Statistical Analysis Plan

Protocol OP-106

A Single Arm, Open-Label, Phase 2 Study of Melflufen in Combination with Dexamethasone in Patients with Relapsed Refractory Multiple Myeloma who are Refractory to Pomalidomide and/or an anti-CD38 Monoclonal Antibody

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DOCUMENT HISTORY

Version	Modified by	Description of Changes
Version 1.0 20 Sep 2017	Biostatistics Consultant, Precision for Medicine	Initial version
Version 2.0 19 Jul 2019	Biostatistics Consultant, Precision for Medicine	Updates for protocol amendment 6, 2019-03-04 Triple-class refractory added as a subgroup of specific interest in all analyses.
Version 3.0 07 Jan 2020	Sr Project Statistician, Oncopeptides AB	General restructuring of document. Discussion on available therapies and expected treatment effect added. Clarification of objectives and endpoints in relation to scientific rationale for NDA submission. Clarification on use of triple-class refractory as main subgroup for analyses. EMD added as a subgroup of specific interest for some analyses. Clarification of analytical definitions.
Version 4 26 Feb 2020	Director of Biostatistics, Oncopeptides AB	Clarification of definitions for analysis populations. Clarification of threshold used for establishing efficacy. Clarification on scope for Clinical Study Report.

LIST OF ABBREVIATIONS

Abbreviation or Term	Definition
ADaM	Analysis Data Model
AE	adverse event
AESI	adverse event of special interest
ALT (SGPT)	alanine aminotransferase
ANC	absolute neutrophil count
AST (SGOT)	aspartate aminotransferase
ATC	Anatomical/Therapeutic/Chemical
BSA	body surface area
C1D1	Cycle 1 Day 1
CBR	clinical benefit rate
CDISC	Clinical Data Interchange Standards Consortium
CM	concomitant medication
CR	complete response
CrCl	creatinine clearance
CRF	case report form
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
dFLC	difference in serum free light chains
DOR	duration of response
DSMC	Data Safety Monitoring Committee
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EMD	extramedullary disease
FAS	Full analysis set
FDA	Food and Drug Administration
FISH	fluorescent in situ hybridization
IMiD	immunomodulatory drug

Abbreviation or Term	Definition
IMWG-URC	International Myeloma Working Group-Uniform Response Criteria
IRC	independent review committee
ISS	international staging system
ITT	intention-to-treat
kg	kilogram(s)
K-M	Kaplan-Meier
LDH	lactase dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram(s)
min	minute
M-protein	monoclonal protein spike
MM	multiple myeloma
MR	minimal response
NCI	National Cancer Institute
NDA	new drug application
NE	not evaluable
ORR	overall response rate
OS	overall survival
PD	progressive disease
PFS	progression free survival
PI	proteasome inhibitor
PR	partial response
PT	preferred term
QoL	quality of life
QT	Interval of time from the start of the Q wave to the end of the T wave
QTcF	Fridericia's formula for the interval of time from the start of the Q wave to the end of the T wave, corrected for heart rate
RR	interval of time between QRS complexes
RRMM	relapsed and refractory multiple myeloma
SAE	serious adverse event

Abbreviation or Term	Definition
SAP	statistical analysis plan
sCR	stringent complete response
SD	standard deviation; stable disease (depending on context)
SDG	(WHO DD) Standardized Drug Groupings
SDTM	Study Data Tabulation Model
sFLC	serum free light chain
SMQ	standardized MedDRA query
SOC	system organ class
SPEP	serum protein electrophoresis
TEAE	treatment emergent adverse event
TTNT	time to next treatment
TTP	time to progression
TTR	time to response
ULN	upper limit of normal range
UPEP	urine protein electrophoresis
VGPR	very good partial response
WBC	white blood cell count
WHO	World Health Organization

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1 INTRODUCTION

This statistical analysis plan (SAP) was prepared in accordance with version 7.0 (amendment 6) of the protocol for study OP-106, dated 4 March 2019. It specifies the main safety and efficacy analyses to be performed for the clinical study report (CSR).

Any changes that are made to the planned analyses after the SAP is finalized, along with an explanation as to when and why they occurred, will be noted in the CSR produced for the study. Any changes made to the planned analyses that are in the protocol are summarized in section 10.5 of this document.

2 OVERVIEW OF STUDY DESIGN

This is a single arm, open-label, Phase 2 multicenter study which will enroll patients with relapsed and refractory multiple myeloma (RRMM) following at least 2 lines of prior therapy, including a drug classified as an immunomodulatory drug (IMiD) and a drug classified as a proteasome inhibitor (PI), and who are refractory to pomalidomide and/or an Anti-CD38 Monoclonal Antibody. Refractory is defined in Section 8.4 of this SAP. A total number of approximately 150 patients are planned to be enrolled in the study, to achieve 130 patients evaluable for efficacy, and 50 patients evaluable for EQ-5D-3L.

Patients will be treated with melflufen 40 mg on Day 1 and dexamethasone 40 mg on Days 1, 8, 15 and 22 of each 28-day cycle. Patients ≥ 75 years of age will have a reduction of the starting dose of dexamethasone from 40 mg to 20 mg on the same schedule.

Patients may receive treatment until there is documented disease progression, unacceptable toxicity or the patient/treating physician determine it is not in the patient's best interest to continue.

Dose modifications and delays in therapy may be implemented based on patient tolerability as detailed in the protocol.

The initial study design proposed to enroll patients refractory to pomalidomide and patients refractory to daratumumab (an anti-CD38 mAb) separately to evaluate clinical benefit in both groups, with a target enrollment of up to approximately 39 efficacy-evaluable (per protocol section 11.4.2.1, different from the definition in section 6.1) patients per group. However, the study was later amended (in protocol version 5, 31 May 2018) to assess the total population and expand the sample size to encompass approximately 150 patients. Based on regulatory considerations, a subgroup of specific interest was subsequently (in protocol version 7, 4 March 2019) identified, i.e., triple-class refractory patients defined as patient's refractory to all 3 currently approved classes of drugs (IMiDs, PIs and anti-CD38 mAbs). This group was identified as having an unmet medical

need, potentially allowing FDA accelerated approval based on ORR and DOR in a single arm study. In addition, based on preliminary signals of efficacy in a population with poor prognosis, extramedullary disease (EMD) was also identified as a subgroup of specific interest.

The study rationale is summarized in section 2.3 of the protocol. See sections 10.4 and 10.5.3 of this document regarding the decision to increase the sample size and to focus on triple-class refractory as a subgroup of primary interest.

3 AVAILABLE THERAPIES AND EXPECTED TREATMENT EFFECT

Currently, there are no treatments for patients with triple-class RRMM which have received FDA regular approval. Patients who are refractory to 5 drugs (penta-refractory) can receive selinexor, but a confirmatory trial and regular FDA approval are pending for this drug, and thus selinexor is not considered to be “available therapy”. Other options for these patients are clinical trials of experimental regimens, retreatment with agents belonging to drug classes to which their disease has already progressed (relapsed or refractory to the last treatment) or hospice/palliative care.

The different treatment options after becoming refractory to anti-CD38 mAb were assessed in a retrospective study [Gandhi, 2019]. None of the 10 assessed treatment regimens provided a durable benefit to the patients after anti-CD38 mAb-refractoriness.

In a 2017 publication, an overall response rate (ORR) less than 15% was observed in RRMM patients who were re-treated with an IMiD or PI after becoming refractory to an IMiD and a PI. The ORR decreased as patients received more lines of treatment after becoming relapsed-refractory. [Kumar 2017].

Patients who become refractory to the major classes of available anti-myeloma therapies have very poor outcomes. Therefore, there is an urgent need for new therapies for patients with RRMM who have exhausted available therapies.

Accordingly, an ORR of at least 15% would represent a clinically relevant treatment effect.

4 STUDY OBJECTIVES AND ENDPOINTS

4.1 Primary Objective

The primary objective of this Phase 2 study is to evaluate the efficacy of melflufen treatment in RRMM patients.

4.1.1 Primary Endpoint

- Overall response rate (ORR).

4.2 Key Secondary Objectives

The secondary objectives of this study are to evaluate the following aspects, listed below by order of relevance:

- Safety and tolerability of melflufen,
- Duration of response (DOR).

4.2.1 Safety and Tolerability Endpoints

- Frequency and grade of treatment emergent adverse events (TEAEs),
- Frequency and grade of TEAEs of special interest,
- Frequency of TEAEs leading to dose modifications,
- Frequency of melflufen dose modifications based on study drug exposure,
- Treatment duration of melflufen,

4.2.2 Key Secondary Efficacy Endpoints

- DOR.

4.3 Other Secondary Objectives

Other objectives of this study are to assess the following aspects, listed below by order of relevance:

- Progression free survival (PFS),
- Overall survival (OS),
- Clinical benefit rate (CBR),
- Distribution of response categories,
- Time to response (TTR),
- Time to progression (TTP),
- Change in relevant laboratory parameters,
- Functional status and well-being.

4.3.1 Other Secondary Endpoints

- PFS,
- OS,
- Proportion of patients per categories of best response; i.e. stringent CR (sCR), complete response (CR), very good partial response (VGPR), partial response (PR) or minimal response (MR),
- TTR,
- TTP,
- Duration of stable disease,
- Duration of disease stabilization,
- Duration of clinical benefit,
- Change from baseline in levels of serum and urine monoclonal protein spike (M-protein),
- Change from baseline in levels of platelet count and absolute neutrophil count (ANC),
- Change from baseline in QLQ-C30 assessment,
- Change from baseline in EQ-5D-3L assessment.

5 DETERMINATION OF SAMPLE SIZE

A total number of approximately 150 patients are planned to be enrolled in the study, to achieve 130 patients evaluable for efficacy, and 50 patients evaluable for EQ-5D-3L. The protocol hypothesizes an observed ORR of 30%, and an exact 95% confidence interval from 22.3% to 38.7%, given a sample size of 130 patients.

The sample size assumes that an ORR of 15% to 30% should warrant a positive benefit-risk ratio in RRMM, in context of available treatment alternatives for these heavily pre-treated patients with a high unmet medical need. Such ORR have previously been evaluated for Accelerated Approval by FDA [FDA review of selinexor] [Chen, 2019].

The targeted effect size along with a satisfactory DOR is expected to satisfy three regulatory goals needed for accelerated approval:

1) demonstrating a clinically meaningful ORR and DOR,
2) demonstrating an advantage over available therapy, and

3) establishing the contribution of melflufen to the melflufen-dexamethasone combination.

In this setting, an ORR of at least 15% and a strong DOR would represent a clinically meaningful treatment effect. Because there is currently no approved treatment meeting the regulatory standard of “available therapy” in this setting, and no established off-label use of drugs that could be regarded as standard of care, the targeted results would also demonstrate an advantage over available therapy. Finally, an ORR of at least 15% would represent a statistically significant difference from ORR reported for treatment with dexamethasone alone (i.e. ORR 2% for 4 mg dose to 4% for 40 mg dose) [Spicka 2019] [POMALYST label] and thus establish the contribution of melflufen to the melflufen-dexamethasone combination.

With a sample size of 110 to 150 patients and an observed ORR of 15%, 20%, 25% or 30%, the corresponding exact 95% confidence interval (Clopper-Pearson method) [Fleiss, 1981] would be ± 7% to 10%, see Table 1.

Table 1: Exact binomial confidence intervals for ORR per sample size

Sample size	n=110	n=120	n=130	n=140	n=150
ORR=15%	9% to 23%	9% to 23%	9% to 22%	10% to 22%	9% to 21%
ORR=20%	13% to 29%	13% to 28%	14% to 28%	14% to 28%	14% to 27%
ORR=25%	17% to 34%	18% to 34%	18% to 33%	18% to 33%	18% to 32%
ORR=30%	22% to 40%	22% to 39%	22% to 39%	23% to 38%	23% to 38%

The sample size calculations cover a range of sample sizes that are applicable both for the total study population and the triple-class refractory population. The expected number of triple-class refractory patients is approximately 2/3 to 3/4 of enrolled patients, i.e. approximately 105 to 120 patients.

The primary endpoint will be considered met if the lower bound of the 95% confidence interval for actual ORR among triple-class refractory patients is higher than 15%.

6 ANALYSIS POPULATIONS

6.1 Analysis Sets

The Full analysis set (FAS) is defined as all patients who fulfil all eligibility criteria at screening and prior to initiation of therapy as per study protocol section 7.2, and according to intention-to-treat principle as per ICH E9. The FAS will be used for summaries of disposition and all analyses of efficacy.

The Safety analysis set is defined as all subjects who received at least one dose of melflufen or dexamethasone. The Safety analysis set will be used for all analyses of safety.

The Efficacy evaluable analysis set as defined in the protocol will not be used for any analyses.

6.2 Subgroups of Specific Interest

Patients that are triple-class refractory, as defined in section 8.4.3, will be the primary subgroup of interest. This subgroup constitutes the majority of patients and will be used for all analyses of efficacy and safety. Triple-class refractory is the proposed indication for the new drug application (NDA) for accelerated approval.

An additional, secondary subgroup of specific interest specified in this SAP, based on preliminary signals of efficacy, are patients with extramedullary disease (EMD), as defined in section 8.4.9. This additional subgroup will be presented separately for selected analyses.

7 DATA MANAGEMENT

7.1 Data Cut-Off

The data cut-off date for the Clinical Study Report (CSR) will be at least 3 months after first administration of melflufen to the last patient enrolled.

Data pertaining to any assessments performed as part of a visit per that date, and any AE or CM starting or ending before or on that date will be included in the database for the CSR.

7.2 Data Validation and Database Lock

Following data cut-off for the CSR, the data will be validated and subject to database lock procedures according to the Data Management Plan (DMP). A final database lock will be performed after additional data pertaining to long term follow-up of QLQ-C30, EQ-5D-3L, PFS and OS has been collected.

Prior to any analysis, the study data will be reviewed for any data inconsistencies and major protocol deviations. Any data inconsistencies remaining after review will be documented according to the DMP and Clinical Data Interchange Standards Consortium (CDISC) requirements. Any changes made regarding analysis sets or analytic definitions will be documented and referred to in the CSR.

7.3 Data Standards

Study datasets will be developed according to CDISC Study Data Tabulation Model (SDTM) Implementation Guide Version 3.2. All datasets used for the analyses and presentations of summary results will be developed according to CDISC analysis data model (ADaM) Implementation Guide Version 1.1. The source data for all ADaM datasets will be SDTM datasets.

8 ANALYTIC DEFINITIONS

Definitions of terms used for the calculation of derived variables and general terms used for the analyses are provided in this section.

8.1 General

8.1.1 Study Day 1

Study Day 1 corresponds to the date of the first dose of any study drug.

8.1.2 Study Day

Unless otherwise specified, the timing of all study-related events, assessments, and interventions will be calculated relative to Study Day 1. For events, assessments, and interventions after Study Day 1, study day represents the elapsed number of days from Study Day 1, inclusive:

Study Day n = (Date of assessment – Date of Study Day 1) + 1 day

Study Day −1 will be the day before Study Day 1, and in general for assessments prior to Study Day 1, study day is defined as:

Study Day n = (Date of assessment – Date of Study Day 1)

For listings (such as for adverse events) that include the derivation of “days since last dose,” this is defined as event date – date of last dose. Events that occur on the same day as the last dose of study drug will therefore be described as occurring zero days from the last dose of study drug.

8.1.3 Baseline

Unless otherwise specified, the baseline value is defined as the most recent assessment prior to administration of the first dose of study drug, melflufen or dexamethasone.

8.1.4 Unscheduled Visits

All results not taken at a scheduled timepoint are unscheduled. Unscheduled assessments are labelled as 'Unscheduled' in the listings and will include the study day from first dose of all dates.

Because unscheduled assessments are not associated with any scheduled timepoint, they are excluded from all summaries by timepoint. Unscheduled assessments will be considered when deriving myeloma response parameters as described in section 8.6.

The study protocol accepts a time window of ± 3 days for scheduled visits and assessments (visit window). In the event multiple protocol-specified assessments are reported within the same visit window the value reported for the scheduled visit should be used in summaries by timepoint, and if this value is missing or unknown the earliest reported value of scheduled and unscheduled assessments within the visit window should be used. Derivations using multiple assessments should be based on assessments from the same visit.

8.1.5 Duration

Duration can be expressed in days, weeks, months, years, or minutes as appropriate.

- **Days** – Duration expressed in days between one date (date1) and another later date (date2) are calculated using the following formula:

  duration in days = (date2- date1+1).

- **Weeks** – Durations expressed in weeks between one date (*date1*) and another later date (*date2*) are calculated using the following formula:

  duration in weeks = (date2-date1+1)/7.

- **Months** – Durations expressed in months between one date (*date1*) and another later date (*date2*) are calculated using the following formula:

  duration in months = (date2-date1+1)/30.4375.

- **Years** – Durations expressed in years between one date (*date1*) and another later date (*date2*) are calculated using the following formula:

  duration in years = (date2-date1+1)/365.25.

- **Minutes** – Durations expressed in minutes between one timepoint (*time1*) and another later timepoint (*time2*) are calculated using the following formula: duration in minutes = (time2-time1)/60.

8.2 Medical Coding

8.2.1 MedDRA

Events recorded as medical history or adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 19.1. Preferred term (PT) and system organ class (SOC) will be summarized.

8.2.2 WHO Drug Dictionary

All prior systemic cancer therapies as recorded on the Multiple Myeloma History - Prior Systemic Cancer Drug Therapy CRF page and prior and concomitant medications as recorded on the Concomitant Medications CRF will be coded using WHO Drug Dictionary (WHO DD) Enhanced version December 2016 B2. Medications are coded to Anatomical/Therapeutic/Chemical (ATC) drug class level 4 and preferred drug names. If ATC drug class level 4 coded is unavailable, level is used; if level 3 coding is unavailable, level 2 is used.

8.3 Patient Characteristics

8.3.1 Age

Age is calculated as the integer duration from the date of birth to the date of informed consent, if age is not recorded in the electronic case report form (eCRF). Age will be categorized as <65, 65 - <75, and ≥75 (years).

8.3.1 Geographic Region

Geographic location of study site will be categorized as United States of America and Rest of World. Rest of World is defined as all other countries.

8.4 Disease Characteristics

8.4.1 Time Since Initial Diagnosis

Time since initial diagnosis in years at study entry will be defined as duration from diagnosis to first dose of study. Partial dates will be imputed according to section 10.1.

8.4.2 Prior and Concomitant Medications

Concomitant medications are defined as medications with start date or end date on or after the date of first dose and start date before the date of the last dose + 30 days or are ongoing at the time of first dose. Prior medications are defined as medications with a stop date before the date of first dose of study drug.

For the purpose of determining if a medication should be noted as a concomitant medication, the imputation rules stated in section 10.1 will be used. Imputed dates will not be presented in the listings.

Patients may have more than one medication per ATC level and preferred name. At each level of patient summarization, a patient is counted once if he/she reported one or more medications at that level.

Transfusions will be defined as WHO DD preferred names of “Platelets” or “Red blood cells”. Growth factor agents will be defined as WHO DD Standardized Drug Groupings (SDG) “Colony stimulating factors”.

8.4.1 Therapeutic Drug Classes

PI is defined as WHO DD SDG “Antineoplastic proteasome inhibitors”.

IMiD is defined as SDG “Antineoplastic thalidomide analogues”.

Anti-CD38 mAb is defined as SDG “Antineoplastic CD38 antigen inhibitors”.

Other mAb is defined as SDG “Monoclonal antibodies – antineoplastics” excluding SDG “Antineoplastic CD38 antigen inhibitors”.

Alkylators is defined as SDG “Antineoplastic alkylating drugs”.

Other antineoplastic drugs for the treatment of multiple myeloma will be referred to as ‘Other’.

Any experimental or investigational drugs that are not covered by WHO DD will be reviewed manually and classified as one of the above therapeutic drug classes if applicable. Classifications will be documented as part of database lock procedures and further described in the CSR.

8.4.2 Prior Regimens

A prior regimen is defined as one or more cycles of a planned treatment program that is considered prior in accordance with exclusion criteria 11 study protocol. This may consist of one or more planned cycles of single-agent therapy or combination therapy, as well as a sequence of treatments administered in a planned manner. For example, a planned treatment approach of induction therapy followed by autologous stem cell transplantation, followed by maintenance is considered one regimen. A new regimen starts when a planned course of therapy is modified to include other treatment agents (alone or in combination) as a result of disease progression, relapse, or toxicity. A new

regimen also starts when a planned period of observation off therapy is interrupted by a need for additional treatment for the disease. [Rajkumar 2011]

Number of prior regimens per patient will be the 'Total Lines of Therapy' as reported by investigator on the Multiple Myeloma History – Prior Systemic Cancer Therapy Summary CRF.

8.4.3 Refractory Status

A patient is defined as refractory to a drug within a prior regimen if the patient fulfills any of the following criteria [Rajkumar 2011]:

1. Reason for termination was PD
2. Best response was PD or SD
3. Relapse or progression occurred within 60 days from last administration

Double-class refractory is defined as refractory to at least one PI and at least one IMiD.

Triple-class refractory is defined as refractory to at least one PI, at least one IMiD, and at least one Anti-CD38 mAb. A patient is defined as intolerant to a specific therapeutic drug class if the patient discontinued the drug due to toxicity, and did not receive a drug in the same therapeutic drug class again prior to entering the current study.

Triple-class refractoriness and intolerance will undergo a manual review and reconciliation of available data reported of prior antimyeloma therapy, date of discontinuation, reason for discontinuation as progression or toxicity date of progression as reported on the Refractory History, Multiple Myeloma History - Prior Systemic Cancer Therapy, or Multiple Myeloma History - Prior Systemic Cancer Drug Therapy CRFs. Classifications will be documented as part of database lock procedures and further described in the CSR.

8.4.4 Transplants

A front-line transplant is defined as the transplant indicated for the first line of therapy. This can be single or tandem transplant. Planned tandem autologous or autologous-allogeneic are considered as one transplant.

A salvage transplant is defined as any transplant given following failure of front-line therapy. Planned tandem autologous or autologous-allogeneic are considered as one transplant.

Time from autologous transplant to relapse is the duration in years from date of transplant (or date of first transplant if given in tandem) to date of relapse. Time from autologous transplant to relapse will be categorized as <1 year, 1 - <1.5 years, 1.5 – 2 years, >2 years.

8.4.5 Cytogenetic Risk Groups

Genetic subtypes from cytogenetics analysis by fluorescence in situ hybridization (FISH) will be categorized into risk groups as follows [Sonneveld 2016]:

- High-risk group: consists of patients who have the genetic subtype t(4; 14), t(14:16), deletion 17p, gain 1q (+1q), t(14,20).[1]
- Standard-risk group: consists of patients who have a genetic subtype recorded but none of the genetic subtypes categorized as high-risk
- Unknown: consists of patients for whom the FISH procedure was not done or unevaluable.

8.4.6 International Staging System (ISS)

ISS Stage and Revised ISS (R-ISS) Stage will be derived [Palumbo, 2015], see Table 2.

ISS will be derived from serum β2 microglobulin and albumin. This derived ISS will in turn be used with serum lactase dehydrogenase (LDH) and high-risk cytogenetics as defined by the R-ISS guidelines to derive R-ISS.

[1] The addition of subtypes gain 1q (+1q), t(14,20) were added to the IMWG definition of high risk cytogenetics [Sonneveld 2016] as an update to initial IMWG guideline [Rajkumar 2011]. As this definition was changed during the study and the protocol did not require testing of the additional high-risk cytogenetic abnormalities, these additional subtypes may be underrepresented.

Table 2: Standard Risk Factors for MM and the Revised ISS (R-ISS)

Standard Risk Factors for MM and the Revised -ISS (R-ISS)	
Prognostic Factor	**Criteria**
ISS Stage	
Stage I	Serum B2-microglobulin < 3.5 mg/L, serum albumin ≥ 3.5 g/dL
Stage II	Not ISS stage I or III
Stage III	Serum B2-microglobulin ≥ 5.5 mg/L
Chromosomal abnormalities (CA) by interphase by florescent in situ hybridization (iFISH)	
High-Risk	Presence of del(17p) and/or translocation of t(4:14) and/or translocation of t(14:16)
Standard-Risk	No high-risk CA
Lactase Dehydrogenase (LDH)	
Normal	Serum LDH < upper limit of normal (ULN)
High	Serum LDH > ULN
A new model for risk stratification of MM R-ISS	
Stage I	ISS stage I and standard-risk CA by iFISH and normal LDH
Stage II	Not R-ISS stage I or III
Stage III	ISS stage III and either high-risk CA by iFISH or LDH

ISS as reported in CRF will be referred to as 'ISS' {I, II, III, Unknown, Not Done};

ISS as derived will be referred to as 'Derived ISS' {I, II, III, Unknown, Not Done};

R-ISS as reported on the CRF will be referred to as 'R-ISS' {R-I, R-II, R-III, Unknown, Not Done}.

R-ISS as derived will be referred to as 'Derived R-ISS' {R-I, R-II, R-III, Unknown, Not Done}.

8.4.7 Monoclonal Protein Spike (M-protein)

M-protein is assessed from serum and urine protein electrophoresis test (SPEP/UPEP), and/or serum free light chain (sFLC).

Measurable M-protein at screening and baseline are defined as follows:

- Measurable SPEP is defined as M-protein ≥ 0.5 g/dL.[2]

[2] IMWG defined measurable serum M-protein as ≥ 1.0 g/dL [Rajkumar 2011].

- Measurable UPEP is defined as M-protein ≥ 200 mg/24 hr.
- Measurable sFLC is defined as involved FLC ≥ 10 mg/dL with abnormal Kappa/Lambda ratio (defined as values outside 0.26-1.65).

If the sFLC kappa/lambda ratio is >1.65, kappa is the involved sFLC, and lambda is the uninvolved sFLC. If the kappa/lambda ratio is <0.26, lambda is the involved sFLC, and kappa is the uninvolved sFLC. Difference in sFLCs (dFLC) is defined as (Involved sFLC – Uninvolved sFLC) and is used for response assessment according to IMWG [Rajkumar 2011].

Maximum percent decrease of M-protein or dFLC as summarized in waterfall plots is defined as maximum decrease from baseline to lowest level (nadir) per patient divided by baseline level, expressed as percent. Maximum percent decreases of less than -100% will be set to -100%.

When estimating maximum percent decrease; If both SPEP and UPEP are measurable at baseline, SPEP will be used. If only SPEP is measurable, SPEP will be used. If only UPEP is measurable UPEP will be used. If neither SPEP and UPEP are measurable, FLC will be used.

8.4.8 Plasma Cell Involvement

Bone marrow plasma cell involvement (%) as assessed by aspiration and biopsy will use the higher value in cases of discrepancy and referred to as maximum plasma cell involvement. Maximum plasma cell involvement will be categorized as (<30%, 30 - <60%, ≥60%).

8.4.9 Presence of Bone Lesions and Extramedullary Disease (EMD)

Presence of bone lesions and/or EMD at baseline will be defined following a manual review and reconciliation of available data reported as investigator assessments of imaging and M-protein laboratory results. Classifications will be documented as part of database lock procedures and further described in the CSR.

8.5 Myeloma and Safety Laboratory Assessments (Hematology, Coagulation, and Serum Chemistry)

8.5.1 Unit Conversion

Reported units will be converted to standard units according to CDISC controlled terminology using the conversion factors shown in Table 3.

Table 3. Conversion factors for laboratory units

Analyte	Original reported unit	Standard unit	Conversion factor
Myeloma Laboratory Assessments			
Urine Monoclonal Protein Spike	mg/24hrs	mg/day	1
Serum Monoclonal Protein Spike	g/dL	g/dL	1
Kappa/Lambda Free Light Chain	Ratio	RATIO	1
Beta-2 Microglobulin	mg/dL	mg/L	Multiplied by 10
Immunoglobulins (A, D, E, G, M), Kappa Free Light Chain, Lambda Free Light Chain,	mg/dL	mg/dL	1
Hematology			
WBC differentials (Basophils, Eosinophils, Monocytes, Lymphocytes, Neutrophils)	%	%	1
Platelets, WBC and WBC differentials (Basophils, Eosinophils, Monocytes, Lymphocytes, Neutrophils)	10^9/L, x10^9/L, K/µL, K/CUMM, x10^3/µL, K/mcL	10^9/L	1
Platelets, WBC and WBC differentials (Basophils, Eosinophils, Monocytes, Lymphocytes, Neutrophils)	/uL, cells/mm3, cells/µL, cells/uL	10^9/L	Divided by 1000
RBC	10^12/L, x10^12/L, M/µL, M/CUMM, MIL/CUMM, x10^6/µL, M/mcL	10^12/L	1
RBC	/uL, cells/mm3, cells/µL, cells/uL	10^12/L	Divided by 1000000
Hematocrit	%	%	1

Analyte	Original reported unit	Standard unit	Conversion factor
Hemoglobin	g/L	g/L	1
Hemoglobin	g/dL	g/L	Multiplied by 10
Serum Chemistry			
ALT, AST, ALP, LDH	U/L, IU/L	U/L	1
Albumin	g/L	g/L	1
Albumin	g/dL	g/L	Multiplied by 10
Bicarbonate/CO2, Chloride, Potassium, Sodium	mmol/L	mmol/L	1
Bicarbonate/CO2, Chloride, Potassium, Sodium	mEq/L	mmol/L	1
Total Bilirubin	umol/L, µmol/L	umol/L	1
Total Bilirubin	mmol/L	umol/L	Multiplied by 1000
Total Bilirubin	mg/dL	umol/L	Multiplied by 17.1037
Calcium	mmol/L	mmol/L	1
Calcium	mg/dL	mmol/L	Multiplied by 0.2495
Creatinine	umol/L, µmol/L	umol/L	1
Creatinine	mg/dL	umol/L	Multiplied by 88.4017
Creatinine	mmol/L	umol/L	Multiplied by 1000
Glucose	mmol/L	mmol/L	1
Glucose	mg/dL	mmol/L	Multiplied by 0.05556
Glucose	g/L	mmol/L	Multiplied by 5.556
Magnesium	mmol/L	mmol/L	1
Magnesium	mEq/L	mmol/L	Multiplied by 0.5
Magnesium	mg/dL	mmol/L	Multiplied by 0.4114
Phosphate	mmol/L	mmol/L	1
Phosphate	mg/dL	mmol/L	Multiplied by 0.3226
Total Protein	g/L	g/L	1

Analyte	Original reported unit	Standard unit	Conversion factor
Total Protein	g/dL	g/L	Multiplied by 10
Uric Acid/Urate	umol/L, µmol/L	umol/L	1
Uric Acid/Urate	mg/dL	umol/L	Multiplied by 59.4849
Uric Acid/Urate	mmol/L	umol/L	Multiplied by 1000
Urea Nitrogen/Blood Urea Nitrogen (BUN)	mmol/L	mmol/L	1
Urea Nitrogen/Blood Urea Nitrogen (BUN)	mg/dL	mmol/L	Multiplied by 0.3571
Coagulation			
INR	Ratio	RATIO	1
Prothrombin Time	s, sec	sec	1
Prothrombin Time	%	--	No conversion

8.5.2 Derived Laboratory Parameters and Subgroups

Creatinine clearance (ml/min) will be derived using the following equation:

CrCl = K × {140 - age × weight} / {72 × serum creatinine}

where K is 1 for males and 0.85 for females, age is integer years, weight in kg, and serum creatinine in mg/dL [Cockroft 1976]. Age at the date of serum creatinine assessment will be used. Weight at the assessment date or nominal visit as serum creatinine will be used.

For hypocalcemia and hypercalcemia (as defined from laboratory ranges), serum calcium values and normal ranges will be corrected using the formula:

Corrected calcium = Serum calcium mg/dL + 0.8 × (4 - serum albumin g/dL)

β2 microglobulin (mg/L) will be categorized as < 3.5, 3.5 – 5.5 and > 5.5.

Platelet count (10^9/L) will be categorized as <75, 75 – 100, >100 – 150, and >150.

ANC (10^9/L) will be categorized as <1.0, 1.0 – 1.5, and >1.5.

Hemoglobin (g/L) will be categorized as <80, 80 – 100, >100.

Lactase dehydrogenase (LDH) will be categorized as <1.5xULN and ≥1.5xULN, where ULN=upper limit of normal range based on reference ranges provided from each site.

Albumin (g/dL) will be categorized as <3.5, and ≥3.5.

Creatinine clearance (ml/min) will be categorized as <45, ≥45 - <60, ≥60 - <90, ≥ 90.

8.5.3 Toxicity Grades

The following laboratory test results will be assigned toxicity grades using CTCAE 4.03:

- Hematology
    - Hemoglobin (decrease)
    - Platelets (decrease)
    - WBC (increase, decrease)
    - ANC (decrease)
    - Lymphocyte Count (increase, decrease)
- Serum Chemistry
    - Alanine transaminase (ALT) (increase)
    - Aspartate transaminase (AST) (increase)
    - Alkaline Phosphatase (increase)
    - Total Bilirubin (increase)
    - Creatinine (increase)
    - Calcium (increase, decrease)
    - Glucose (increase, decrease)
    - Albumin (decrease)
    - Uric Acid/Urate (increase)
    - Magnesium (increase, decrease)
    - Phosphorus/Phosphate (decrease)
    - Potassium (increase, decrease)

For ANC and platelet count, the time to onset of grade 3 or 4 toxicity by cycle and overall will be derived. Time to onset of grade 3 or 4 toxicity by cycle is defined as the duration in days from day 1 of the cycle to day of grade 3 or 4 toxicity, whichever occurs first. Time to onset of grade 3 or 4 toxicity overall is defined as

the duration in days from treatment start to day of grade 3 or 4 toxicity, whichever occurs first.

8.6 Myeloma Response Parameters

All tumor response and progression-depended endpoints will be assessed using the International Myeloma Working Group Uniform Response Criteria (IMWG-URC) [Rajkumar 2011].

8.6.1 Response Rates

The overall response rate (ORR) is defined as the proportion of patients for whom the best overall confirmed response is stringent complete response (sCR), complete response (CR), very good partial response (VGPR), or partial response (PR).

The clinical benefit rate (CBR) will be defined as the proportion of patients with the best overall confirmed response of minimal response (MR) or better.

Stable disease (SD) will be defined as the proportion of patients with the best overall confirmed response of SD.

Disease stabilization will be defined as the proportion of patients with the best overall confirmed response of SD or better.

'Best overall confirmed response' is the best response achieved on study based on two consecutive assessments according to IMWG-URC.

'Best unconfirmed response' defined as the best response achieved on study, i.e. a response may not be confirmed by a consecutive assessment.

Responses of not evaluable (NE) will be determined if no measurable disease at baseline or no post-baseline response assessment. No post-baseline response will be presented separately for patients still on study at the time of the data cut or if patient has withdrawn from study.

8.6.2 Progression Free Survival (PFS)

PFS is defined as the duration in months from start of treatment until first evidence of confirmed disease progression. Disease progression is defined according to IMWG-URC as PD or death due to any cause, whichever occurs first. PFS will be right-censored according to the conventions described in Table 4.

Table 4: Conventions for Censoring of PFS

Situation	Date of Progression or Censoring	Outcome
No post baseline response assessments	Date of first dose	Censored
Non-protocol systemic anticancer therapy started before documentation of PD or death	Date of last response assessment prior to start of new anticancer therapy	Censored
Death or PD after more than 1 consecutively missed response assessment	Date of last response assessment without documentation of PD that is before the first missed visit	Censored
Unconfirmed PD as the final response assessment	Date of latest PD assessment	Progressed
Alive and without PD documentation	Date of last response assessment	Censored
Death or PD between scheduled response assessments	Date of death or preceding response assessment showing PD, whichever occurs first	Progressed
Death before first response assessment	Date of death	Progressed

These conventions are adapted from the December 2018 FDA Guidance for Industry, 'Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics', and on the April 2015 FDA Guidance for Industry 'Clinical Trial Endpoints for the Approval of Non-Small Cell Lung Cancer Drugs and Biologics'.

Event-free rates will be defined using K-M product-limits and categorized by consecutive periods of 3 months from treatment start.

End of treatment as used for swim lane plots (section 9.5.3) is defined as the End of Treatment visit.

8.6.3 Duration of Response (DOR)

DOR will be estimated for patients who achieve a PR or better. DOR is defined as the duration in months from first documentation of a confirmed response to first evidence of confirmed disease progression or death due to any cause.

Disease progression, and dates of progression and censoring, will be determined as described for the analysis of PFS (section 8.6.2).

8.6.4 Time to Response (TTR)

TTR will be estimated for patients with confirmed responses of PR or better. TTR is defined as the duration in months from the study treatment start to the first occurrence of a response of PR or better.

8.6.5 Time to Progression (TTP)

TTP will be estimated for patients with confirmed PD. TTP is defined as the duration in months from treatment start to first evidence of disease progression.

Disease progression, and dates of progression and censoring, will be determined as described for the analysis of PFS (section 8.6.2), with the exception that patients who die will be censored as of the last response assessment prior to death.

8.6.6 Time to Next Treatment (TTNT)

Analyses of TTNT will use two alternative definitions, referred to as $TTNT_A$ and $TTNT_B$.

$TTNT_A$: Duration will be time (months) from the study treatment start to the start of first post study myeloma therapy (excluding radiotherapy). Patients who have no post study myeloma therapy will be censored at the earlier of date of death and date of last contact.

$TTNT_B$: Duration will be time (months) from the study treatment start to the start of the first post study myeloma therapy (excluding radiotherapy) or death. Patients who have no post study myeloma therapy and do not have a date of death will be censored at the date of last contact.

8.6.7 Duration of Stable Disease

Duration of SD will be estimated for patients whose best response is SD confirmed by two consecutive post-baseline myeloma response assessments. The duration is defined as the time in months from the study treatment start to disease progression or death due to any cause.

Disease progression, and dates of progression and censoring, will be determined as described for the analysis of PFS (section 8.6.2).

8.6.8 Duration of Disease Stabilization

Duration of disease stabilization will be estimated for patients whose best response is SD confirmed by two consecutive post-baseline myeloma response assessments or better. The duration is defined as the time in months from the study treatment start to disease progression or death due to any cause.

Disease progression, and dates of progression and censoring, will be determined as described for the analysis of PFS (section 8.6.2).

8.6.9 Duration of Clinical Benefit

Duration of clinical benefit will be estimated for patients whose best confirmed response is MR or better. Duration is defined as the time in months from first post-baseline documentation of a confirmed MR or better to disease progression or death due to any cause.

Disease progression, and dates of progression and censoring, will be determined as described for the analysis of PFS (section 8.6.2).

8.6.10 Overall Survival

OS is defined as the time in months from the date of the first dose of study drug to date of death due to any cause. Patients who are alive will be censored at the last follow up visit or data cut-off date for patients still on-study.

8.6.11 Assessments by Independent Review Committee (IRC)

Response, confirmed response, and confirmed progression are also determined according to IMWG-URC by an IRC. This parallel set of data will be appended to the database and analyzed as a sensitivity analysis.

8.6.12 Long Term Follow-up for PFS and OS

According to the study protocol, patients who discontinue therapy for reasons other than disease progression should continue to have monthly disease assessments done until confirmed progression or initiation of subsequent therapy.

Following confirmed disease progression or initiation of subsequent therapy, follow-up for overall survival status, second primary malignancies and subsequent therapy will take place every three months +/- 7 days for 24 months.

8.7 Functional Status and Well-being

Analyses of QLQ-C30 and EQ-5D-3L will be described as part of an updated SAP prior to analyses for a CSR addendum, see section 10.5.5.

8.8 Exposure

The study drugs for this study are melflufen and dexamethasone.

8.8.1 Overall Study Drug Exposure

Duration of treatment with study drug in weeks is defined as the longer of (date of last dose + 28 days – date of first dose + 1 for melflufen) or (date of last dose – date of first dose + 1 for dexamethasone) divided by 7.

8.8.2 Melflufen Exposure

Duration of melflufen treatment in weeks is defined as (date of last dose + 28 days – date of first dose + 1) divided by 7.

Melflufen treatment cycle is defined as cycle during which at least one dose of melflufen was administered. A treatment cycle starts on the date of melflufen administration.

Cumulative dose of melflufen in mg is the sum of all melflufen doses administered.

Average dose of melflufen in mg/week is defined as the cumulative dose divided by the duration of melflufen treatment.

The dose intensity of melflufen is defined as the ratio of the average dose of melflufen to the prescribed dose, where prescribed dose is 40 mg per 4 weeks = 10 mg/week, and expressed as a percent.

A dose delay is defined as a consecutive dose of melflufen administered on day 32 or later following a preceding dose of melflufen. Dose delays will be categorized as delays in weeks as 1 (day 32 to 38), 2 (day 39 to 45), 3 (day 46 to 52), 4 (day 53 to 59), and >4 weeks (day 59 or later) for each cycle.

A dose reduction is defined as a consecutive dose of melflufen lower than a preceding dose of melflufen.

8.8.3 Dexamethasone Exposure

Duration of dexamethasone treatment in weeks is defined as (date of last dose – date of first dose + 1) divided by 7.

Cumulative dose of dexamethasone in mg is the sum of all dexamethasone doses administered

The dose intensity of dexamethasone is defined as the ratio of (cumulative dose divided by the Duration of dexamethasone treatment) to the prescribed dose, where prescribed dose is 160 mg per 4 weeks = 40 mg/week for patients with age <75 years, or 80 mg per 4 weeks = 20 mg/weeks for patients with age ≥75 years, and expressed as a percent.

A dose delay is defined as a dose of dexamethasone administered on day 4 or later following the planned dosing days 1, 8, 15 and 22 respectively, and before the day of a planned subsequent dose. A missed dose of dexamethasone is a planned dose that is not given before the day of a planned subsequent dose (e.g. if planned dose on day 8 is not given before day 15).

A dose reduction is defined as a consecutive dose of dexamethasone lower than a preceding dose of dexamethasone.

8.8.4 Action Taken with Study Drug

The protocol and eCRF use the terms dose held and dose delay. A dose held is the same as a dose delay. The term dose delay is used herein and will be used for the CSR.

Dose delays or dose reductions in summaries of scheduled study drug administration will be analyzed using the derived continuous variables described in sections 8.8.2 and 8.8.3 and not as reported in the CRF. The 'Dose adjustment' as reported in CRF {NO ACTION TAKEN, DOSE HELD, DOSE REDUCED, and DRUG PREMANENTLY DISCONTINUED} and dose adjustment according to CDISC Controlled terminology (CT) {DOSE NOT CHANGED, DOSE REDUCED, DRUG INTERRUPTED, and DRUG WITHDRAWN} will be included in listings. CRF entry 'DOSE HELD' correspond to CT 'DRUG INTERRUPTED', and CRF entry 'DRUG PERMANENTLY DISCONTINUED' correspond to CT 'DRUG WITHDRAWN'.

8.9 Safety Evaluation

8.9.1 Adverse Events

An **adverse event** (AE) is any untoward medical occurrence in a study patient administered an investigational product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including laboratory finding), symptom, or disease temporally associated with participation in an investigational study, whether or not considered drug-related. In addition to new events, any increase in the severity or frequency of a pre-existing condition that occurs after the patient begins study is considered an AE. This includes any adverse reactions, injury, toxicity, or sensitivity reaction.

Further details for the definition of SAE is provided in study protocol section 9.1.1.

A **serious adverse event** (SAE) is defined as any AE, occurring at any dose that meets any one or more of the following criteria:

- Is fatal or immediately life-threatening
- Results in persistent or significant disability/incapacity
- Constitutes a congenital anomaly/birth defect

- Is medically significant, i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above
- Requires inpatient hospitalization or prolongation of existing hospitalization (AEs requiring hospitalization of less than 24 hours, will not be reported as SAEs unless another seriousness criteria are fulfilled)

Further details for the definition of SAE is provided in study protocol section 9.2.1.

A **treatment-emergent adverse event** (TEAE) is an AE with an onset or increase in severity level after the initial dose of study drug and no later than day 30 after the last dose of study drug or initiation of new multiple myeloma therapy, whichever is sooner.

A **treatment-related adverse event** is an AE that is recorded by the investigator as possibly or probably related to either or both of melflufen and dexamethasone. A melflufen related AE is an AE that is noted as possibly or probably related to melflufen independently of relationship with dexamethasone, and a dexamethasone related AE is an AE that is noted as possibly or probably related to dexamethasone independently of relationship with melflufen.

Patients may have more than one adverse event per SOC and preferred term. At each level of patient summarization, a patient is counted once if he/she reported one or more adverse events at that level. For such cases, the maximum CTCAE toxicity grade and strongest causal relationship to study drug will be used in the incidence calculations.

8.9.2 Dose Modifications due to Adverse Event

Dose delays or dose reductions in summaries of ‘Action taken with study drug’ due to AE will be analyzed as reported in the CRF {NO ACTION TAKEN, DOSE HELD, DOSE REDUCED, DRUG INTERRUPTED, and DRUG PREMANENTLY DISCONTINUED}. Listings will include Action taken as reported on CRF and Action taken as mapped according to CDISC Controlled terminology (CT) {DOSE NOT CHANGED, DOSE REDUCED, DRUG INTERRUPTED, and DRUG WITHDRAWN}.

8.9.3 Adverse Events of Special Interest

AEs of special interest (AESIs) are TEAEs defined as follows:

- Neutropenia: Standardized MedDRA Query (SMQ) {“Haematopoietic leukopenia”}
- Thrombocytopenia: SMQ {“Haematopoietic thrombocytopenia”}
- Anemia: SMQ {“Haematopoietic erythropenia”}
- Febrile neutropenia: PT {“Febrile neutropenia”}[3]
- Infections: SOC {“Infections and infestations”}
- Hemorrhage: SMQ {“Haemorrhage terms, excluding laboratory terms”}
- Thrombocytopenia concomitant to hemorrhage: Hemorrhage with an onset date within ± 7 days of the onset and/or resolution date of a grade 3 or 4 thrombocytopenia.
- Neutropenia concomitant to infection: Infection with an onset date within ± 7 days of the onset and/or resolution date of a grade 3 or 4 neutropenia.

8.9.4 Deaths

Deaths will be categorized as occurring within 30 days of the last dose of study drug or more than 30 days after the last dose respectively. Deaths related study drug occurring more than 30 days after the last dose will also be categorized.

Early deaths will be defined as occurring within 60 days of first dose of study drug.

8.10 Protocol Deviations

Major 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 patient’s rights, safety, or well-being. Protocol deviations will be identified and classified prior to any database snapshot or database lock.

9 STATISTICAL METHODS

9.1 General Considerations

All statistical summaries and analyses will be performed in SAS® version 9.4 or higher (SAS Institute Inc., Cary, NC, USA).

[3] PT “Febrile neutropenia” is listed as an individual PT and is also included in the SMQ “Haematopoietic leukopenia”. Hence, that PT will be counted in the 2 separate AESIs.

In general, summaries of all data will be presented for the total group and for the triple-class refractory subgroup in each analysis set. Data from the EMD subgroup will be presented separately for selected analyses.

Statistical analyses will be reported using summary tables, figures, and data listings. No inferential statistical comparisons using p-values will be performed.

For continuous variables, the number of patients with non-missing data (n), mean, standard deviation (SD), median, minimum, and maximum will be presented.

For discrete data, the frequency and percent distribution will be presented. Unless otherwise indicated, percentages will be calculated based upon the number of patients in the FAS in each study group as the denominator. Graphical methods will be used, as appropriate, to illustrate study endpoints.

Confidence intervals, when presented, will be constructed at the 95% level and will be provided for the triple-class refractory subgroup and for the total group. For binomial variables, exact distribution methods will be employed. The distribution of time-to-event endpoints will be summarized by the Kaplan-Meier (K-M) method. Quartiles including median will be estimated by K-M method along with their 95% confidence intervals based on a log(-log(survival)) distribution.

Assuming raw or derived variables are recorded to “x” decimal places; range and quartiles will be presented to x decimal places, mean and median to x+1, and SD and confidence intervals to x+2 decimal places. Presented decimal places should however not be greater than 4.

Percentages will be presented to 1 decimal place, with the exception of 0, which will be presented without percent, and 100, which will be presented without decimal places. Categorization of percentages will be done before rounding.

Tables that summarize categorical data will present data as “0”, if the number of events is zero. Denominators for percentages will be based on the number of patients with non-missing data in the population used in each column. A “missing” category will be included for any parameter for which information is missing, without a percentage.

Individual patient data recorded on the electronic case report forms (eCRFs) and any derived data will be presented by study group and by patient in data listings.

9.2 Disposition of Patients

The following patient disposition information will be summarized for the FAS:

- Number of treated patients

  - Number that are daratumumab refractory
  - Number that are pomalidomide refractory
  - Number that are refractory to both pomalidomide and daratumumab.
- Number (%) of treated patients by geographic region (United States of America and Rest of World), country and site.
- Number (%) of treated patients who are on treatment
- Number (%) of treated patients who discontinued treatment
- Primary reason for treatment discontinuation
- Number (%) of treated patients in long-term PFS follow-up
- Number (%) of treated patients in long-term OS follow-up
- Number (%) of treated patients who discontinued the study
- Primary reason for study discontinuation

9.3 Protocol Deviations

Major protocol deviations will be summarized by deviation type for the FAS. All protocol deviations will also be provided in a listing.

9.4 Demographic, Baseline Characteristics, and Prior Therapy

9.4.1 Demographic and Baseline Characteristics

The following demographic and baseline characteristics will be summarized for the FAS.

- Age (years) and age categories
- Sex
- Race
- Ethnicity
- Baseline ECOG performance status
- Baseline fertility status
- Baseline weight (kg)

9.4.2 Medical History

The number (%) of patients who experienced a prior disease or disorder will be summarized by SOC and PT for the FAS.

9.4.3 Disease Characteristics

The following disease characteristics at diagnosis will be summarized for the FAS based on data recorded on the Multiple Myeloma History at Diagnosis CRF:

- Stage of disease (ISS and R-ISS)
- Heavy chain and light chain status, heavy chain and light chain combinations (e.g., IgG-lambda, IgG-kappa)
- Presence of bone lesions
- Presence of extramedullary disease
- Cytogenetic risk groups

The following disease characteristics at baseline/study entry will be summarized for the FAS:

- Stage of disease (ISS, Derived ISS, R-ISS, Derived R-ISS)
- Time from diagnosis to first dose of study drug in years
- Type of measurable disease
- SPEP, UPEP, Kappa/Lambda values
- Heavy chain and light chain status, heavy chain and light chain combinations
- Maximum plasma cell involvement (%)
- Presence of bone lesions
- Presence of extramedullary disease
- Cytogenetic risk groups
- Laboratory Assessments
    - β2 microglobulin as values and categories
    - Platelet count as values and categories
    - ANC as values and categories
    - Hemoglobin as values and categories
    - LDH as values and categories

- Albumin as values and categories
- Creatinine
- Creatinine clearance (ml/min) as values and categories
- Corrected calcium

9.4.4 Prior Myeloma Therapy

The following information related to prior myeloma therapy will be summarized for the FAS:

- Number of regimens of prior treatment for multiple myeloma
- Number (%) of patients with at least one prior regimen including a therapeutic drug class, i.e. IMiD, PI, Alkylators, anti-CD38 mAb, Other mAb, and Other.
- Number (%) of patients who are refractory to a prior regimen including a therapeutic drug class.
- Number (%) of patients who received an IMiD and PI (double-class)
- Number (%) of patients who received an IMiD, PI, and anti-CD38 mAb (triple-class)
- Number (%) of patients who are double-class refractory (IMiD and PI)
- Number (%) of patients who are refractory to most recent prior regimen
- Best response to most recent prior regimen
- Number (%) of patients per last prior therapeutic class.
- Number (%) of patients refractory to any agent per last prior therapeutic class.
- Number (%) of patients who are refractory to IMiD, PI, Alkylators, anti-CD38 mAb, Other mAb, or Other per the most recent prior regimen by therapeutic classes.
- Number (%) of patients with at least one prior autologous transplant, and number (%) of patients with at least two prior autologous transplants
- Number of prior autologous transplants
- Time (years) from front line transplant to relapse
- Number (%) of patients with prior radiotherapy

9.4.5 Prior and Concomitant Medications

Concomitant medications will be summarized by ATC class and preferred name using as counts and percentages. The summaries will be ordered by descending frequency of ATC class and preferred name within each ATC class in the total group. Prior medications will be listed without summary.

A separate summary table will summarize the number and percentage patients with transfusions and taking growth factor agents.

9.5 Efficacy Analyses

The primary population for all efficacy analyses will be the FAS. All tumor response and progression-depended endpoints will be assessed using the International Myeloma Working Group Uniform Response Criteria (IMWG-URC) [Rajkumar 2011].

9.5.1 Response Rates

The primary endpoint, ORR will be summarized with the corresponding two-sided 95% exact binomial confidence interval (Clopper-Pearson method [Fleiss, 1981]).

CBR and disease stabilization, and best confirmed responses (sCR, CR, VGPR, PR, MR, SD, PD, or not evaluable (NE)) will be summarized. In addition, best unconfirmed response will be summarized.

9.5.2 Changes in M-protein

“Waterfall” plots will display the maximum percent decrease in the M-protein being used to determine response for all patients. Bars will be stacked per best responses.

9.5.3 Progression Free Survival

K-M product-limits will be used to estimate the distribution of PFS. Quartiles including the median and the two-sided 95% confidence intervals based on the log(-log(survival)) distribution will be presented. The number of patients censored, and types of events and censoring events will be summarized. Event free rates (with 95 % confidence intervals) will be presented based on the K-M curve. A K-M plot showing the estimated PFS distribution will be provided. These analyses will be provided for the FAS.

Potential follow-up for PFS will be summarized for the FAS using the reverse K-M method where the censoring variable is inverted [Schemper and Smith, 1996]. The median potential follow-up time will be summarized.

"Swim lane" plots based on PFS will be provided for the FAS. The plots will be stacked by day of first documentation of the different response levels (SD, MR, PR, VGPR, CR, sCR) on study.

9.5.4 Duration of Response (DOR)

The distribution of DOR will be estimated and summarized using the same method as for PFS.

DOR will be summarized for patients in FAS whose best overall confirmed response is sCR, CR, VGPR, or PR.

9.5.5 Time to Response (TTR)

TTR will be summarized as a continuous variable using descriptive statistics. A K-M plot showing the estimated time to response distribution will be provided.

TTR will be summarized for the FAS.

9.5.6 Time to Progression (TTP)

The distribution of TTP will be estimated and summarized using the same method as for PFS.

TTP will be summarized for the FAS.

9.5.7 Time to Next Treatment (TTNT)

The distribution of $TTNT_A$ and $TTNT_B$ will be estimated and summarized using the same method as for PFS.

$TTNT_A$ and $TTNT_B$ will be summarized for the FAS.

9.5.8 Duration of Stable Disease

Duration of SD will be estimated and summarized using the same method as for PFS.

Duration of SD will be summarized for the FAS.

9.5.9 *Duration of Disease Stabilization*

Duration of disease stabilization will be estimated and summarized using the same method as for PFS.

Duration of disease stabilization will be summarized for the FAS.

9.5.10 Duration of Clinical Benefit

Duration of clinical benefit will be estimated and summarized using the same method as for PFS.

Duration of clinical benefit will be summarized for the FAS.

9.5.11 Overall Survival (OS)

OS will be estimated and summarized using the same method as for PFS, including median potential follow-up time.

OS will be summarized for the FAS.

9.5.12 Analyses by Subgroups

EMD presence at baseline is a subgroup of specific interest (section 6.2). Summary tables for ORR, CBR, disease stabilization rate, best confirmed response, PFS, DOR, and OS will be presented for patients with EMD at baseline.

ORR, CBR, disease stabilization rate, and best confirmed response will also be summarized for the following subgroups.

In addition, forest plots presenting the K-M median estimate and 95% confidence interval for efficacy endpoints PFS, DOR, TTR, TTP, duration of SD, duration of clinical benefit, and OS will be provided for the following subgroups. The summaries will be based on the FAS.

- Age (<65, 65 - <75, ≥75 years)
- Sex (male, female)
- Race (White, All Other Races)
- Geographic region (United States of America, Rest of World)
- Presence of Extramedullary Disease at Baseline (Derived per section 8.4.9; yes, no)
- Prior autologous stem cell transplant (yes, no)
- Number of prior regimens (<4, 4 - 5, ≥6)
- Maximum plasma cell involvement (%) at baseline, as assessed with bone marrow assessment (<30, 30 - <60, ≥60)
- Baseline creatinine clearance (ml/min) (<45, 45 - < 60, 60 - < 90, ≥90)
- Baseline LDH (<1.5×ULN, ≥1.5×ULN)
- Baseline albumin (g/L) (<35, ≥35)

- R-ISS at baseline (Derived per section 8.4.6; R-I, R-II, R-III, unknown)
- ISS at baseline (Derived per section 8.4.6; I, II, III, unknown)
- Cytogenetic risk groups (standard risk, high risk, unknown)
- Refractory status:
    - Refractory to an alkylator (yes, no)
    - Refractory to an anti CD38 mAb (yes, no)
    - Refractory to a PI and IMiD but not to an anti CD38 mAb (yes, no)

9.5.13 Assessments by IRC

Summaries of ORR, CBR, best confirmed response, disease stabilization rate, PFS, DOR, duration of stable disease, TTR and TTP will be repeated for the assessments performed by IRC. These summaries will be provided for the FAS.

Summaries of ORR, CBR, PFS and DOR by subgroups of disease characteristics (section 9.5.12) will be repeated for the assessments performed by IRC and provided for the FAS.

9.5.14 Functional Status and Well-being

Analyses of QLQ-C30 and EQ-5D-3L will be described as part of an updated SAP prior to analyses for a CSR addendum, see section 10.5.5.

9.6 Safety Analysis

All analyses of safety will be based on the Safety analysis set.

9.6.1 Exposure

9.6.1.1 Overall Study Drug Exposure

Duration of treatment will be summarized as a continuous variable using descriptive statistics.

Treatment cycles and patients dosed by cycle will be summarized as counts and percentages, and as a continuous variable using descriptive statistics.

9.6.1.2 Melflufen Exposure

Duration of treatment, treatment cycles, cumulative dose, infusion time, average dose, and dose intensity will be summarized as continuous variables using descriptive statistics.

Number of patients dosed, treatment cycles (overall and per dose), patients with dose modifications, cycles with dose modifications, cycles with dose

reduction after dose delay of 3 weeks or longer, reason for dose reduction, patients with dose delay by cycle and categories of delay, and patients with dose reductions by cycle, will be summarized as counts and percentages.

9.6.1.3 Dexamethasone Exposure

Duration of treatment, number of doses, cumulative dose, and dose intensity will be summarized as continuous variables using descriptive statistics.

Dose modifications and reasons for permanent discontinuation will be summarized as counts and percentages.

9.6.2 Adverse Events

Number and percentage of patients with TEAEs will be summarized by categories of maximum severity, relationship with study drug (either, melflufen, and dexamethasone), seriousness and dose modifications of study drug (either, melflufen, and dexamethasone).

Number and percentage of TEAEs will be summarized by SOC and PT by categories of severity, relationship with study drug, seriousness and dose modifications of study drug. Summaries that are displayed by SOC and PT will be ordered by descending order of incidence per SOC and PT within each SOC for the total group.

Number and percentage of patients with TEAEs, SAEs, fatal TEAEs, and AEs leading to study drug discontinuation, by SOC and PT will also be summarized by subgroups listed in section 9.6.10.

Separate listings of serious AEs, AEs leading to dose modification of melflufen, AEs leading to discontinuation of melflufen, AEs leading to dose modification of dexamethasone, or AEs leading to discontinuation of dexamethasone will be provided. A separate listing will be provided for the SOC of “neoplasms benign, malignant and unspecified”. AEs that are not treatment-emergent will be provided in listings.

9.6.3 Adverse Events of Special Interest

AESI neutropenia will be summarized as counts and percentages, overall and per severity grade.

AESI neutropenia concomitant to infection will be summarized as counts and percentages.

AESI febrile neutropenia will be summarized as counts and percentages, overall and per severity grade.

AESI infection will be summarized as counts and percentages, overall and per severity grade.

AESI thrombocytopenia will be summarized as counts and percentages, overall and per severity grade.

AESI thrombocytopenia concomitant to hemorrhage will be summarized as counts and percentages.

For the AESIs of neutropenia, thrombocytopenia, anemia, infection, and hemorrhage, the maximum toxicity grade during each cycle and at the End of Treatment visit will be summarized respectively. These tables will be presented for three subsets of cycles during which the AESI's starts: 1) excluding last cycle per patient; 2) including the last cycle per patient; and 3) only the last cycle per patient.

9.6.4 Deaths

Number of deaths and the cause of death, as collected on the Patient Death CRF, will be summarized as counts and percentages, overall, and as categorized. All deaths which occur on study are recorded on the Patient Death CRF, i.e. on treatment and off treatment. The total number of deaths will not be equivalent to the number of fatal TEAEs.

A listing of all deaths will be provided.

9.6.5 Hematology, Serum Chemistry, and Coagulation

Results and change from baseline at each scheduled visit for all hematology, serum chemistry, and coagulation parameters will be summarized with descriptive statistics.

Toxicity grade of applicable parameters will be summarized as counts and percentages in shift tables of baseline versus worst toxicity grade through the End of Treatment visit. Number of patients with grade 3 or higher toxicity will be summarized as counts and percentages by cycle. A separate listing of all laboratory results corresponding to grade 3 or 4 will be provided.

For hemoglobin, ANC and platelet count, the maximum toxicity grade recorded during each cycle and at the End of Treatment visit will be summarized separately.

For ANC and platelet count, results and change from the Day 1 pre-infusion value at Days 8, 15, and 22 during each cycle will be summarized as descriptive statistics. Corresponding line series plots of average values will also be provided.

For ANC and platelet count, the time to onset (days) of grade 3 or 4 toxicity will be summarized by cycle and overall.

9.6.6 Vital Signs

Results and change from baseline for blood pressure, pulse, respiratory rate and temperature will be summarized by visit. Results and change from pre-infusion to post-infusion for blood pressure, pulse, respiratory rate and temperature will be summarized by cycle. The nominal pre and post infusion timepoints on the CRF will be used as vital signs assessment time is not collected.

9.6.7 ECOG Performance Status

ECOG performance status will be summarized as counts and percentages using shift tables of baseline versus worst performance status during study. The number of patients with improvement of ≥1 unit and ≥2 units respectively at the last available visit and at the End of Treatment visit will be summarized as counts and percentages.

9.6.8 Physical Examination

Physical examination results will be listed without summary.

9.6.9 12-Lead Electrocardiograms

QTc-Fridericia (QTcF) interval results and changes from baseline will be summarized with descriptive statistics at baseline and End of Treatment visit. QTcF is calculated in the database as $QTcF = QT / (RR)^{1/3}$ assuming units of milliseconds.

9.6.10 Analyses by Subgroups

The following safety endpoints will be provided for the EMD subgroup, based on the FAS:

- Frequency of TEAEs, SAEs, fatal TEAEs, TEAEs leading to discontinuation, and TEAEs leading to dose modifications
- Maximum severity grade of TEAEs
- Frequency and grade of AESIs,
- Frequency of melflufen dose modifications based on study drug exposure,
- Treatment duration of melflufen

Analysis of TEAEs, AESIs, SAEs, fatal TEAEs, TEAEs leading to discontinuation, and TEAEs leading to dose modifications will be provided by the following subgroups:

- Age (<65, 65 - <75, ≥75 years)
- Sex (male, female)

- Race (White, All Other Races)
- Geographic region (United States of America, Rest of World)

10 STATISTICAL/ANALYTICAL ISSUES

10.1 Handling of Dropouts or Missing Data

10.1.1 Efficacy Assessments

The handling of dropouts and missing disease status assessments for the efficacy variables is described in their definitions. Table 4*: Conventions for Censoring of PFS* describes how dropouts and missing data impact the calculation of the time to event variables. Missing data will not be estimated or carried forward for any of the other summaries.

10.1.2 Safety Assessments

10.1.2.1 Adverse Events

Adverse events with missing relationship are considered related for purposes of summaries. Imputed relationship will not be included in the listings.

Adverse events with missing severity are considered severe (grade 3) for purposes of summaries. Imputed severity will not be included in the listings.

Adverse events with missing action taken with study drug are excluded from analyses.

10.1.2.2 Laboratory Assessments

The following imputations will be made for missing reported units:

- Creatinine clearance: ml/min
- ALT: U/L
- Albumin values less than 10: g/dL
- INR: RATIO
- Prothrombin Time (PT): seconds (sec)
- Hematocrit values greater than 1: %
- Hemoglobin values less than 20: g/dL
- RBC: 10^12/L.
- WBC and WBC differential counts with values less than 10: 10^9/L.

Prothrombin times reported as %, which will not be imputed, will be omitted from summaries.

10.1.3 Dates and Times

If only a partial date is available and is required for a calculation (e.g., time since diagnosis, time since most recent relapse, determination of whether a medication is concomitant or an AE is treatment-emergent), the following standards will be applied:

- Start dates (e.g., AE onset date or start date of medication, date of diagnosis, date of relapse)

  For missing start day only - Day will be imputed as the first day of the month (i.e., 1) with the following exception: if the partial date falls in the same month and year as the date being used in the calculation (e.g., first dose date, informed consent date), then the partial date will be imputed to equal the date being used for the calculation.

  For missing start day and month - Day and month will be imputed as the first day of the year (i.e., 1 January) with the following exception: if the partial date falls in the same year as the date being used in the calculation (e.g., first dose date, informed consent date), then the partial date will be imputed to equal the date being used for the calculation.

- Stop dates (e.g., AE resolution date or stop date of medication)
  For missing stop day only - Day will be imputed as the last day of the month (i.e., 28, 29, 30, or 31)

  For missing stop day and month - Day and month will be imputed as the last day of the year (i.e., 31 December)

Any partial dates will be displayed in data listings without imputation of missing days and/or months (e.g., MAR2011, 2009).

If time is not available but is required for a calculation (e.g., timing of AE vs study drug administration) the most conservative approach should be used, i.e. assuming that the time of AE was after study drug administration or that the time of concomitant medication was after AE.

10.2 Multiplicity

No inferential statistical comparisons using p-values are planned as part of this SAP. Confidence intervals will however be provided for descriptive purposes, and the increasing probability of type I error by number of statistical conclusions

should be considered when interpreting the results. The efficacy endpoints are listed by order of relevance and this hierarchy should be considered in summary conclusions.

10.3 Data Maturity

The data cut-off date for the CSR will be at least 3 months after first administration of melflufen to the last patient enrolled. With a data cut-off of at least 3 months after first administration of melflufen in the last patient enrolled, at least 24 weeks follow-up (up to 6 cycles) would be accrued for more than 90% of all patients. This would represent an adequate amount of follow-up time for assessment of ORR and evaluation of safety, and a limited risk of having too few patients remaining at risk in secondary time-to-event efficacy endpoints.

10.4 Interim Analysis for Futility

In the initial study design one group of approximately 39 efficacy evaluable patients that were refractory to pomalidomide and one group of approximately 39 efficacy-evaluable patients that were refractory to daratumumab were planned to be enrolled. Patients refractory to both drugs were assigned to both groups.

A Simon two-stage optimal design [Simon 1989] was used for each group separately to determine whether study drug had sufficient activity to warrant further development in each group. For each group, using Simon's optimal two-stage design (with significance level 10% and power of 80%), a true ORR of 15% or less was considered unacceptable (null hypothesis) whereas a true ORR of at least 30% (alternative hypothesis) would merit further study. In the first stage, 19 efficacy evaluable patients were to be accrued. If there were 3 or fewer responses observed, then the results were to be further reviewed by the Data Safety Monitoring Committee (DSMC) in order to determine if the second stage for the specific group would continue. An interim analysis for futility was conducted after 19 patients had been enrolled in each group and were evaluable for response. The response rates were 5/19 in the pomalidomide refractory group and 3/19 in the daratumumab refractory group. The DSMC assessed the benefit/risk balance and found the balance to be positive in both of the groups as well as for the total study population. Due to the overall positive benefit/risk balance, the DSMC recommended that the study recruitment proceed without changes or limitations.

10.5 Changes to Planned Analyses

10.5.1 Protocol Amendments

The following protocol amendments have had implications on planned analyses:

In protocol version 3.0, 19 Dec 2016, the following was added;

1. Response assessments were to be evaluated by IRC.

In protocol version 5.0, 31 May2018, the following was added;

1. Expansion of the study sample size
2. Population considered one group, since majority of patients were refractory to both pomalidomide and daratumumab (patients refractory to pomalidomide and patients refractory to daratumumab are no longer evaluated separately)
3. Addition of the objective to assess functional status and well-being
4. Addition of the possibility to follow patients for OS for more than 24 months"

In protocol version 7.0, 04 Mar 2019, the following was added;

1. Expand the drug class of anti-CD38 monoclonal antibodies (mAbs) from being limited to daratumumab only to include all anti-CD38 mAbs, i.e. accepting patients refractory to e.g. isatuximab (currently in phase 3 clinical trials) as eligible.
2. Adding transparency of a targeted sub-group of special interest, consisting of patients who are triple-class refractory (i.e. refractory to an immunomodulatory drug (IMiD), a proteasome inhibitor (PI) and an anti-CD38 mAb).
3. Addition of the assessment of functional status and well-being at follow up visits

10.5.2 Analysis Sets

The Efficacy evaluable analysis set will not be used for any analyses. The protocol defines this analysis set as all patients who receive at least 2 doses of melflufen, have a baseline disease assessment and at least 1 post-baseline disease assessment. The definition has been modified to include all patients who receive at least 1 dose and have a baseline and at least 1 post-baseline response assessment, or who discontinued treatment due to progressive disease or death prior to the first post-baseline response assessment.

Instead, it was decided to define the Full analysis set (FAS) as all patients who fulfil all eligibility criteria at screening and prior to initiation of therapy as per study protocol section 7.2, to be consistent with the intention-to-treat principle as per ICH E9. The FAS will be used for all analyses of efficacy.

10.5.3 Subgroups of Specific Interest

The decision to expand enrollment to 150 patients and to focus on analyses combining the patients that are refractory to pomalidomide and the patients that are refractory to daratumumab is described in section 11.3 of amendment 6 of the protocol (version 7, 4 March 2019). It was also decided to introduce a subgroup of specific interest and to provide summaries and analyses for patients who are triple-class refractory, as defined in section 8.4 of this SAP. This subgroup was identified as having an unmet medical need, potentially allowing FDA accelerated approval based on ORR and DOR in a single arm study.

In addition, based on preliminary signals of efficacy, EMD was also identified as a subgroup of specific interest due to the poor prognosis of these patients. Data from the EMD subgroup will be presented separately for selected analyses.

10.5.4 Objectives and Endpoints

The purpose of this SAP update (version 3) was to clarify objectives and endpoints in relation to scientific rationale for NDA submission for accelerated approval, as was advised by FDA at a pre-NDA meeting on December 3rd 2019. The primary objective in this SAP relates to evaluation of efficacy, and the primary endpoint is ORR. DOR is considered the most relevant secondary efficacy endpoint. The evaluation of safety and tolerability is specified as a secondary endpoint. The ordering of endpoints is changed to reflect relevance and analytical hierarchy. It is clarified that patients with triple-class refractory RRMM is the subgroup of primary interest for these objectives.

10.5.5 Clinical Study Report

As a clarification to section 12.5 of the study protocol, the CSR will be based on a data cut-off occurring at least 3 months after first administration of melflufen in the last patient enrolled. A future CSR addendum will be written based on data pertaining to QLQ-C30 and EQ-5D-3L, and long term follow-up of PFS and OS, at least 12 months after first administration of melflufen in the last patient enrolled unless all patients have discontinued from the study before that.

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