the DLT analysis set. This number may be higher than the number of subjects screened for a dose level, if subjects receive different dosing than planned.
- Number of subjects with a DLT per investigator's judgement as recorded in eCRF
- Number of subjects with documented end of treatment (of subjects in safety analysis set)

A listing of End of treatment reason will be provided.

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10.2 Protocol Deviations / Exclusion from Analysis Populations

10.2.1 Important Protocol Deviations

Except for the dosing criterion for the DLT analysis set, this is not applicable for this iAP for SMCs.

10.2.2 Reasons Leading to the Exclusion from an Analysis Population

Subjects who did not receive at least 80% of the planned dose are excluded from the DLT analysis set unless they can be considered in another dose level as described above.

11 Demographics and Other Baseline Characteristics

Not applicable for this iAP, some individual data to appear as part of the patient profiles.

12 Previous or Concomitant Medications/Procedures

Not applicable for this iAP, some individual data to appear as part of the patient profiles.

13 Study Treatment: Compliance and Exposure

Not applicable for this iAP, some individual data to appear as part of the patient profiles.

14 Efficacy Analyses

Not applicable for this iAP, some individual data to appear as part of the patient profiles.

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15 Safety Analyses

The subsections in this section include specifications for summarizing safety endpoints that are common across clinical studies such as adverse events, laboratory tests and vital signs.

The primary endpoint during dose escalation is the occurrence of DLTs, AEs and other safety related measurements.

The analysis population for the DLT analysis will be the DLT analysis set, for all other safety analyses it will be the safety analysis set.

15.1 DLT analysis

The primary objective of the SMC meetings is to regularly monitor the overall safety of the subjects enrolled in the trial. An important part of that is reviewing DLTs. Besides individual medical judgement on DLTs, a summary analysis of DLTs is performed using a Bayesian two-parameter logistic modeling approach to model the relation of dose to the occurrence of DLTs. The results from updating this model will assist the SMC in their dosing decisions.

A listing of DLTs as flagged by investigator in eCRF will be provided. It is possible that there is a discrepancy between final SMC decision of SMC and investigator flag in eCRF. Therefore the title of this listing needs to clearly state "DLTs as per investigator flag in eCRF". The listing will be sorted by regimen, dose level and subject ID. This listing will additionally contain age, sex, type of myeloma, AEterm, SOC, PT, grade, SAE (yes/no), relatedness to M3258 (yes/no), relatedness to dexamethasone (yes/no) (if applicable, in part B only), start date (+treatment day), stop date (+treatment day), duration of DLT, action taken with M3258, if treatment was stopped before start of AE: days since stop of treatment, and outcome.

A DLT profile plot of all subjects in the SAF Analysis Set with DLT decisions from previous SMCs will be produced (per regimen). This will show an open square for all subjects who did not have a DLT, a closed square for those who experienced a DLT, and an open circle for those who were excluded from the DLT Analysis Set. This plot will have Cohort Number or subject index on the x-axis and dose level (mg) on the y-axis.

Bayesian two-parameter logistic model

Summary statistics of the posterior probability distribution of the DLT rate (2.5%, 25%, 50%, 75%, and 97.5% quantiles) for each predefined dose level will be updated by estimation according to the logistic model. Using data from all subjects evaluable for DLT or who experienced a DLT at the completion of a new cohort (and data from all previous cohorts: DLT analysis set), the Bayesian logistic model provides a recommended dose level for the next cohort based on minimal

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loss. This recommendation will be shared with the SMC after the SMC has made the decision upon DLTs. In preparation of the SMC, the model will be updated with potential scenarios' data (e.g. 3 subjects evaluable on current dose level, 0 DLTs, the same with 1 DLT, 2 subjects evaluable 0 DLT etc….), to have the results ready at SMC.

Recommendation is based on a loss function (probabilities of being in 1 of the 4 intervals will be multiplied with a loss term as follows:

0 * P(target dosing (estimated DLT rate in (0.2-0.35])) + 1 * P(under dosing (estimated DLT rate in [0-0.2])) +2* P(for over dosing (estimated DLT rate in (0.35-0.6]) + 3 * P(excessive dosing (estimated DLT rate in (0.60-1])).

The recommended dose level resulting from the model for the next cohort is the dose with the lowest loss function. This Bayesian escalation approach will be used to assist the SMC to select the next dose from a predicted set of acceptable doses, i.e., 10 mg, 20 mg, 35 mg, 50 mg. It is possible to choose a dose(s) not within the pre-specified dose-escalation plan. In this case the estimated posterior probabilities of the selected dose will also be provided to the SMC.

The model will continue to be updated at each SMC until the SMC has decided to stop dose escalation.

Prior distribution and likelihood are used to calculate the posterior probabilities based on Bayes theorem.

The likelihood is defined based on a binomial distribution, modelling the rate of subjects with at least 1 DLT.

The relationship between dose and toxicity rate is defined by

$$P(DLT|d_j,\alpha,\beta) = \frac{\exp\left(\alpha + \exp(\beta) * \log\left(\frac{d_j}{d_{ref}}\right)\right)}{1 + \exp\left(\alpha + \exp(\beta) * \log\left(\frac{d_j}{d_{ref}}\right)\right)}$$

Where $d_j \in \{10\text{ mg}, 20\text{ mg}, 35\text{ mg}, 50\text{ mg}\}$ (or different) and (α,β) are bivariate normally distributed. Reference dose d_{ref} is 90 mg. The chosen prior for monotherapy escalation has the following parameters

$E(\alpha) = -0.708$,

$E(\beta) = -0.389$,

$SD(\alpha)=1.2$, $SD(\beta) = 0.9$, $Cov(\alpha, \beta) = 0$.

The prior distribution has not been changed compared to the protocol defined.

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Handling of changes in regimen

For different regimens, separate models will be used. In general, the same specifications outlined above will be used for each of these models, applicable to the dose given on the treatment days, unless otherwise specified. This means that in a once daily (QD) regimen, 90 mg as reference dose refers to the dosing of 90 mg daily. In a twice weekly regimen (on day 1,4,8,11, etc) the 90 mg reference dose refers to a dosing of 90 mg on day 1, day 4 etc. The approach is not considering weekly cumulative dosing.

Rationale for keeping the same prior: It is assumed that changes in regimen occur due to the fact that the observed dose-toxicity relationship was not as a priori expected. It is further assumed that after the change in regimen the dose- probability of DLT relationship in the new regimen is coming closer to the a priori expected dose-toxicity relationship.

15.2 Patient profiles

The SMC will receive patient profiles containing:

- Subject disposition (still in trial, or withdrawn with reason for withdrawal)
- Demographics and baseline characteristics (e.g., cancer diagnosis, staging)
- Medical history
- History of disease under study
- Previous and concomitant medications
- Prior anti-cancer drug therapies
- Prior anti-cancer radiotherapy
- Prior anti-cancer surgeries
- Concomitant procedures
- Study drug administration, and dose adjustments
- All serious and non-serious AEs (with details like e.g. grade, start and stop date), including but not limited to:
  - DLTs
  - AESIs
  - AEs leading to dose reduction or temporary discontinuation
  - AEs leading to permanent treatment discontinuation
  - AEs leading to death
- Laboratory data (hematology, coagulation, biochemistry, urinalysis)

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- ECG results
- Vital signs

Patient profiles will be provided for the current cohorts under review and updated patient profiles will be provided for subjects from previous cohorts that had changes from last SMC meeting.

15.3 Adverse Events

The severity of adverse events will be graded using the NCI-CTCAE version 5.0, except where CTCAE grades are missing. No imputation of missing grades will be performed. Adverse events will be coded according to the latest MedDRA version at the time of the data cut-off.

- **TEAEs**: Any AEs that are reported (serious and non-serious) will be considered treatment emergent adverse events (TEAEs), with the exception of those that started prior to the first dose of study treatment (unless a worsening of the event is recorded after the first dosing, in which case the event will be counted as a TEAE), or AEs starting more than 30 days after the last dose of study treatment.
- **Related Adverse Events**: AEs with relationship missing, unknown or yes. Relationship is judged separately for M3258, and dexamethasone.
- **SAEs**: Serious adverse events (as recorded on the AE eCRF page, Serious Adverse Event = 'Yes').
- **AEs Leading to Treatment Discontinuation**: AEs leading to permanent discontinuation of study treatment (as recorded on the AE eCRF page, Action taken with study treatment = 'Drug withdrawn'). Treatment discontinuation is recorded separately for M3258, and dexamethasone.
- **AEs Leading to Death**: AEs leading to death (as recorded on the AE eCRF page, Outcome = 'Fatal').

AEs will be summarized by MedDRA PT as event category and MedDRA primary SOC as summary category. In general, each subject will be counted only once within each PT or SOC.

AEs with missing classifications regarding relationship to study treatment, and those with start date on or after the start of study treatment, will be considered as related to the study treatment.

Missing data handling

Incomplete AE-related dates will be handled as follows:

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- If the onset date is missing completely or missing partially – but the onset month and year, or year, are equal to that of the study treatment start – then the onset date will be replaced by the minimum of the start of study treatment and the AE resolution date.
- In all other cases, the missing onset day or month will be replaced by 1.
- Incomplete stop dates will be replaced by the last day of the month (if day is missing only), if not resulting in a date later than the date of participant's death. In the latter case, the date of death will be used to impute the incomplete stop date.
- In all other cases the incomplete stop date will not be imputed. If the stop date of an AE is after the date of cut-off, the outcome of the AE is ongoing at cut-off.
- Further information after cut-off (such as fatal outcome) might be taken from the Safety database and reported separately.

15.3.1 All Adverse Events

Adverse events will be summarized by worst toxicity (according to NCI-CTCAE version 5.0)] per participant, using preferred term as event category and primary system organ class (SOC).

If an adverse event is reported for a given participant more than once during study intervention, the worst toxicity and the worst relationship to study intervention will be tabulated.

In case a participant had events with missing and non-missing grades, the maximum of the non-missing grades will be displayed.

AE tables will be restricted to TEAEs only. The AE tables will include the number and percentage of subjects with at least one TEAE, by MedDRA SOC and PT (both sorted alphabetically), unless otherwise stated.

All AEs will be tabulated by regimen, dose level and overall in a table showing the incidence of TEAEs, by SOC and PT (both sorted alphabetically).

A listing of all TEAEs will be provided. This listing will be sorted by regimen, dose level and subject. This listing will additionally contain age, sex, type of myeloma , SOC, PT, grade, SAE (yes/no), DLT per investigator (yes/no), relatedness to M3258 (yes/no), to dexamethasone (yes/no) (if applicable, in part B only), start date (+treatment day), stop date (+treatment day), duration of TEAE, action taken with M3258, if treatment was stopped before start of AE: days since stop of treatment, and outcome.

Additionally, a listing of all adverse events grade >=3 (incl non TEAEs) and SAEs will be provided: This listing is to be produced twice, once sorted by regimen, dose level and subject ID

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and once sorted by SOC and PT. These will also include age, sex, type of myeloma, grade, SAE (yes/no), DLT per investigator (yes/no), relatedness to M3258 (yes/no), relatedness to dexamethasone (yes/no) (if applicable, in part B only) start date (+treatment day), stop date (+treatment day), duration of AE, if treatment was stopped before start of AE: days since stop of treatment, and outcome.

15.3.2 Adverse Events Leading to Study Intervention Discontinuation

A listing of TEAEs leading to treatment discontinuation, interruption, or dose reduction of each study drug will be provided (one for M3258, additionally in part B: one for dexamethasone). This listing, sorted by regimen, dose level and subject ID, will include: dose level, subject ID, age, sex, type of myeloma, AE investigator term, SOC, PT, relationship to M3258 and dexamethasone (as applicable), seriousness, action taken with M3258 or dexamethasone (as applicable) (displayed as: Disc/IR/DR),)), start date (+treatment day), stop date (+treatment day), duration of AE, if treatment was stopped before start of AE: days since stop of treatment, and outcome.

15.4 Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

15.4.1 Deaths

Not applicable for this iAP, are included in other listings

15.4.2 Serious Adverse Events

Not applicable for this iAP, are included in other listings.

15.5 Clinical Laboratory Evaluation

Laboratory values (including corresponding normal ranges) from the Lab will be used for patient profiles, an Edish plot, and line plots

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Laboratory results will be classified according to the latest NCI-CTC Version [at the moment 5.0]. Some of the toxicity gradings are based on laboratory measurements in conjunction with clinical findings. The classification will be derived from the laboratory results at a given assessment, thus ignoring additional clinical findings, except for the evaluation of blood glucose toxicity grade 1 and 2 the fasting state is required. Ignoring the fasting state might lead to overreporting of grade 1 and 2 events. Therefore, blood glucose grading will focus on grade 3 and 4 reporting only.

If it increases interpretability, graphical displays can be shown on a log-scale.

Line plots (with x-axis time, y-axis lab value), using different colors per regimen, dose level and different line types to identify participants, will be provided for the following lap parameters:

- Neutrophils
- Platelets
- Lymphocytes
- Hemoglobin

If available (and feasible due to potential differences between labs) reference lines for ULN and LLN should be added to the plots.

Hepatotoxicity assessment

A plot of peak ALT versus peak total bilirubin, both relative to the upper limit of normal (ULN) will be provided. This eDISH plot (evaluation of drug-induced serious hepatotoxicity) will have reference lines at 3×ULN for ALT and at 2×ULN for total bilirubin. Subjects outside the lower left box will be identified by subject-ID.

15.6 Vital Signs

Not applicable for this iAP, except for display of individual values in patient profiles

15.7 Other Safety or Tolerability Evaluations

Not applicable for this iAP, except for display of individual values in patient profiles

A listing of AEs of special interest will be provided. This will be sorted by regimen, dose level and subject. This listing will additionally contain age, sex, type of myeloma, SOC, PT, grade, SAE (yes/no), DLT per investigator (yes/no), relatedness to M3258 (yes/no), to dexamethasone (yes/no) (if applicable, in part B only), start date (+treatment day), stop date (+treatment day), duration of

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Ac, action taken with M3258, if treatment was stopped before start of AE: days since stop of treatment, and outcome.

16 Analyses of Other Endpoints

16.1 Pharmacokinetics

PK concentration measurements will be descriptively summarized using: number of non-missing observations (N), arithmetic mean (Mean), standard deviation (SD), coefficient of variation (CV%), minimum (Min), median (Median) and maximum (Max). PK parameters will be summarized additionally, using the geometric mean (GeoMean), the geometric coefficient of variation (GeoCV) and the 95% confidence interval for the GeoMean (LCI 95% GM, UCI 95% GM). For time to reach maximum observed concentration (t_{max}), only n, Min, Median, and Max will be reported. PK parameters read directly from the measurements (i.e. C_{max}) will be reported with the same precision as the source data. All other PK parameters will be reported to 3 significant figures.

Descriptive statistics of PK concentration data will be calculated using values with the same precision as the source data and rounded for reporting purposes only. Descriptive statistics will only be calculated for N>2 in which a measurement of <LLOQ represents a valid measurement.

Values below the lower limit of quantification of the assay (LLOQ) will be taken as zero for summary statistics of PK concentration data, PK parameter estimation (e.g. AUC) and for graphical presentations. It is expected that samples with concentrations above the upper limit of quantification (ULOQ) will be diluted and retested before the time of final analysis.

The following conventions will be applied when reporting descriptive statistics of PK data:

Mean, Min, Median, Max GeoMean, 95% CI:	3 significant digits
SD	4 significant digits
CV%, GeoCV%:	1 decimal place

The following PK parameters of M3258 and Dexamethasone (if applicable, in part B) will be calculated for both single and multiple dose, as applicable:

- C_{max}: Observed maximum plasma concentration
- C_{max}/Dose: Observed maximum plasma concentration, normalized by actual dose
- t_{max}: Time to reach maximum observed plasma concentration

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- $AUC_{0-\infty}$: Area under the concentration-time curve from time zero extrapolated to infinity,

based on the predicted value for the concentration at t_{last}

- AUC_{extra}: The AUC from time t_{last} extrapolated to infinity given as percentage of $AUC_{0-\infty}$. AUC_{extra} = (extrapolated area/$AUC_{0-\infty}$)*100.

- AUC_{0-t}: Area under the concentration-time curve from time zero to the last sampling time at

which the concentration is at or above the lower limit of quantification (LLOQ)

- AUC_{τ}: Area under the plasma concentration versus time curve within one dosing interval. Tau = 24hours. For multiple dose the pre-dose concentration will be duplicated and used as the 24 hour concentration, to allow AUC_{τ} to be calculated (assuming steady state).

- AUC_{0-8}: Area under the plasma concentration versus time curve to 8 hours.

- $t_{1/2}$: Apparent terminal half-life

- λ_z: Apparent terminal rate constant

- CL/F: Apparent body clearance of drug following extravascular administration

- Vz/F: Volume of distribution of the drug following extravascular administration

Dose Normalized AUC ($AUC_{0-\infty}$, AUC_{0-t}, AUC_{τ} and AUC_{0-8}) will also be provided to enable comparisons between dose groups. Dose normalized AUC will be presented in a summary table.

For multiple dose the following will also be calculated, where possible:

C_{trough}	The concentration observed immediately before next dosing (corresponding to predose or trough concentration for multiple dosing)
$R_{acc(AUC\tau)}$	The accumulation factor to assess the increase in exposure until steady state is reached. $R_{acc(AUC\tau)}$= (AUC_{τ} after multiple dose (at steady state)) / (AUC_{τ} after single dose)
$R_{acc(Cmax)}$	The accumulation factor to assess the increase in maximum concentration until steady state is reached. $R_{acc(Cmax)}$ = (C_{max} after multiple dose (at steady state))/ (C_{max} after single dose)
$R_{acc(AUC0-\infty)}$	The accumulation factor to assess the increase in exposure via $AUC_{0-\infty}$. $R_{acc(AUC0-\infty)}$= (AUC_{τ} after multiple dose (at steady state)) / ($AUC_{0-\infty}$ after single dose)

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$CL_{SS/f}$	The apparent total body clearance of study intervention at steady state following extravascular administration, taking into account the fraction of dose absorbed. $CL_{ss/f} = Dose_{p.o.} / AUC_{\tau}$

Available individual M3258 and Dexamethasone (as applicable, in part B) plasma concentrations will be listed and summarized by regimen, dose, study day, analyte and scheduled collection time, including summary statistics where data allows. Individual as well as mean concentration-time profiles will be plotted on linear and log scales as follows:

- Spaghetti plots showing all individuals per regimen (where applicable) and dose group; Day1 Cycle 1 and Day 15 Cycle 1.
- Individual per subject plots overlaying Cycle Day 1 and Cycle 1 Day 15 concentration profiles Mean concentration-time profile per Dose group with Cycle 1 Day 1 and Cycle 1 Day 15 overlaid (linear ±SD, and semi-log)
- Mean concentration -time profiles per Day, overlaying Single and Multiple Dose (Day 1 and Day 15)

For M3258, PK parameters, as described above, will be calculated using commercial software (Phoenix® WinNonlin®). Available PK parameters will be listed and summarized by regimen, dose, study day and Analyte. Nominal collection times may be used for PK determinations in support of the SMC review.

The following plots will also be provided, for Key PK parameters:

- Dose Normalized Cmax and AUC_{τ} versus Dose level as a scatter plot with regression line. Plot axes will start at the origin (0,0), but the regression line should fit the data and not be forced through the origin.

PK listing creation and PK parameter calculation is outsourced to Covance by Merck Quantitative Pharmacology.

For the first 1-2 SMC meetings pre-clinical data/animal PK parameters may be presented in a table alongside observed human PK parameters in order to compare the ratios of AUC and C_{max}. This will be compiled by Merck Quantitative Pharmacology.

16.2 Pharmacodynamics

The pharmacodynamic parameter analyzed for SMCs are the results from the LMP7 (β5i) assay.

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Sample collection for LMP7 is on Day1 (predose, 2h, 6h and 24h (24h=C1D2 predose only part A)) and on day15 (predose, 2h and 6h). On the plate for the assay there will two wells for each sample and blank wells (sample without substrate). Before using the data, the mean of the blank wells needs to be subtracted from the mean of the two wells per timepoint. It is assumed that this correction will already be done at the lab and only corrected values will be delivered.

The preprocessed data will be analyzed as ratio to the preprocessed baseline value ("residual activity").

Line plots will show the individual residual activity over time (with x-axis time, y-axis LMP7 residual activity), using different colors per dose level and different line types to identify participants. If possible (sufficient data in a dose level), LOESS lines per dose level can be plotted.

Summary line plots will show the mean per dose level

Dot plots will show data of individual participants at specific selected timepoints versus dose (x-axis dose, y-axis LMP7 residual activity). Selected timepoints are:

- Day 1 24h = C1D2 predose
- Day 15 predose (if day 15 predose is no longer sampled, this will be day 8 predose)

The off-target β5c assay will be be handled in the same way as the LMP7 assay, i.e. using the same plots. The expectation is to see only minimal inhibition in this assay (no changes from baseline activity to residual activity after dosing).

If Citrulline data become available, they will be plotted in subject line plots. Of note, citrulline is an exploratory biomarker and is being characterized in this clinical setting. Consequently, caution must be used in the interpretation of these data as their significance and implications are unclear.

16.2.1 Bayesian modeling considering toxicity and pharmacodynamics

Additional modeling will be performed by biostatistics to assess the feasibility of a dual modelling approach (4) utilizing DLT probabilities and early pharmacodynamics data for dose recommendations in future dose escalation studies. In this study the results will usually only be used for internal information, not for dosing decisions in SMCs. The results will usually not be shown, distributed or discussed at/with the SMC, unless considered necessary by the team.

In this dual modelling approach, two separate models will be used: the Bayesian 2-parameter logistic regression model (see Section 15.1) to model toxicity, and a conditional linear model to model the relationship between efficacy and log-log dose levels. With this conditional linear model, the efficacy response y_i of participant i, for a trial with n participants, is modelled as

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$$y_i = \theta_1 + \theta_2 \log(\log(d_{(i)})) + \epsilon_i$$

where $i = 1, \ldots, s$ for $s \leq n$, $d_{(i)}$ is the dose administered to participant i, and ϵ_i are independently normally distributed error terms with mean 0 and variance σ^2.

To obtain a dose recommendation for the next cohort using both models in a trial with dose levels $d_1 < \ldots < d_k$, a gain function for dose d_j will be used which takes into consideration the trade-off between safety and efficacy:

$$G_j = \frac{\theta_1 + \theta_2 \log(\log(d_j))}{1 + \exp(\alpha + \beta \log(d_j))}$$

The dose d_j that is recommended for the next cohort is chosen such that it maximizes G_j and that its posterior estimate of toxicity is below or equal to the target toxicity.

For this study, early efficacy will be assessed via residual LMP7 activity (in percent, compared to baseline). LMP7 residual activity will be used in a transformed version, such that the efficacy response for participant i is

$$y_i = -\log\left(\frac{LMP7\ activity\ at\ day\ x\ hour\ z}{LMP7\ activity\ at\ baseline}\right)$$

Similar to the DLT model (Section 15.1), a prior distribution is used for the efficacy model to incorporate prior knowledge/expectations, e.g. from pre-clinical models. This prior knowledge is expressed in terms of pseudo data. For this study, the assumptions are: CCI [redacted] CCI [redacted]. This pseudo data leads to the following prior parameters for the normal-gamma prior distribution for the efficacy model:

- $E(\theta_1) = -0.5566, \quad E(\theta_2) = 0.9349$

The prior precision of the pseudo data is assumed to be Gamma distributed with shape = 1 and rate = 0.025. Just as in Section 15.1, the prior distribution and likelihood are used to calculate the posterior probabilities based on Bayes theorem.

The modeling in this section will be performed in R with crmPack. For illustration purposes, Figure 1 shows a graphical representation of the dual modelling approach, including the gain function, based on the prior parameters. If the DLT model recommends a lower dose than the gain function, the recommendation of the DLT model will be followed.

Note that due to technical restrictions of crmPack, the prior for the DLT model is set up in a slightly different way as in Section 15.1. However, the underlying assumptions are the same for both models.

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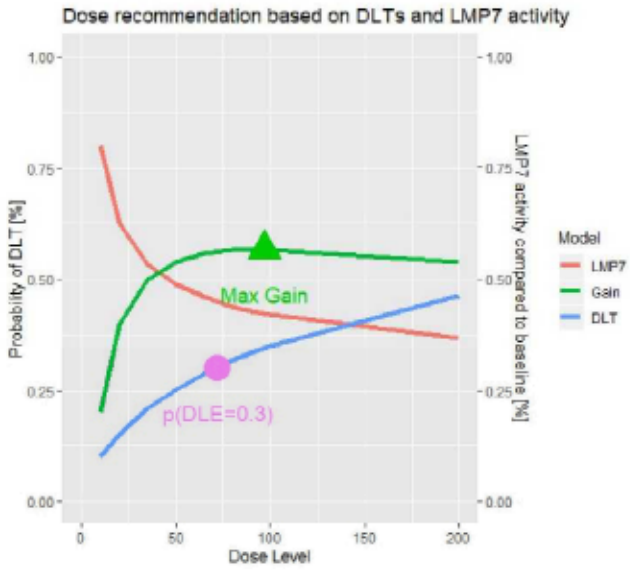

Figure 1 Plot of DLT model, LMP7 model, and gain function for prior parameters

16.3 Pharmacometric modeling analysis

The objective of the Pharmacometric modelling analysis is to perform an explorative analysis for dose escalation, RDE (and if applicable MTD) selection. The following modeling approaches may be used, and the results may be shared with the team and SMC:

- To assess the exposure of M3258, a preliminary Pop PK model may be developed (Section 16.3.1).
- To assess the effect of M3258 concentrations on LMP7 residual activity a preliminary PKPd model may be developed (Section 16.3.2).
- To assess the effect of M3258 on neutrophil suppression a preliminary PK safety model may be developed (Section 16.3.3)
- The data from current study may be pooled with phase 2/3 study data and may be reported separately in a Pharmacometric modeling analysis report (PMAR) (separate analysis plan).

The population PK, PKPd, PK-safety models may be developed after the availability of PKPd data from the first 3 cohorts.

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16.3.1 NLME PK model analysis

16.3.1.1 Objectives

To characterize the exposure of M3258, a NLME approach may be applied integrating PK data from the first 3 cohorts (MS201814-0010) in RRMM patients and subsequent cohorts.

The objectives of this NLMdE PK analysis are:

i. to describe M3258 exposure in RRMM patients,

   a. estimated PK parameters (C_{max}, AUC_{0-24} of Day 1, Cycle 1) up to cohort 3 and project predicted PK parameters at steady state ($C_{max\ ss}$, $C_{trough\ ss}$, AUC_{ss}) for 4th and subsequent cohort's pending data availability.

   b. update PK model in *step a* in subsequent cohorts and project for the next cohorts.

   c. The projected PK parameters may be used by Biostatistics team for further analyses.

ii. to assess interindividual variability (IIV) in PK

   a. preliminary exploratory analysis may be conducted and will be finalized once Phase 2/3 study data become available

iii. to explore and potentially identify covariate effects on IIV.

   a. preliminary exploratory analysis may be conducted and will be finalized once Phase 2/3 study data become available

The pooled NLME PK may be detailed in a separate analysis plan 'Pharmacometric modeling analysis report for M3258' and reported separately.

16.3.2 NLME PKPd model analysis

The objectives of this NLME PKPd analysis may be to

i. characterize the PKPd relationship between M3258 concentration on LMP7 residual activity up to cohort 3 and project predicted Pd parameters for 4th and subsequent cohort's pending data availability

ii. perform simulations utilizing the developed NLME PKPd model assessing the LMP7 residual activity % under different dosing scenarios

The results of the NLME PKPd modeling analysis may be provided in a separate "PMAR for M3258".

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16.3.2.1 LMP7 Residual Activity

The Pd data may be modeled using the LMP7 residual activity measured in the ex- vivo assay (other data transformations may be investigated).

Measured or predicted M3258 concentrations (C_{M3258}) may be used to drive the Pd effect and modeled such that the relationship is adequately captured, e.g. by estimating the parameters of an E_{max} model.

$$LMP7_{ij} = \left(\frac{E_{max,i} \cdot C_{M3258,ij}}{EC50_i + C_{M3258,ij}}\right)$$

with *Emax* the maximum residual activity and *EC50* the drug concentrations producing half-maximal activity in subject *i* at time *j*. A power coefficient (Hill factor) may be added. Other PK/Pd models may be tested as well.

16.3.3 PK Safety

The objectives of this PK safety analysis may be to

i. develop a PKPd model to describe the neutrophil suppression through drug-specific parameters and system-related parameters up to cohort 3 and project predicted Pd parameters for 4th and subsequent cohort's pending data availability and feasibility

ii. perform simulations utilizing the developed NLME PKPd model assessing the % neutrophil suppression under different dosing scenarios

The results of the NLME PKPd modeling analysis may be provided in a separate "PMAR for M3258".

16.3.3.1 Neutrophil Suppression

The Pd data may be modeled to determine the effect of M3258 concentrations on the proliferation of neutrophil count. A neutrophil suppression model such as Friberg et.al, 2002 (5) model may be used. In brief the drug conc is assumed to reduce the proliferation rate or induce cell loss by inhibitory linear function or an E_{max} model.

16.3.4 Assumptions

This NLME analysis may be conducted under the following assumptions:

- Replacing missing actual time of PK and/or Pd sampling by the scheduled time (per protocol) after previous dose, does not impact the overall result.
- Discarding non-first dose with missing actual dosing time as well as PK and/or Pd samples scheduled after this dose, does not impact the overall result.
- All PK parameters will be assumed to be log-normally distributed.

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- The residual unexplained variability will be assumed to be normally distributed after suitable data transformation, if needed.

16.3.5 Data Handling Procedures

The NONMEM input file (NIF, i.e. a database combining PK and Pd data in a specific format) is to be prepared internally under the responsibility of the Pharmacometrics team and provided as .csv file. Additional data pre-processing will be performed by the pharmacometrician using R scripts, if necessary.

16.3.6 Data Assembly Methods and Data Specifications

Pharmacometrics team will assemble the data in collaboration with data management, bioanalytical and clinical pharmacology teams. Draft specification is designed based upon the protocol defined study design. The final specification will be available after 4th cohort.

16.3.7 Handling BLQ and Missing Data

The NLME PK and PK/Pd analysis may be performed with actual dosing and sampling time points.

If the exact dosing time (of a non-first dose) is unknown, this dose and the plasma concentrations related to this dose will be excluded from analysis.

If the exact sampling time point is unknown, the scheduled time point related to the previous dose will be used instead.

The method for handling of BLQ data will be determined by a scientific judgment aligned to the best-established practices (6) and shall be explicitly recorded and stated in the NLME PK analysis report.

Demographic data as assessed at screening (or baseline) will be used. Missing covariate (demographic) data that do not change with time will be replaced by the population median (continuous data) or by the most frequent value in the population (categorical data). If a covariate observation is missing in more than 20% of the subjects, this covariate will be excluded from the analysis, or evaluated after multiple imputation if it is considered critical to the scope of the analysis.

16.3.8 Exploratory statistical and graphical data analysis

Prior to the modelling activities exploratory graphical and statistical data summaries will be created to gain a better understanding of the underlying study population, the studied PK and Pd data informing the structural model development process and candidate covariate explorations. For more details see Appendix 18.1.

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16.3.9 Overall Modeling Methodology

The parameters of the NLME PK and PKPd model will be estimated using NONMEM version 7.3 software. Further technical details (e.g., assessment of model stability and criteria for model selection) and software that will be used are given in Appendix 18.1 of this iAP.

The final NLME PK model development based on combined FIH and subsequent future study data will be detailed in a separate modeling and simulation analysis plan.

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18 Appendices

18.1 Details on Pharmacometric Analysis

This document contains technical details that are related to the NLME PK and PK/Pd analyses of M3258.

18.1.1 Software

The software package NONMEM (version 7.3.0) (Beal SL and Sheiner LB, 1992) (7) will be used for the NLME PK and PK/Pd analyses, installed on six HP BL 460 C Servers with two Intel® Xeon® E5-2650 v2 octacore processors (speed 2.60 GHz) and with 64 Gb RAM each and the LINUX (Novell SLES11 (64-bit) SP3) operating system, with CPU allocation controlled by a Univa Grid Engine (version 8.2). The NONMEM runs on the servers will be organized by Perl-speaks-NONMEM (PsN, version 4.4.8, http://psn.sourceforge.net/index.php), that will also be used to aid the development of the nonlinear mixed-effect models using NONMEM. The used Fortran compiler will be GNU Fortran (gcc version 4.7.2, http://gcc.gnu.org/fortran). Pirana software (version 2.9.2; http://www.pirana-software.com/) will be used to organize the runs and produce runs summary. The statistical, R (http://www.r-project.org/ version 3.2.2 or higher), as well as 'Xpose4' (version 4.5.3 or higher; http://xpose.sourceforge.net/) and/or 'Xpose' (version 0.4.3; https://github.com/UUPharmacometrics/xpose) will be used for the exploratory analysis and post-processing of NONMEM output, for example to assess the goodness-of-fit. The integrated development environment RStudio Server (version 0.99.486 or higher) will also be used. All preceding software are installed in a validated GxP environment. R (Simulx R package [*mlxR* version 2.2.0 or higher]) and/or NONMEM will be used to perform simulations.

18.1.2 Modeling Methodology

Estimation methods in NONMEM will be first-order conditional (FOCE) with additive or log-additive models for the residual unexplained variability (RUV) and first-order conditional with interaction (FOCEI) with proportional or additive + proportional models for the RUV (U. Wahlby et al, 2001; U. Wahlby et al, 2002) (8,9), if supported by the data. If a method is implemented to estimate the likelihood of BLQ data, the Laplacian method will be required. Additional methods including stochastic approximation expectation maximization (SAEM) and importance sampling may be applied to overcome numerical difficulties in model convergence, if necessary.

Precision of parameter estimates will be assessed by the covariance matrix, derived from the Fisher information matrix obtained in the covariance step. In case of numerical difficulty to estimate this matrix, confidence intervals of parameter estimates will be obtained by a bootstrap method.

Stability of NONMEM models will be assessed on the basis of some of the following criteria:

- Acceptable basic goodness of fit plots (i.e. values randomly scattered around the line of identity)
- Number of significant digits ≥ 3 for all estimated parameters

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- Successful covariance step. If successful covariance step is missing, a nonparametric bootstrap ($n \geq 10$) will be applied to obtain an estimate of parameter precision (standard error, SE)
- Model parameter estimates not close to a boundary
- Condition number (ratio of largest to smallest eigenvalue) < 1000
- Correlation less than 0.95 between any two parameters
- Stability of final solution for base model to perturbations of the initial values

Model selection will be based on:

- The comparison of full vs. reduced models is based on the Log-Likelihood Criterion: the difference in the minimum value of the objective function between hierarchical models is asymptotically chi-square distributed with degrees of freedom equal to the difference in number of parameters between the full and reduced models. A reduction in the objective function value (OFV) ≥ 10.83 (one degree of freedom), corresponding to $p<0.001$, will be used.
- Non-nested models will be compared using standard likelihood-based methods, e.g. -2 times the maximized log likelihood or AIC.
- Decrease in unexplained variability. Extension of a model by adding independent variables should usually be accompanied by a decrease in random inter- and/or intra individual variability.
- Goodness of fit plots, e.g. relevant residuals against time randomly distributed around zero.
- Scientific/(patho)physiologic plausibility of the model and the 95% confidence interval does not include the NULL value.

18.1.2.1 NLME PK and PK/Pd Modeling

The general procedure that will be followed for the development of the NLME PK and PK/Pd models is outlined below:

- Exploratory Data Analysis
- Structural Model Development
- Statistical Model development
- Preliminary Covariate Analysis

Upon the availability of subsequent study data following analysis steps will be performed: (i) Covariate analysis, (ii) model refinements, (iii) sensitivity analysis as well as (iv) model evaluations. For details refer to the 'modeling and simulation analysis plan' of M5049.

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18.1.2.1.1 Exploratory Data Analysis

Prior to the NLME PK and PK/Pd analyses, the following outputs will be produced as part of the exploratory data analyses:

- Summary statistics of the dependent variables and study population characteristics (demographics, covariates) at baseline
- Scatterplots of dependent variables versus time by dose group/cohort;

Further exploratory analyses may be performed. These will be fully described in the separate 'modeling and simulation analysis report' of M3258.

18.1.2.1.2 Structural Model Development

Different structural PK (e.g., one- or two-compartment model with first order linear absorptions and elimination) and Pd models (e.g., Emax model) will be evaluated as necessary and if the data set allows.

Goodness-of-fit of the structural model will be assessed by diagnostic plots:

- Observations versus population, and versus individual predictions and/or log-log plots
- Population, individual and conditional weighted residuals versus time
- Above plots stratified by dose group/cohort and/or significant covariates, if necessary
- Visual predictive checks (VPCs) (Bergstrand et al, 2011) (10)

18.1.2.1.3 Statistical Model Development

Additive, log-additive, proportional and additive + proportional error models will be explored for the RUV. Exponential variability models will be explored for IIV in PK and additive and/or exponential variability models will be explored for IIV in Pd model parameters. As a start diagonal Ω-structure (variance-covariance matrix of the deviation of individual values from population means for the various model parameters) will be employed, the inclusion of off-diagonal elements will be investigated subsequently.

If required, inter-occasion variability (IOV) will be modeled as described in Karlsson and Sheiner, 1993 (11).

The goodness of fit and appropriateness of the random effects models will be assessed by means of diagnostic plots as mentioned in the previous section as well as:

- Plots of observations versus time with population and individual fits
- Histogram of (random effects) ETA estimates
- Correlation-plots of individual ETA estimates
- (Absolute) individual weighted residuals versus individual predictions
- (Conditional) weighted residuals versus time
- Histogram of population and individual weighted residuals

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18.1.2.1.4 Preliminary Covariate Analysis

Dependent on the data availability and informativeness (i.e. range/distribution of covariates in study 0001), graphical explorations will be performed to identify potential covariate relationships on PK and/or Pd parameters. A full covariate analysis is planned in a later stage using both FIH and subsequent future study data and will be detailed in the 'modeling and simulation analysis plan' of M3258.

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