STATISTICAL ANALYSIS PLAN

A phase 3 randomized, open-label, multicenter study comparing isatuximab (SAR650984) in combination with pomalidomide and low-dose dexamethasone versus pomalidomide and low-dose dexamethasone in patients with refractory or relapsed and refractory multiple myeloma

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ADA:	anti-drug antibody
ATC:	anatomic category
BOR:	best overall response
CA:	cytogenetic abnormality
CI:	confidence interval
CR:	complete response
DOR:	duration of response
ECOG:	Eastern Cooperative Oncology Group
eCRF:	electronic case report form
EORTC:	European Organization for Research and Treatment of Cancer
EQ:	EuroQol
FLC:	free light chain
HLGT:	high level group term
HLT:	high-level term
HR:	hazard ratio
IAT:	indirect antiglobuline test
IMP:	Investigational Medicinal Product
IMWG:	International Myeloma Working Group
IPd:	isatuximab pomalidomide dexamethasone
IRC:	independent response committee
IRT:	interactive response technology
ISS:	international staging system
ITT:	intent to treat
LDH:	lactate dehydrogenase
MedDRA:	Medical Dictionary of Regulatory Activities
MM:	multiple myeloma
MR:	minimal response
MRD:	minimal residual rate
MY:	myeloma specific module
NE:	non-evaluable
ORR:	objective response rate
OS:	overall survival
PCSA:	potentially clinically significant abnormality
Pd:	pomalidomide dexamethasone
PD:	progressive disease
PFS:	progression free survival
PK:	pharmacokinetic
PR:	partial response
PS:	performance status
PT:	preferred term, prothrombin time
QLQ:	quality of life questionnaire

R-ISS:	revised international staging system
RS:	raw score
SOC:	system organ class
TEAE:	treatment-emergent adverse event
TT1R:	time to first response
TTBR:	time to best response
VAS:	visual analogue scale
VGPR:	very good partial response
WHO-DD:	World Health Organization-Drug Dictionary

1 OVERVIEW AND INVESTIGATIONAL PLAN

1.1 STUDY DESIGN AND RANDOMIZATION

This is a prospective, multicenter, multinational, randomized, open-label, parallel group and 2-arm study evaluating the clinical benefit of isatuximab in combination with pomalidomide and low-dose dexamethasone as compared to pomalidomide and low-dose dexamethasone for the treatment of patients with refractory or relapsed and refractory multiple myeloma who have received at least two lines of therapy including lenalidomide and a proteasome inhibitor (bortezomib, carfilzomib or ixazomib) alone or in combination and have demonstrated disease progression on or within 60 days of completion of the last therapy.

After confirmation of eligibility criteria, patients will be randomly assigned, using an interactive response technology (IRT), in a 1:1 ratio to one of the two arms:

- Isatuximab in combination with pomalidomide and low dose dexamethasone (IPd, experimental arm).
- Pomalidomide and low-dose dexamethasone (Pd, control arm).

The duration of the study for a patient will include a period for screening of up to 3 weeks. The cycle duration is 28 days. Patients will continue study treatment until disease progression, unacceptable toxicity, patient wish, or any other reason, whichever comes first.

Randomization will be stratified according to:

- Age (<75 years versus ≥75 years).
- Number of previous lines of therapy (2 or 3 versus >3).

Approximately 300 patients (150 patients per arm) will be randomized from approximately 140 sites. Patient enrollment will be stopped after progression free survival (PFS) analysis or when 300 patients will have been randomized, whichever is first.

1.2 OBJECTIVES

1.2.1 Primary objectives

The primary objective of this study is to demonstrate the benefit of IPd arm in the prolongation of PFS as compared to Pd arm in patients with refractory or relapsed and refractory multiple myeloma.

1.2.2 Secondary objectives

The key secondary objectives are:

- To evaluate the ORR as per IMWG criteria in each arm.
- To compare the OS between the 2 arms.

The other secondary objectives are:

- To evaluate the Time to Progression (TTP) in each arm.
- To evaluate the PFS in high risk cytogenetic population defined as patients carrying del(17p), t(4;14), t(14;16) in each arm.
- To evaluate the Duration of Response (DOR) in each arm.
- To evaluate the safety of the combination of IPd versus that of Pd in both treatment arms.
- To determine the pharmacokinetic (PK) profile of isatuximab in combination with pomalidomide.
- To evaluate the immunogenicity of isatuximab.
- To assess disease-specific and generic health-related quality of life (HRQL), disease and treatment-related symptoms, health state utility and health status.

1.2.3 Exploratory objectives

The exploratory objectives are:

- To explore the relationship between immune genetic determinants and efficacy endpoints.
- To explore pharmacokinetics (PK) and pharmacodynamic (PDy) relationships.
- To explore the minimal residual disease (MRD) rate in both treatment arms.

1.3 DETERMINATION OF SAMPLE SIZE

The sample size calculation is based on the primary efficacy endpoint (ie, PFS). The following assumptions were used:

- Pd arm has a median PFS of 4.0 months.
- IPd arm will have 40% risk reduction in hazard rate in comparison to Pd arm. The targeted hazard ratio is 0.60, which corresponds to an improvement in the true median progression free survival time from 4 months to 6.67 months.
- A log-rank test at a one-sided 2.5% significance level.

Based on the above assumptions, a total of 162 PFS events are needed to achieve a 90% power for the study.

Objective for OS also support the sample size calculation using the following assumptions:

- Pd arm has a median OS of 13.0 months.
- IPd will have 31.5% risk reduction in hazard rate in comparison to Pd arm. The targeted hazard ratio is 0.685 and this is expected to correspond to a difference of 6 months in median OS between the control arm and the experimental arm.
- A log-rank test at a one-sided 2.5% significance level.

- An interim analysis for efficacy assessment on OS is planned at the time of primary analysis on PFS which is estimated to occur when about 36% of the OS events will be observed. An O'Brien and Fleming α-spending function will be used to obtain the nominal significance levels for the interim and final analyses of survival.

Based on the above assumptions, a total of 220 deaths are needed to achieve 80% power for the study.

Approximately 300 patients (150 in each arm) would be adequate to achieve the targeted number of events for both PFS and OS. After the PFS analysis, no additional patient will be randomized and OS analysis will be performed on the number of patients already randomized.

1.4 STUDY PLAN

The complete study plan is presented in Section 1.1 of the protocol.

1.5 MODIFICATIONS TO THE STATISTICAL SECTION OF THE PROTOCOL

Two changes were made from the protocol to the SAP version 1 (approved on 06-APR-2017)

- The population flag for PRO has been removed and the analysis population has been clarified in the section 2.4.9 (analyses of quality of life/health economics variables)
- A biomarker population was added for biomarker analyses

1.6 STATISTICAL MODIFICATIONS MADE IN THE STATISTICAL ANALYSIS PLAN

The statistical analysis plan history table below gives the timing, rationale, and key details for major changes to the statistical analysis features in the amended statistical analysis plan.

Table 1 - Statistical analysis plan statistical changes

SAP version number	Date approved	Rationale	Description of statistical changes
3	20-Oct-2020	An amendment (Amendment 6) to the protocol was issued after the primary analysis to add a second interim analysis for OS. The current version of SAP is consistent with this protocol amendment.	An interim analysis has been added at approximately 90% of events. The boundaries for final analysis were updated.
3	20-Oct-2020	To further evaluate the impact of study treatments on subsequent therapies	The following analyses have been added: - Analysis of PFS2 as per investigator - Summary of further anti-myeloma treatments by drug class and by number of lines

SAP version number	Date approved	Rationale	Description of statistical changes
			- ORR, VGPR rate and CR rate on subsequent therapy by number of subsequent line and selected drug class or agent - PFS on first line of further therapy (based on investigator assessment)
3	20-Oct-2020	One analysis was added to better characterize the cytogenetic profile of patients	Summary of gain(1q21) abnormality at baseline
3	20-Oct-2020	Clarification	Definition of R-ISS stage was clarified
3	20-Oct-2020	One analysis was added to identify the TEAEs related to COVID19	Summary of COVID19 related TEAEs
3	20-Oct-2020	Some analyses were planned only for the primary analysis or will not be provided at time of second interim and final OS analyses because not deemed relevant at this stage of the study	A table describing analyses that will be provided at time of primary analysis of PFS and second interim and final OS analyses has been added in section 3.
2	07-Nov-2018	Safety analyses were added to better characterize the safety profile and to account for FDA comments on the submission strategy	The following analyses have been added: - Cumulative exposure to treatment in patient-years - Isatuximab dose reductions - Infusions without IR medication - Exposure-adjusted analyses of TEAEs - Indirect antiglobulin test - Neutropenic complications - Thrombocytopenia and haemorrhages - Hemolytic disorders - Autoimmune disorders
2	07-Nov-2018	Sensitivity analyses for PFS and OS were added to further evaluate the efficacy of study treatments	The following sensitivity analyses have been added: - Analysis of PFS as per investigator assessment, ignoring symptomatic deterioration has been added - Analysis adjusting OS for switch to subsequent anti-cancer treatment therapy

SAP version number	Date approved	Rationale	Description of statistical changes
2	07-Nov-2018	Additional exploratory endpoints were added to further characterize the efficacy of study treatments	The following analyses have been added: - Time to first response - Time to best response - Overall response rate based on investigator assessment - Proportion of patients with VGPR or better as best overall response
2	07-Nov-2018	Subgroup analyses were added to further evaluate the efficacy in specific subgroups	The following subgroup analyses have been added: - Age as per eCRF - Regulatory region - Refractory to lenalidomide
2	07-Nov-2018	Some subgroup variables were removed because not deemed relevant based on number of patients and/or further clinical evaluation	The following subgroup analyses have been removed: - Age per IRT - Previous allogenic transplantation - Previous therapy with anti-CD38 mAb - Existing plasmacytomas - Refractory to lenalidomide in last previous regimen - Refractory to IMiD
2	07-Nov-2018	Based on clinical consideration, death due to PD occurring within 45 days after first documentation of PD were used to confirm PD (including death occurring after initiation of further therapy)	- Death due to PD occurring within 45 days after a first documentation of PD based on M-protein is considered as confirmation of PD
2	07-Nov-2018	The following data handling conventions were added to account for cases not described in the previous version of the SAP and that were reported in the database	The following conventions have been added: - Patients who received only one prior therapy will be classified in the "2 or 3 prior lines" stratum as per eCRF. - Convention for missing/partial death dates

SAP version number	Date approved	Rationale	Description of statistical changes
2	07-Nov-2018	To clarify some definitions and analyses	The following definitions have been updated: - Baseline value - Intolerance to lenalidomide and/or PI - Overall number of cycles started - Isatuximab infusion interruption - Planned dose intensity of pomalidomide - Persistent and indeterminate ADA The following analyses have been updated: - Evaluation of confounding for primary analysis (following FDA comment) - Analysis of cytogenetic abnormalities - Analysis of MRD - Analysis of PK parameters - Analyses of ePRO
2	07-Nov-2018	Due to issues in data collection	Removal of analysis of thyroid function parameters

2 STATISTICAL AND ANALYTICAL PROCEDURES

2.1 ANALYSIS ENDPOINTS

2.1.1 Demographic and baseline characteristics

The baseline value is defined as the last value or measurement taken up to the date and time of the first dose of study treatment. For efficacy laboratory parameters (eg, serum and urine M-protein), unscheduled assessment performed on the date of first study treatment administration (Cycle 1 Day 1) will be considered as baseline value; for other laboratory tests, unscheduled assessment performed on the date of first study treatment administration will be considered as post baseline. For patients randomized and not treated, the baseline value is defined as the last available value obtained up to the date and time of randomization.

All baseline safety and efficacy parameters (apart from those listed below) are presented along with summary statistics in the safety and efficacy sections (Section 2.4.5 and Section 2.4.4).

Demographic characteristics

Demographic variables include gender (Male, Female), race (White, Black, Asian, American Indian/Alaska Native, Native Hawaiian/Other Pacific Islander, Not reported, Unknown), ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not reported, Unknown), geographical region (Eastern Europe, Western Europe, North America, Asia, Other countries, see definition in Appendix G), regulatory region (Western countries, Other countries, see definition in Appendix G), age in years (quantitative and qualitative variables : <65, [65 - 75[and ≥75 years), weight (kg), and eastern cooperative oncology group (ECOG) performance status (PS) at baseline.

Medical or surgical history

Medical or surgical history includes relevant history of previous or associated pathologies other than multiple myeloma including respiratory function history and smoking status.

This information will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 21.0 or higher. Respiratory function history will be analyzed using two groupings (see details in Section 2.1.4.1).

MM characteristics at diagnosis

The following multiple myeloma characteristics at initial diagnosis will be described:

- Time from initial diagnosis of MM to randomization (in years).
- ISS stage (as collected in eCRF).
- MM type: heavy and light chain component (as collected in eCRF).
- Bi-clonal status (as collected in eCRF).

MM characteristics at study entry

The following MM characteristics at study entry will be described:

- ISS stage (see definition in Table 2), β2-microglobulin level in mg/L (quantitative results and by category : <3.5 mg/L, [3.5-5.5 mg/L[and ≥5.5 mg/L), albumin in g/L (quantitative results and by category: <35 g/L and ≥35 g/L).
- Revised ISS (see definition in R-ISS, Table 3), serum LDH (≤ULN, >ULN) and cytogenetic abnormality (CA).
- Cytogenetic abnormalities from central FISH assessment:
  - Number and percentage of patients with cytogenetic abnormality for del(17p), t(4;14), and t(14;16). Abnormality is defined as at least 30% of abnormal plasma cells for t(4;14), and t(14;16), and at least 50% of abnormal plasma cells for del(17p)
  - Type of risk: Standard risk, high-risk (defined as presence of del(17p) and /or translocation t(4;14) and /or translocation t(14;16) abnormality) and unknown/missing
  - Number of patients with 2 abnormalities: del(17p) and t(4,14); and, del(17p) and t(14,16)
- Gain(1q21) abnormality. Abnormality is considered positive if present in at least 30% of analyzed plasma cells. Isolated gain(1q21), defined as gain(1q21) abnormality and otherwise standard-risk cytogenetics will also be summarized.
- MM type: Heavy and light chain components (as collected in eCRF).
- Bi-clonal status (as collected in eCRF).
- Refractory status
  - Relapsed and refractory: non-responsive while on salvage therapy or progresses within 60 days of last therapy in patients who have achieved minimal response or better at some point previously before then progressing in their disease course,
  - Primary refractory: never achieve MR or better in any prior therapies,
  - Relapse: all cases not meeting the relapse and refractory or primary refractory definition.
- Measurable paraprotein at baseline (according to central laboratory) (Table 4),
- % of plasma cells in bone marrow at baseline (quantitative and qualitative variables: 0%,]0-5%[, [5-20%[, [20-50%[and ≥50%),
- Patients with plasmacytoma (as per investigator and IRC),
- Patients with bone lesions and number of lesions (as per investigator and IRC)

Table 2 - ISS staging definition

Stage	Definition
Stage I	β2-microglobulin <3.5 mg/L and albumin ≥35 g/L
Stage II	[β2-microglobulin <3.5 mg/L and albumin <35 g/L] or [β2-microglobulin 3.5 - <5.5 mg/L]
Stage III	β2-microglobulin ≥5.5 mg/L

Table 3 - R-ISS staging definition

Stage	Definition
Stage I	β2-microglobulin <3.5 mg/L and albumin ≥35 g/L and no high-risk CA and LDH ≤ULN
Stage II	Not R-ISS stage I or III
Stage III	β2-microglobulin ≥5.5 mg/L and either high-risk CA by iFISH or LDH >ULN
Not classified	Inconclusive iFISH unless stage III can be determined on LDH and β2 microglobulin only

High-risk CA by iFISH: Presence of del(17p) and /or translocation t(4;14) and /or translocation t(14;16)

CA: Cytogenetic abnormalities

iFISH: interphase fluorescent in situ hybridization

Table 4 - Derivation of measurable paraprotein type at baseline

Measurable paraprotein at baseline	Criteria
Serum M-Protein	Serum M-protein ≥0.5 g/dL and urine M-protein <200 mg/24 hours or negative or missing urine M-protein
Urine M-Protein	Serum M-protein <0.5 g/dL or negative serum M-protein and urine M-protein ≥200 mg/24 hours
Serum and urine M-protein	Serum M-protein ≥0.5 g/dL and urine M-protein ≥200 mg/24 hours

Prior anti-myeloma therapies

- Prior anti-myeloma treatments

  Prior anti-myeloma treatments are collected by regimen in the eCRF. The following variables will be summarized/derived:

  - Number of prior regimens,
  - Number of prior lines (as defined in Appendix E of the study protocol): a line of therapy consists of ≥1 completed cycle of a single agent or a regimen consisting of a combination of several drugs, or a planned sequential therapy of various regimens,
  - Main anti-myeloma therapies by class and agent
    - Alkylating agents: cyclophosphamide, melphalan, bendamustine,
    - Proteasome inhibitors: bortezomib, carfilzomib, ixazomib,
    - Immunomodulators: lenalidomide, thalidomide, pomalidomide,

- Monoclonal antibodies: elotuzumab and other anti CD38 agents (daratumumab, MOR202)
- Anthracyclines
- Vinca alkaloids
- Corticosteroids
- HDAC inhibitors

In addition, the refractory status to immunomodulators and/or proteasome inhibitors will be derived. A patient will be considered to be refractory to a drug if any of the following conditions is met:

- Progression date and end date are complete and progression is before drug end date or within (≤) 60 days of drug end date. If only the day is missing for either date or both dates, the 2 dates should be separated by no more than 1 month,
- Best overall response is SD or PD,
- Reason for treatment discontinuation is "Disease progression".

- Intolerance to lenalidomide and/or proteasome inhibitors
  - Derived from patients who discontinued lenalidomide and/or proteasome inhibitor after a minimum of approximately 2 consecutive cycles (49 days corresponding to 2 4-week cycles minus 1 week) for AE.
- Description of last regimen given prior to study entry:
  - Time from completion of last line of treatment to first study treatment administration (months),
  - Main treatments,
  - Best response to last regimen,
  - Duration of last regimen of therapy,
  - Refractory status as defined above.

- Prior transplant: number (%) of patients with transplant, type of transplant (autologous, allogenic), number of transplant by patient.
- Prior surgery: number (%) of patients with any prior surgery related to MM, type of procedure and time from last surgery to first study treatment administration (months).
- Prior radiotherapy: number (%) of patients with any prior radiotherapy related to MM, intent and time from last radiotherapy to first study treatment administration (months).

2.1.2 Prior or concomitant medications (other than anticancer therapies)

All medications taken within 21 days before randomization and until the end of the study are to be reported in the case report form pages.

All medications will be coded using the World Health Organization-Drug Dictionary (WHO-DD) using the version MAR2018 or higher.

- Prior medications are those the patient used prior to first investigational medicinal product (IMP) intake. Prior medications can be discontinued before first administration or can be ongoing during treatment phase.

- Concomitant medications are any treatments received by the patient concomitantly to the IMP(s), from first administration to the last dose + 30 days. A given medication can be classified both as a prior medication and as a concomitant medication. Any anti-cancer treatment administered after the date of the last study treatment administration will not be considered as a concomitant medication and will be regarded as a further anti-myeloma therapy (see Section 2.1.9). The analysis of concomitant medications will include the IR medications (see below).
- Post treatment medications are those the patient took in the period running from 30 days after the last dose up to the end of the study.

IR medications

As defined in Section 8.2.2 of the study protocol, patients will routinely receive premedications prior to isatuximab infusion to reduce the risk and severity of infusion reactions (IRs) commonly observed with monoclonal antibodies. Premedications are defined in the protocol as non-investigational medicinal product(s) and should be reported in a specific form of the eCRF. Analysis of premedications will focus on those given (drug class, start and stop dates) for prophylaxis reason. Dexamethasone being part of study treatment and reported in IMP form of the CRF, only steroids reported in the IR medication eCRF form will be described with IR medication.

Medication given in curative intent of IR will be also analyzed by type (Diphenhydramine or equivalent, steroids, paracetamol or equivalent).

Any technical details related to computation, dates, imputation for missing dates are described in Section 2.5.

2.1.3 Efficacy endpoints

2.1.3.1 Primary efficacy endpoint(s)

The primary endpoint is Progression Free Survival (PFS) defined as the time from the date of randomization to the first documented date of progressive disease or death due to any cause before the analysis cut-off, whichever comes first. Patients without disease progression or death before the analysis cut-off or the date of initiation of further anti-myeloma treatment, will be censored at the earliest of the date of the last valid disease assessment not showing disease progression performed prior to initiation of a further anti-myeloma treatment (if any) or the analysis cut-off date, whichever comes first.

An independent response committee (IRC) blinded to the randomization arm and to the patient characteristics will evaluate disease assessments at each time point and determine disease response including progression status per IMWG criteria (1) (Appendix D). The full details regarding the determination of the progressive disease are provided in protocol and the IRC charter. The date of disease progression as determined by the IRC will be used for primary PFS analysis.

A patient without PFS event (death or disease progression) and without any valid post-baseline disease assessments will be censored at the day of randomization (Day 1).

Additional details regarding the definition of PFS and handling of events and censoring are given in Appendix E.

Other censoring rules used for sensitivity analyses are provided in Section 2.4.4.1.1.

Assessment of progression

Efficacy assessment will be performed on Day 1 of every cycle during treatment. After treatment discontinuation, for patients who discontinued study treatment for reasons other than progression, disease assessments will be performed every 4 weeks during follow-up until PD.

Response and progression as per IRC will be determined on the basis of central laboratory findings, bone marrow biopsy/aspiration if any, and evaluation of plasmacytomas/bone lesions if any, according to IMWG criteria (Appendix D). Progression based on paraprotein will have to be confirmed based on 2 consecutive assessments. An assessment performed after the initiation of a further anti-myeloma treatment will be used to confirm progressive disease. In addition, death due to progressive disease occurring within 45 days of the first documentation of progression (regardless initiation of further therapies) will be used to confirm PD.

Progression based on plasmacytomas/bone lesions does not require confirmation.

Symptomatic deterioration will not be considered progression in the primary analysis of PFS.

Progression cannot be diagnosed on free light chain (FLC) progression only. For patients with non-measurable M-Protein on Cycle 1 Day 1, PD can be diagnosed on the following parameters:

- For patients with only FLC measurable: M-protein, plasmacytomas, according to IMWG criteria described above
- For patients with non-measurable disease: M-protein, plasmacytoma, according to IMWG criteria described above

Date of disease progression determination

The date of the disease progression is the earliest date that indicates disease progression (provided that the progression is subsequently confirmed in case of progression requiring confirmation). Details will be provided in the Independent Review Charter.

Determination of the PFS status for the primary analysis

The following rules will be applied to determine if a patient has an event or is censored for the PFS primary analysis:

- For a patient who did not die and did not reach progressive disease before the cut-off date, the patient is censored and the censoring date is determined as follows:
  - If the patient received any further anti-myeloma treatment, then the censoring date is the date of last valid disease assessment without evidence of PD before the start of further anti-myeloma treatment, or the cut-off date, whichever comes first,
  - If the patient did not take any further anti-myeloma treatment then the censoring date is the date of last valid disease assessment without evidence of PD or the cut-off date, whichever comes first.
- For a patient who died or reached progressive disease before the cut-off date:
  - If the patient received any further anti-myeloma treatment before death or progression is documented, then the censoring date is the date of last valid disease assessment without evidence of PD before the start of further anti-myeloma treatment,
  - If the patient reached the PFS endpoint before initiation of further anti-myeloma treatment, the date of the event will be the date of progressive disease or death if no progression occurred.

Valid disease assessment

A valid post-baseline disease assessment is one for which the "time point response" is not "NE" (not evaluable) as per IMWG (see Appendix D). If the date of assessment is missing, the disease assessment is not valid.

Date of last valid disease assessment without evidence of PD: For a given time point not showing disease progression, if several exams are performed at different dates, the date of the last valid disease assessment is the date of latest exam.

Non-evaluable cases

Missing exams: if one protocol planned examination is missing for a given disease assessment, the overall response should generally be NE or response assessment should be downgraded to the lowest IMWG response criteria unless there is clear evidence of progression (independently of the missing examination). Specific rules applying to missing serum or urine M-protein are described in the IRC charter.

For the primary analysis of PFS, progression or death occurring after a disease evaluation with an overall time point response(s) equal to NE will be considered as an event in the analysis.
Such progression or death will be censored in the PFS sensitivity analysis #5 if occurring more than 8 weeks after the last valid tumor assessment without progression.

2.1.3.2 Secondary efficacy endpoint(s)

2.1.3.2.1 Key secondary efficacy endpoints

Two key secondary efficacy endpoints are considered:

- Overall Response Rate (ORR), as per IMWG criteria.
- Overall Survival (OS).

Best Overall Response (BOR) and Clinical Benefit Rate will also be derived.

Overall response rate (ORR)

ORR is defined as the proportion of patients with stringent complete response (sCR), complete response (CR), very good partial response (VGPR), and partial response (PR), as BOR, assessed by the IRC using the IMWG response criteria.

For patients with non-measurable M-Protein on Cycle 1 Day 1 the only 3 possible overall responses are: CR, non-PD or PD (see Appendix D).

An additional analysis of ORR using investigator assessment of response will also be performed.

Overall survival (OS)

OS is defined as the time from the date of randomization to date of death from any cause. If death is not observed before the analysis data cut-off date, OS will be censored at the last date that the patient is known to be alive or at the cut-off date, whichever comes first.

Best Overall Response (BOR)

BOR is defined as the best sequential response, using the IRC's assessment of response, from the start of treatment until disease progression (provided that the progression is subsequently confirmed in case of progression requiring confirmation), death, initiation of further anti-myeloma treatment, or cutoff date, whichever occurs first. The ordering of evaluations from best to worse is: stringent complete response (sCR), complete response (CR), very good partial response (VGPR), partial response (PR), minimal response (MR), stable disease (SD), progressive disease (PD), not evaluable (NE). In addition, for patients with VGPR as BOR, the following subcategories will be assessed by the IRC: biochemical CR and near CR.

A confirmation assessment for disease response is required in this study (either MR or better, or PD, except PD diagnosed on radiological assessment).

BOR according to investigator assessment of response will also be provided.

Clinical Benefit Rate (CBR)

CBR is defined as the proportion of patients achieving a MR or better as BOR.

VGPR Rate

VGPR rate is defined as the proportion of patients achieving a VGPR or better as BOR.

2.1.3.2.2 Other secondary efficacy endpoints

Other secondary efficacy endpoints will be evaluated as follows:

Time to Progression (TTP)

TTP is defined as the time from the date of randomization to the date of first documentation of progressive disease (as determined by IRC). The same definition of progression and same censoring rules as for the PFS primary endpoint will be used.

PFS in the high risk cytogenetic population

It is defined as PFS (Section 2.1.3.1) in the subgroup of patients carrying del(17p) and/or t(4;14) and/or t(14;16) assessed by FISH.

Duration of response (DOR)

DOR is defined as the time from the date of the first IRC determined response that is subsequently confirmed to the date of first documented progression as assessed by IRC or death, whichever happens first. In the absence of the confirmation of subsequent disease progression or death before the analysis cut-off date, the DOR will be censored at the date of the last valid disease assessment not showing disease progression performed prior to initiation of a further anti-myeloma treatment or the analysis cut-off date, whichever is earlier.

Duration of response is determined only for patients who have achieved a response of PR or better (subsequently confirmed).

Time to first response (TT1R)

TT1R is defined as the time from randomization to the date of first IRC determined response (PR or better) that is subsequently confirmed. In the absence of response, patients will be censored at the earliest of the date of the last valid disease assessment before disease progression or death, the date of the last valid disease assessment before initiation of a further anti-myeloma treatment (if any) or the analysis cut-off date, whichever comes first.

Time to best response (TTBR)

TTBR is defined as the time from randomization to the date of first occurrence of IRC determined best overall response (PR or better) that is subsequently confirmed. In the absence of response patients will be censored at the earliest of the date of the last valid disease assessment before

disease progression or death, the date of the last valid disease assessment before initiation of a further anti-myeloma treatment (if any) or the analysis cut-off date, whichever comes first.

Minimal residual disease (MRD)

MRD will be assessed by next-generation sequencing in bone marrow samples from patients who achieve CR, to determine the depth of response at the molecular level.

2.1.3.2.3 Other exploratory efficacy endpoints

PFS2

PFS2 is defined as time from the date of randomization to the date of first documentation of PD (as reported by the investigator) after initiation of further anti-myeloma treatment or death from any cause, whichever happens first. For patients alive without a progression after initiation of further anti-myeloma treatment before the analysis cut-off date, PFS2 will be censored at the date of the last follow-up visit not showing disease progression after initiation of further anti-myeloma treatment or the analysis cut-off date, whichever comes first. Additional details regarding the definition of PFS2 and handling of events and censoring are given in Appendix H.

ORR on further therapy

ORR on further anti-myeloma treatments will be based on BOR as reported by the investigator.

PFS on first line of further therapy

PFS on first line of further therapy is defined as time from the start date of first line of further therapy to the date of first documentation of PD (as reported by the investigator) after initiation of first line of further therapy or death from any cause, whichever happens first. For patients alive without a progression after initiation of further therapy before the analysis cut-off or the start date of next line of further treatment, PFS on further therapy will be censored at the earliest of the date of the start of next line of further treatment (if any), the date of the last follow-up visit not showing disease progression or the analysis cut-off date, whichever comes first.

If the first line of further therapy includes daratumumab then the start date of first line of further therapy will be defined as the start date of daratumumab.

2.1.4 Safety endpoints

The safety analysis will be based on the reported adverse events (AEs) and other safety information, such as clinical laboratory data, vital signs, weight and Eastern Cooperative Oncology Group (ECOG) performance status (PS).

Observation period

The observation period starts from the time when the patient gives informed consent and is divided into 3 periods:

- The **pre-treatment** period is defined as the time from the signed informed consent date up to the first dose of study treatments.
- The **treatment** period is defined as the time from the first dose of study treatments administration to the last dose of study treatments + 30 days.
- The **post treatment** period is defined as the period of time starting the day after the end of the treatment period up to the end of the study (as defined in the protocol).

2.1.4.1 Adverse events variables

AEs (including serious adverse events [SAEs] and AEs of special interest [AESI]) will be collected from the time of signed informed consent until the end of study.

Adverse event observation period

- Pre-treatment adverse events are defined as any adverse event reported during the pre-treatment period.
- Treatment-emergent adverse events (TEAEs) are adverse events that developed or worsened or became serious during the treatment period.
- Post-treatment adverse events are adverse events that developed or worsened or became serious during the post-treatment period.

All AEs (including SAEs and AESI) will be graded according to National cancer institute common terminology for adverse events (NCI-CTCAE) v4.03 and coded to a lower-level term (LLT), preferred term (PT), high-level term (HLT), high-level group term (HLGT) and associated primary system organ class (SOC) using the version of Medical Dictionary for Regulatory Activities (MedDRA) currently in effect at Sanofi at the time of database lock.

Adverse events of special interest

AESI include the following terms:

- Acute infusion reactions (IRs) of Grade 3 or 4.
- Pregnancy of female patient entered in a study as well as pregnancy occurring in a female partner of a male entered in a study with IMP.
- Symptomatic overdose (serious or non-serious) with study treatment (isatuximab, pomalidomide or dexamethasone).
- Second Primary Malignancy.

Infusion reactions

IRs are commonly observed with monoclonal antibodies and typically occur within 24 hours from the start of each isatuximab infusion.

Whenever possible, a diagnosis of the IR (eg, Cytokine release syndrome, infusion related reaction, anaphylactic reaction, hypersensitivity) will be reported by the investigator in a specific AE page instead of individual symptoms.

In addition, symptoms of the IRs will be reported on a separate eCRF form.

IRs will be analyzed using the Investigator reported term collected in the specific AE forms.

Another analysis will be based on any TEAEs (both regardless of relationship and related TEAEs) occurring within 24 hours from the start of any isatuximab infusion (ie, TEAEs with onset on the same calendar day of the isatuximab infusion or on the following day).

A similar analysis including TEAEs occurring within 24 hours in the "Hypersensitivity and CRS" CMQ will also be performed.

All TEAEs (not only limited to those occurring within 24h of any isatuximab administration) from the above listed CMQ will also be analyzed in both arms.

Respiratory AEs

Analysis of selected respiratory TEAEs will focus particularly on the following groupings:

- Lower Respiratory adverse events, selected using CMQ 'Lower respiratory events'.
- Respiratory infections, selected using CMQ 'Respiratory infections'.

Late respiratory adverse events (ie, occurring, worsening or becoming serious more than 30 days after last dose) will be analyzed as part of the post-TEAEs analysis.

Neutropenia and neutropenic complications

Neutropenia, febrile neutropenia and neutropenic infections will be analyzed using the following data source:

- Neutropenia based on laboratory results.
- Febrile neutropenia selected using CMQ 'Febrile neutropenia'
- Neutropenic infections: defined as NCI-CTCAE Grade ≥ 2 infections from SOC 'Infections and Infestations' (selected using CMQ 'GLB_SOC infections and infestations') concomitant with NCI-CTCAE Grade 3-4 neutropenia from laboratory results. Infection and Grade 3-4 neutropenia will be considered as concomitant if one of the following condition is met:
  - neutrophils count value measured the day of the start of the AE infection,

- the last neutrophils count value measured before the start date of the AE infection is within 7 days before the start of the AE infection,
- the first neutrophils count value measured after the start date of the AE infection is within 2 days after the start of the AE infection.

Thrombocytopenia and hemorrhages

- Thrombocytopenia will be analyzed based on laboratory results
- Hemorrhages will be selected using the TEAEs from the CMQ 'Haemorrhage terms (excl laboratory terms)'.
- Moreover, severe thrombocytopenia (ie, Grade 4) with concomitant hemorrhage will be displayed if relevant (ie, in case of imbalance between treatment arms). The first hemorrhages event occurring within 8 days after any occurrence of the thrombocytopenia (Lab) will be used for this analysis.

Hemolytic disorders

Hemolytic disorders will be selected using the TEAEs from the CMQ 'Haemolytic disorders Broad'.

Hemolytic disorders that occurred within 8 days after the blood cell transfusion (red blood cells or platelets) will be displayed.

Tumor lysis syndrome

Tumor lysis syndrome will be identified using the TEAEs from the CMQ 'Tumour lysis syndrome'.

Autoimmune disorders

Autoimmune disorders will be selected using the TEAE from the CMQ 'GLB_HLGT Autoimmune disorders'.

Second primary malignancies

Second primary malignancies will be selected using CMQ 'Second primary malignancies' and will be sub-categorized as 'haematological', 'non-hematological skin tumors', 'non-hematological non-skin tumors' and 'other tumors'.

COVID19

COVID19 related TEAEs will be selected using CMQ 'COVID19_specific list'.

2.1.4.2 Deaths

The deaths observation periods are per the observation periods defined above.

- Death on-treatment: deaths occurring during the TEAE period.
- Death post-treatment: deaths occurring during the post-treatment period.

2.1.4.3 Laboratory safety variables

Clinical laboratory data consists of blood analysis (including hematology, biochemistry) and urinalysis. Clinical laboratory values will be converted into standard international units and international units that will be used in all listings and tables.

Blood samples for clinical laboratories will be taken as defined in the study flowchart and as clinically indicated. The following laboratory parameters will be analyzed and will be classified as follows:

- Hematology
  - **Red blood cells (RBC) and coagulation**: hemoglobin, hematocrit, RBC, prothrombin time (PT) or international normalized ratio (INR), activated partial thromboplastin time (aPTT),
  - **Platelet count,**
  - **White blood cells (WBC):** WBC with differential, absolute neutrophil count (ANC), lymphocyte count.
- Biochemistry
  - **Metabolism:** fasting glucose, total protein, albumin,
  - **Electrolytes**: sodium, potassium, chloride, calcium, corrected serum calcium, bicarbonate/carbon dioxide, magnesium, phosphate,
  - **Renal function**: serum creatinine, estimated creatinine clearance by MDRD formula, urea or blood urea nitrogen (BUN), uric acid,
  - **Liver parameters**: alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, lactate dehydrogenase (LDH), total and direct bilirubin,
  - **Pregnancy test**: female patients of childbearing potential,
- Urinalysis
  - **Quantitative urinalysis** (at baseline only): red blood cells, protein, glucose, pH, ketones, bilirubin, leucocytes,
  - **Qualitative urinalysis** (during treatment period): blood, leukocytes, protein, glucose, ketone, pH, bilirubin,

Technical formulas are described in Section 2.5.1.

2.1.4.4 Vital signs variables

Vital signs include: heart rate, systolic and diastolic blood pressure, weight and ECOG PS (0, 1, 2, 3, 4).

2.1.4.5 Electrocardiogram variables

Electrocardiogram assessments will be described as normal or abnormal. An interpretation of the results (normal/abnormal) is to be entered in the eCRF. In case of abnormal result a description of the finding should be reported. If the abnormality meets the definition of TEAE it will also have to be reported as AE.

2.1.4.6 Other safety endpoints

Other safety endpoints include:

- IR laboratory tests (IPd arm only):
  - Cytokines (TNF-α, IL-1-β, IL-4, IL-6, IFN-γ),
  - Markers of complement (C3a, C4, CH50),
  - Serum tryptase.
- Indirect antiglobuline test (IAT)

2.1.5 Pharmacokinetic variables

The population PK parameters of isatuximab and their inter-patients will be estimated. The effect of pomalidomide, pathophysiological and demographic covariates on main PK parameters will be assessed.

Empirical Bayesian estimation of individual parameters and of individual exposure (Area Under the Curve [AUC]) will also be performed.

Analysis of PK variables will be presented in a separate report.

2.1.6 Immunogenicity

Human anti-drug antibodies (ADAs) to isatuximab will be assessed during the study as described in the protocol for the IPd arm only and will be analyzed using the ADA population (see Section 2.3.4).

Periods of observation:

- ADA pre-treatment period: The ADA pre-treatment period is defined as the time from signed informed consent to the first isatuximab administration.
- ADA on-study observation period: the ADA on-study observation period is defined as the time from first isatuximab administration until the end of the study.

ADA attributes:

- **Pre-existing ADAs** are defined as ADAs that were present in samples drawn during the pre-treatment period.
- **Treatment boosted ADAs** are defined as pre-existing ADA with an increase in titer value between pre-treatment and post-treatment samples of at least two titer steps. Assuming a 2-fold serial dilution schema is used for the study, this means that the post-treatment sample titer value is at least (≥) 4 fold of pre-treatment titer value.
- **Treatment induced ADAs** are defined as ADAs that developed at any time during the ADA on-study observation period in patients without pre-existing ADA, including patients without pre-treatment samples.
- **Transient ADA response** is defined by:
  - Treatment-induced ADA detected only at one sampling time point during the ADA on-study observation period (excluding the last sampling time point) OR,
  - Treatment-induced ADA detected at two or more sampling time points during the on-study observation period, where the first and last ADA-positive samples (irrespective of any negative samples in between) are separated by a period less than 16 weeks and the subject's last sampling time point is ADA-negative.
- **Persistent ADA response** is defined by:
  - Treatment-induced ADA detected at two or more sampling time points during the ADA on-study observation period, where the first and last ADA-positive on-study samples are separated by a period of 16 weeks or longer (irrespective of any negative samples in between),
- **Indeterminate ADA response** is defined by:
  - Treatment-induced ADA detected only the last sampling time point with all prior samples being negative, OR,
  - The last two samples are ADA-positive and separated by a period of less than 16 weeks.

ADA response endpoints:

- **ADA negative patients** are patients without any treatment induced or treatment boosted ADA during the on-study observation period.
- **ADA incidence** is defined as proportion of **ADA positive patients**, ie, patients with at least one treatment induced or treatment boosted ADA at any time during the on-study observation period.
- **ADA prevalence** is defined as proportion of all patients tested positive for ADAs (including preexisting ADAs, treatment boosted ADAs and treatment induced ADAs) at any time point.

2.1.7 Health-related quality-of-life endpoints

Health-related quality of life (HRQL) will be assessed using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire – Cancer specific module with

30 items (EORTC QLQ-C30) and the EORTC QLQ myeloma-specific module with 20 items (MY20). Health status and health utility will be assessed using the EuroQol measure with 5-dimensions and 5-levels per dimension EQ-5D-5L (2,3,4,5,6).

The QLQ-C30 incorporates a Global Health Status/QoL scale, five functional scales (Physical functioning [PF2], Role functioning [RF2], Cognitive functioning [CF], Emotional functioning [EF] and Social functioning [SF]), three symptom scales (Fatigue [FA], Pain [PA] and Nausea/Vomiting [NV]) and six additional single items (Dyspnoea [DY], Insomnia [SL], Appetite Loss [AP], Constipation [CO], Diarrhoea [DI] and Financial Difficulties [FI]) as symptoms commonly reported by cancer patients and the perceived financial impact of the disease.

The EORTC QLQ-MY20 (MY20) is meant for use among patients with multiple myeloma cancer and comprised of:

- 2 functional subscales (body image, future perspective), (higher scores better = greater functionality).
- 2 symptoms scales (disease symptoms and side-effects of treatment) (higher scores worse = more symptomatic).

Raw scores (RS)/scores for the EORTC are calculated using EORTC QLQ-C30 and EORTC QLQ-MY20 scoring formulas (detailed in Appendix F):

- RS is the mean of the component items.
- For the Functional scales: Score = [1− ((RS− 1)/range)]x100.
- For Symptom scales / single items scales and the Global health status/QoL scale: Score = [(RS − 1)/ range]x100.

The range is the difference between the maximum and the minimum response to individual items.

The EQ-5D-5L incorporates the EQ-5D descriptive system and a visual analogue scale (VAS).

The EQ VAS records the respondent's self-rated health on a 20 cm vertical, visual analogue scale with endpoints labelled 'the best health you can imagine' and 'the worst health you can imagine'. This information can be used as a quantitative measure of health as judged by the individual respondents.

The EQ-5D-5L descriptive system comprises the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems and extreme problems.

For EQ-5D-5L, VAS will be described as given by patient and health utility index will be calculated according to EuroQol specific country algorithms. In case a specific country algorithm is missing the value sets based on the UK population will be used to generate health utility scores.

Rules of handling with missing items are detailed in Appendix F for the EORTC questionnaires while missing values are treated in the Crosswalk value sets for the EQ-5D-5L.

2.1.8 Exploratory biomarker analysis

2.1.8.1 Immune Genetic Determinants

A blood sample will be collected at Day 1 of Cycle 1. Leukocyte DNA will be extracted and analyzed for immune genetic determinants (such as FcγR polymorphisms, HLA and KIR genotypes) and correlated with parameters of clinical response.

Germline genetic data of FcγR, HLA and KIR genes will be analyzed on blood samples collected on D1 of Cycle 1:

- FCGR polymorphisms (FCGR2A and FCGR3A): For each gene, the results will be of the form AA, Aa or aa with A and a-alleles, the major and minor allele, respectively.
- HLA genotypes: HLA-A, HLA-B and HLA-C have been typed (see Table 5).

Table 5 - Epitopes of HLA Class I recognized by KIR

		Amino-acid at position[a]					
HLA class I	Epitope	77	80	81	82	83	
HLA-B	Bw6	Ser	Asn	Leu	Arg	Gly	
	Bw4	Asn	Thr	Ala	Leu	Arg	
	Bw4	Asn	Ile	Ala	Leu	Arg	
	Bw4	Asp	Thr	Leu	Leu	Arg	
	Bw4	Ser	Thr	Leu	Leu	Arg	
	Bw4	Ser	Thr	Ala	Leu	Arg	
HLA class I	Epitope	77	80	81	82	83	Associated allotypes
HLA-A	Aw4	Asn	Ile	Ala	Leu	Arg	A*23; A*24
	Aw4	Ser	Ile	Ala	Leu	Arg	A*32
	A3	Key residues not yet published					A*03
	A11	Key residues not yet published					A*11
HLA class I	Epitope	77	80				
HLA-C	C1	Ser	Asn				
	C2	Asn	Lys				

[a] Numbering from the first codon of the mature protein

- KIR genotypes: The presence or absence of 16 KIR genes will be screened. A KIR gene will be defined as present if at least one assay gives positive results; otherwise it will be defined as negative.

Results of immune genetic determinants analyses will be presented in a separate report.

In addition, samples (serum) will be collected to evaluate the potential isatuximab interference with the M protein assessment in immunoelectrophoresis and immunofixation assays. These additional samples will be collected at all time-points that M protein is analyzed for patient treated in IPd arm.

2.1.9 Further therapy after discontinuation of investigational medicinal product administration during the study

Further therapies after discontinuation of IMP include further anti-myeloma treatments.

Time to Next Treatment

TNT is defined as the time from randomization to the start of further anti-myeloma treatment. Patients who do not receive any further anti-myeloma treatment before the cut-off date will be censored at the date of their last FU visit or the cut-off date, whichever comes first. Patients with no FU visit will be censored at their last study treatment administration or the cut-off date whichever comes first.

2.2 DISPOSITION OF PATIENTS

This section describes patient disposition for both patient study status and the patient analysis populations.

Screened patients are defined as any patients who signed the study informed consent.

Randomized patients consist of all patients with a signed informed consent who have been allocated a randomization number by the IRT, regardless of whether the patient was treated or not.

For patient study status, patients in each of the following categories will be presented in the clinical study report using a flowchart diagram or summary table:

- Screened patients.
- Screen failure patients and reasons for screen failure (if any).
- Randomized patients.
- Randomized but not treated patients.
- Randomized and treated patients.
- Patients who discontinued study treatment.
- Patients still on treatment.
- Status at last study contact.
- Patients with date of last contact obtained before the cutoff date and duration from last contact to cut-off date (0-2 weeks, 2-4 weeks, 4-8 weeks, >8 weeks).

A summary of the reasons for definitive and premature treatment discontinuation by treatment group will be provided. Definitive treatment discontinuation is defined as the discontinuation of all the study drugs. Premature treatment discontinuation is defined as the discontinuation of at least one of the study drugs but at least one is continued.

For all categories of patients (except for the screened and non-randomized categories) percentages will be calculated using the number of randomized patients as the denominator.

All critical or major deviations potentially impacting efficacy analyses, randomization, and drug-dispensing irregularities and other major or critical deviations will be summarized in tables giving numbers and percentages of deviations by treatment group.

Additionally, the following analysis populations will be summarized in a table by number of patients on the randomized population and on safety population respectively:

- Randomized population.
- Efficacy population: intent-to-treat (ITT) population.
- Safety population.
- Pharmacokinetics population.
- ADA population.
- Biomarker population.

Definition of study populations are provided in Section 2.3.

2.2.1 Randomization and drug dispensing irregularities

Randomization and drug-dispensing irregularities occur whenever:

1. A randomization is not in accordance with the protocol-defined randomization method, such as a patient is randomized based on an incorrect stratum, or a patient is randomized twice.

   OR

2. A patient is dispensed an IMP not allocated by the protocol-defined randomization, such as a patient at any time in the study is dispensed a different IMP than as allocated, or a non-randomized patient is treated with IMP reserved for randomized patients.

Randomization and drug-dispensing irregularities will be monitored throughout the study and reviewed on an ongoing basis.

All randomization and drug-dispensing irregularities will be documented in the clinical study report. These irregularities will be summarized by treatment group on the randomized population (number and percentages). Non-randomized, treated patients will be described separately.

Randomization and drug-dispensing irregularities to be prospectively identified include but are not limited to:

Randomization and drug allocation irregularities
IMP dispensation without IRT transaction
Erroneous therapy dispensation (ie patient is dispensed a combination of drugs that does not correspond to the randomization arm)
Patient randomized twice
Stratification error

2.3 ANALYSIS POPULATIONS

The randomized population includes all randomized patients as defined in Section 2.2.

For any patient randomized more than once, only the data associated with the first randomization will be used in any analysis population. The safety experience associated with any later randomization will be assessed separately.

2.3.1 Efficacy populations

2.3.1.1 Intent–to-treat

The intent-to-treat population is the randomized population. In this population, patients will be analyzed according to the treatment group allocated by IRT, regardless of whether patients receive any study drug or receive a different study drug from which they were randomized.

This population is the primary population for all efficacy parameters.

2.3.2 Safety population

The safety population will include patients from the ITT population who actually received at least one dose or part of a dose of the study treatments. This population is the primary population for the analysis of safety parameters. All analyses using this population will be based on the treatment actually received.

In addition:

- Non-randomized but treated patients will not be part of the safety population; however, their safety data will be presented separately.
- Randomized patients for whom it is unclear whether they took the IMP will be included in the safety population as randomized.
- Patients who receive at least 1 isatuximab dose (even incomplete or by error at one cycle) during the trial, will be analyzed in the IPd arm.

2.3.3 Pharmacokinetics population

The PK population will include safety population patients from the IPd arm who receive at least 1 dose of isatuximab, even if incomplete, with data for at least 1 PK parameter available post-baseline.

2.3.4 ADA population

The ADA population will include safety population patients from the IPd arm with at least one ADA assessment during the ADA on-study observation period with a reportable result.

2.3.5 Biomarker population

The analysis population for immune genetic biomarkers will be defined as the set of patients from ITT population evaluable for at least one of the genetic biomarkers

2.4 STATISTICAL METHODS

Continuous data will be summarized using the number of available data, mean, standard deviation (SD), median, minimum and maximum for each treatment group. Categorical and ordinal data will be summarized using the number and percentage of patients in each treatment group.

2.4.1 Demographics and baseline characteristics

Parameters described in Section 2.1.1 will be summarized on the randomized population by treatment group (as allocated by IRT) and overall treatment groups using descriptive statistics. Analyses for the safety population will be included in the appendices if the size of the safety population is different (>10%) from the size of that in the primary analysis population for any treatment group.

Past medical or surgical history will be summarized by SOC and PT (SOC will be sorted according to the internationally agreed order and PT by decreasing frequency).

2.4.2 Prior or concomitant medications (other than anticancer therapies)

The prior and concomitant medications will be presented for the randomized population.

Medications will be summarized by treatment group according to the WHO-DD dictionary, considering the first digit of the anatomic category (ATC) class (anatomic category) and the first 3 digits of the ATC class (therapeutic category). All ATC codes corresponding to a medication will be summarized, and patients will be counted once in each ATC category (anatomic or therapeutic) linked to the medication. Therefore patients may be counted several times for the same medication.

The table for prior medications will be sorted by decreasing frequency of ATC followed by all other therapeutic classes based on the overall incidence across treatment groups. In case of equal frequency regarding ATCs (anatomic or therapeutic categories), alphabetical order will be used.

The tables for concomitant and post treatment medications will be sorted by decreasing frequency of ATC followed by all other therapeutic classes based on the incidence in the IPd arm. In case of equal frequency regarding ATCs (anatomic or therapeutic categories), alphabetical order will be used.

In addition, other analyses including number (%) of patients with concomitant red blood cells transfusion (red blood cells or platelets) and concomitant use of GCSF/GMCSF (prophylaxis and curative intent) will be provided on the safety population.

IR medications

Number (%) of patients with IR medications (prophylaxis and curative intent) including diphenhydramine (or equivalent), paracetamol and steroids as defined in Section 2.1.2 will be provided. Number of infusions with prophylactic IR medications, number of infusions with curative IR medications and number of infusions without any IR medication will also be summarized. Further analyses on cumulative steroids exposure may be performed as needed.

2.4.3 Extent of investigational medicinal product exposure and compliance

The extent of study treatment exposure will be assessed and summarized by actual treatment within the safety population (Section 2.3.2).

2.4.3.1 Extent of investigational medicinal product exposure

The overall study treatment exposure (all study treatments together) will be assessed by the following variables:

- Overall number of cycles started, defined by the total number of cycles in which at least one dose of any study treatments is administered
- Cumulative exposure to treatment (in patient-years), derived by summing the duration of exposure for all patients by treatment group
- Overall duration of exposure in weeks defined as [(Last day of last cycle – first day of first cycle)/7].

  The first day of first cycle is defined as the date of first dose of study treatment at Cycle 1.

  The last day of last cycle is defined as the last date among the following:

  IPd arm:

  - Date of last dose of isatuximab + 7 days if last cycle is Cycle 1 or date of last dose of isatuximab + 14 days if last cycle is Cycle 2 or later,
  - Min(date of last dose of pomalidomide + 8 days, date of death),
  - Date of last dose of dexamethasone + 7 days.

  Pd arm:

  - Min(date of last dose of pomalidomide + 8 days, date of death),
  - Date of last dose of dexamethasone + 7 days.

Total number of cycles started, number of cycles started by patient as a quantitative variable and by category (ie, number (%) of patients receiving at least 1 cycle, at least 2 cycles, etc), will be summarized by descriptive statistics in each treatment group.

The following variable will be computed to describe overall dose modification (cycle delay):

- Cycle delay: A cycle start date is defined by the earliest date of isatuximab, pomalidomide and dexamethasone within a cycle. A cycle is deemed as delayed if the start date of the current cycle – 28 – start date of the previous cycle is >3 days. Cycle delay is not defined for the first cycle.

Cycle delay will be analyzed at the patient and cycle levels by treatment group as follows:

- Patient level:
  - Number of patients treated (used for % calculation for this level),
  - Number (%) of patients with at least one cycle delay,
    - Between 4 and 7 days,
    - >7 days.
- Cycle level:
  - Number of cycles administered (used for % calculation for this level),
  - Number (%) of cycles delayed.
    - Between 4 and 7 days,
    - >7 days.

2.4.3.2 Isatuximab exposure

The isatuximab dose information will be assessed by the following variables:

- Number of cycles started.
- Duration of isatuximab exposure (in weeks), defined as follow:
  - [Date of last dose of isatuximab + 7 days - first dose of isatuximab]/7 if last cycle is Cycle 1,
  - [Date of last dose of isatuximab + 14 days - first dose of isatuximab]/7 if last cycle is Cycle 2 or later.
- Cumulative dose (mg/kg): the cumulative dose is the sum of all doses of isatuximab administered from first to last administration.
- Actual dose intensity (ADI) in mg/kg/week: defined as the cumulative dose (in mg/kg) divided by the duration of isatuximab exposure (in weeks).
- Planned dose intensity in mg/kg/week corresponds to the planned dose (mg/kg) at C1D1, regardless of dose changes, multiplied by the theoretical total number of doses during the started cycles (4 for weekly dose, 2 for Q2W dose), and divided by the theoretical cycle duration expressed in weeks (ie, 4 weeks per cycle started).

- Relative dose intensity (RDI) in %:

$$100 \times \frac{ADI\ (mg/kg/week)}{Planned\ Dose\ Intensity\ (mg/kg/week)}$$

Total number of cycles started, number of cycles started by patient as a quantitative variable and by category (ie, number (%) of patients receiving at least 1 cycle, at least 2 cycles, etc), duration of isatuximab exposure, cumulative dose, ADI and RDI will be summarized by descriptive statistics.

The following variables will be computed to describe isatuximab dose modifications (delay/omission/interruption):

- Isatuximab infusion delays (within cycle): an infusion is deemed to have been delayed if the actual start of infusion is >1 day beyond the theoretical day of treatment for weekly dose, and >2 days beyond the theoretical day of treatment for Q2W dose. Infusion delay does not apply to the first infusion of each cycle.
- Isatuximab infusion interruption: an infusion is considered to be interrupted if the isatuximab administration is stopped during an infusion before it is completed, regardless it is restarted or not.
- Dose omission: a dose is considered omitted if the dose is not administered for the scheduled visit and there are positive dose(s) afterwards.
- Dose reduction: Although not allowed in the study protocol for isatuximab, potential dose reduction as defined in Table 6 will be screened and reported in the clinical study report. The first administration will not be counted as a dose reduction. A dose is considered to be administered at a reduced dose if the actual dose administered at the current administration is at least one level below the prior administration.

Table 6 - Dose levels for isatuximab dose reduction

	Starting dose	Dose level -1
Actual dose level	10 mg/kg	5 mg/kg
Dose level interval	> 7.5 mg/kg	>0 mg/kg and ≤7.5 mg/kg

Dose modification will be analyzed at the patient and total number of isatuximab infusions levels as follows:

- Patient level:
  - Number of patients treated (used for % calculation for this level),
  - Number (%) of patients with at least one infusion delay,
  - Number (%) of patients with at least one isatuximab dose omission,
  - Number (%) patients with a least 1 infusion interruption,
  - Number (%) patients with a least 1 dose reduction.

- Total number of isatuximab infusions level:
  - Total number of isatuximab infusions (used for % calculation for this level),
  - Number of isatuximab infusions interrupted (total, re-started and not re-started),
  - Number (%, calculated using the total number of infusion interrupted) of isatuximab administrations interrupted at:
    - 1st infusion,
    - 2nd infusion,
    - Subsequent infusions.
  - Time from infusion start to first interruption in minutes (quantitative and qualitative: 5 - 10, 11 - 30, 31 - 40, 41 - 50, 51 - 60, 61 - 90, 91 - 120, >120),
  - Duration of infusion: defined as the time from the start (date/time) of infusion to the end (date/time) of infusion. It will be summarized for first and subsequent infusions.

2.4.3.3 Pomalidomide and dexamethasone exposure

The pomalidomide and dexamethasone dose information will be assessed by the following variables:

- Number of cycles started
- Duration of exposure (in weeks):
  - Pomalidomide: [Min(date of last dose of pomalidomide + 8 days, date of death) – date of first dose of pomalidomide]/7,
  - Dexamethasone: [Date of last dose of dexamethasone + 7 days – date of first dose of dexamethasone]/7.
- Cumulative dose (mg): the cumulative dose is the sum of all doses of pomalidomide/dexamethasone, expressed in mg, given from first to last administration.
- Actual dose intensity (ADI) in mg/week: defined as the cumulative dose (in mg) divided by the duration of exposure (in weeks).
- Planned dose intensity (mg/week) corresponds to the planned dose (mg/kg) at C1D1, regardless of dose/schedule changes, multiplied by the theoretical total number of doses during the started cycles divided by the theoretical cycle duration expressed in weeks (ie, 4 weeks per cycle started).
- Relative dose intensity (RDI) in %:

$$100 \times \frac{ADI\ (mg/week)}{Planned\ Dose\ Intensity\ (mg/week)}$$

- Dose reduction: a dose is considered to be administered at a reduced dose if the actual dose administered at the current administration is at least one level below the prior administration:

Table 7 - Dose levels for pomalidomide dose reduction

Starting dose (PO)	Dose level -1	Dose level -2	Dose level -3
4 mg	3 mg	2 mg	1 mg

PO = per os

Table 8 - Dose levels for dexamethasone dose reduction

	Starting dose (PO or IV)	Dose level -1	Dose level -2	Dose level -3	Dose level -4
Actual dose level	40 mg	20 mg	12 mg	8 mg	4 mg
Dose level interval	> 30 mg	>16 mg and ≤30 mg	>10 mg and ≤16 mg	>6 mg and ≤10 mg	>0 mg and ≤6 mg
Actual dose level	20 mg (patients ≥75 years old)	12 mg	8 mg	4 mg	-
Dose level interval	>16 mg	>10 mg and ≤16 mg	>6 mg and ≤10 mg	>0 mg and ≤6 mg	

PO = per os; IV = intravenous

- Dose delay for dexamethasone (within cycle): a dose is deemed to have been delayed if the study treatment is >1 day beyond the theoretical day of treatment. Dose delay does not apply to first dose.
- Dose omission:
  - For pomalidomide: a dose is considered to be omitted if the number of positive dose is less than 21 within a completed cycle or if the dose is zero and there are positive dose(s) afterwards within an incomplete cycle,
  - For dexamethasone: a dose is considered omitted if the dose is not administered for the scheduled visit and there are positive dose(s) afterwards.

(See Section 2.5.3 for calculation in case of missing or incomplete data).

2.4.4 Analyses of efficacy endpoints

All efficacy analyses will be performed in the ITT population. All analyses using the stratification factors will be performed using the stratification factor as per IRT. A sensitivity analysis of PFS will be performed using the stratification factor as per eCRF, if relevant.

Patients who received only one prior therapy will be classified in the "2 or 3 prior lines" stratum as per eCRF. In case the stratum "≥75 years old and >3 previous lines of therapy" has a small sample size (less than 20 patients), this stratum will be collapsed with the "<75 years old and >3 previous lines of therapy" stratum.

2.4.4.1 Analysis of primary efficacy endpoint(s)

Primary analysis will consist of PFS comparison between IPd group versus Pd group through a log-rank test procedure stratified by stratification factors as entered in the IRT (ie, age and number of previous lines of therapy) and using a 1-sided 0.025 alpha level.

The cut-off date for the analysis of PFS is the actual date when the 162 events (first occurrence of either disease progression or death due to any cause) have been observed. Due to operational aspects some events could be observed after the cut-off date, a sensitivity analysis using the date of the last observed event as cut-off date may be performed at the full one-sided alpha level of 0.025. At the time of final PFS analysis, the critical value for the Wald test on PFS hazard ratio would be 0.734.

In addition, the following estimates will be provided:

- The hazard ratio (HR) and its 95% confidence interval (CI) will be estimated using the Cox proportional hazards model stratified by the same stratification factors as those used for the log-rank test described above. Underlying assumptions of the Cox Proportional hazards model will be assessed by graphical methods (ie, log-log graphical methods).
- PFS data will be analyzed using the Kaplan-Meier method by treatment group in the ITT population:
  - Kaplan-Meier estimates of the 25^{th}, 50^{th} and 75^{th} percentiles and their associated 95% CIs will be provided. The 95% confidence intervals will be constructed using a log-log transformation of the survival function and the methods of Brookmeyer and Crowley.
  - Number of patients at risk as well as the probabilities of surviving without disease progression at least 2, 4, 6, 8, 10, 12, 14 and 16 months with 95% CIs will be estimated for each treatment group using the Kaplan-Meier method.
  - Kaplan-Meier curves will be plotted. These plots will include the number of patients at risk at key time points by treatment group.
- For patients with events, the type of event (confirmed disease progression or death) will be summarized by treatment group using counts and percentages. The type of disease progression will also be presented (progression diagnosed on M-protein or radiological progression).
- For patients who died without evidence of disease progression, the time from the last disease assessment to the death will be summarized by treatment group using number, mean, standard deviation, median and range.
- The number (%) of censored patients, the reason and timing of their censoring (ie, censored at randomization, censored at the last valid disease assessment before the initiation of further anti-myeloma treatment, censored at last valid disease assessment before the cut-off date, censored at the cut-off date), and the time from the last disease assessment to the cut-off date will be summarized by treatment group. For each censoring reason, when applicable, distinction will be made between cases where no event was observed and cases where an event was observed after the censoring.

- Follow-up duration (months) will be defined as the time interval from the date of randomization to the date of last contact with the patient. Patients who have died will be censored on their date of death. Median follow-up duration (months) will be estimated using the Kaplan-Meier method.
- Potential follow-up regardless of deaths (months), defined as the time interval from the date of randomization to the cutoff date, will be described.

2.4.4.1.1 Sensitivity analyses

Sensitivity analyses of PFS will be performed at a 1-sided 0.025 alpha level. The same statistical methods used in the primary analysis will be applied to the PFS data using different censoring and event rules as defined below. Additional details are provided in Appendix E.

The sensitivity analyses will include:

- PFS analysis without censoring for further anti-myeloma treatment
- PFS analysis using investigator assessment of response
- Initiation of further anti-myeloma treatment considered as PFS event
- Analysis based on scheduled assessment dates instead of actual assessment dates and late PFS censored (analysis done if lack of adherence to the protocol-defined schedule of disease assessments between the treatment groups has been detected)

Sensitivity analysis #1 (All PFS events, regardless of further anti-myeloma treatment)

PFS endpoint will be analyzed based on IRC disease assessments, ignoring further anti-myeloma treatment. Progression or deaths occurring after any further anti-myeloma treatment will be considered as PFS events in this analysis.

Sensitivity analysis #2 (PFS as per investigator, ignoring symptomatic deterioration)

PFS endpoint will be determined and analyzed using investigator's disease assessment, with the same censoring rules as for the PFS primary analysis.

The concordance/discordance between the IRC and the investigator assessment of PD will be summarized by treatment group using counts and percentages. For patients with PD per both the IRC and the investigator, the concordance of the timing of the events will be summarized by treatment group using counts and percentages.

Sensitivity analysis #3 (PFS as per investigator, including symptomatic deterioration as an event)

PFS endpoint will be determined and analyzed using investigator's disease assessment, including symptomatic deterioration (clinical progression with no progression on imaging or M-protein per investigator) as an event. If symptomatic deterioration is observed in absence of documented disease progression per IMWG criteria, the date of progression will be the date of symptomatic

deterioration. If both symptomatic deterioration and documented disease progression per IMWG criteria are reported, the date of event will be the earliest of the date of documented progression and the date of symptomatic deterioration.

Sensitivity analysis #4 (PFS considering initiation of further anti-myeloma treatment as an event)

PFS endpoint will be analyzed based on IRC disease assessments, including initiation of further anti-myeloma treatment as an event. If further anti-myeloma treatment is initiated in absence of documented disease progression per IMWG criteria, the start date of the further anti-myeloma treatment will be used as the date of PFS event. If both initiation of further anti-myeloma treatment and documented disease progression per IMWG criteria are reported, the date of event will be the earliest of the date of documented progression and the start date of further anti-myeloma treatment.

Sensitivity analysis #5

Adherence to the protocol-defined schedule of disease assessments will be assessed by comparing the timing of disease assessments between the treatment groups (the day of the disease assessment relative to the date of Cycle 1 Day 1). If an imbalance is observed between the treatment groups, the PFS endpoint based on the IRC disease assessments will be re-derived using nominal assessments days instead the actual assessment day for progression dates and last valid tumor assessment dates. The visit windows for defining uniform progression and assessment dates are provided in Appendix E. In this sensitivity analysis progression or death occurring more than 8 weeks after the last valid tumor assessment without progression will be censored.

2.4.4.1.2 Subgroup analyses

Evaluation of Consistency:

The consistency of the results from the primary analysis will be evaluated across pre-defined subgroups in patients with available results. The definition of each subgroup is defined in Table 9. Depending upon the study results, additional subgroups may be examined, and subgroups with small sample sizes may be pooled to create a larger meaningful subgroup. For each subgroup, the treatment effect HR and its associated 95% confidence interval will be estimated. A forest plot summarizing the results for each subgroup will be provided.

For each pre-defined factor among the demographic/baseline characteristics defined in Table 9, PFS will be analyzed using a Cox proportional hazards model with terms for the factor, treatment and their interaction. The test of the interaction will be performed at the 10% alpha level.

Table 9 - PFS subgroup analyses: covariates investigated

Prognostic factor	Description
Age (eCRF)	<65 vs [65 - 75[vs ≥75 years
Number of previous lines of therapy (IRT)	(2 or 3) vs >3
Gender	Male vs female
Race	Caucasian vs Asian vs other
Region of the world (geographical)	Western Europe vs Eastern Europe vs North America vs Asia vs Other countries
Region of the world (regulatory)	Western countries vs Other countries
ECOG PS at baseline	0 or 1 vs 2
ISS staging at study entry	I vs II vs III
R-ISS staging at study entry	I vs II vs III
Cytogenetic abnormality (del(17p), t(4;14), t(14;16))	At least one vs. none
Cytogenetic abnormality del(17p)	Yes vs No
MM type at diagnosis	IgG vs non IgG
Baseline creatinine clearance (MDRD formula)	>60 ml/min vs ≤60 ml/min
Refractory to PI	Yes vs No
Refractory to lenalidomide	Yes vs No

Evaluation of confounding:

Since the results from the primary analysis could be impacted by confounding factors, any potential issues will be examined and, if confirmed, an exploratory analysis of the primary endpoint will be done accordingly. A multivariate Cox proportional hazards model will be used to identify prognostic factors among the demographic and baseline characteristics factors described in the table above using a stepwise selection procedure with a 15% significance level for removing effects. For significant prognostic factors identified in the multivariate model, the balance between treatment groups will be assessed. If major confounding is identified through screening for treatment group imbalances in a prognostic factor at baseline, an exploratory analysis of PFS will be done after adjusting for the prognostic factors in the multivariate Cox proportional hazards model. Differences between the adjusted and unadjusted models will be discussed in the clinical study report.

2.4.4.2 Analyses of secondary efficacy endpoints

ORR, BOR, VGPR rate and CBR

Best overall response, ORR, VGPR rate and clinical benefit rate according to IRC and investigator assessments will be summarized on the ITT population with descriptive statistics at the time of the primary analysis on PFS (based on data collected up to the PFS analysis cut-off date). Confidence intervals will be computed using the Clopper-Pearson method.

ORR (according to IRC assessment) will be compared between treatment groups using a Cochran-Mantel-Haenszel test stratified by stratification factors as entered in the IRT.

The proportion of patients with BOR≥VGPR (according to IRC assessment) will also be compared between the 2 arms using the test as for ORR (for descriptive purpose only).

OS

The analysis of OS will consist of comparison between IPd group versus Pd group through a 1-sided log-rank test procedure stratified by stratification factors as entered in the IRT (ie, age and number of previous lines of therapy).

This analysis will be performed at the time of the primary analysis on PFS (at about 36% information fraction), at the second interim analysis on OS and at the end of the study (final analysis on OS). An O'Brien and Fleming α spending function will be used to obtain the nominal significance levels for the interim and final analyses of survival. The nominal significance (one-sided) level for the final survival comparisons would be of 0.0200 for 220 death events (corresponding to a HR of 0.758).

In addition, the following estimates will be provided for OS:

- The hazard ratio (HR) and its 95% CI will be estimated using the Cox proportional hazards model stratified by the same stratifications factors as those used for the log-rank test. Underlying assumptions of the Cox proportional hazard model will be assessed by graphical methods (ie, log-log graphical methods).
- OS data will be analyzed using the Kaplan-Meier method by treatment group in the ITT population:
  - Kaplan-Meier estimates of the 25th, 50th and 75th percentiles and their associated 95% CIs will be provided,
  - Number of patients at risk as well as the probabilities of surviving at least 6, 12, 18, 24 and 36 months with 95% CI will be estimated for each treatment group using the Kaplan-Meier method.
- The number of censored patients, the reasons for their censoring (ie, alive at the cut-off date, alive at the last contact before the cut-off date, and lost to follow-up) and the time between the date of last contact and the cut-off date will be summarized by treatment group.
- Kaplan-Meier curves will be plotted.

Sensitivity analyses adjusting OS for switch to subsequent anti-cancer treatment could also be performed at interim and/or final analyses (e.g. using inverse probability of censoring weighting (IPCW) method) (7).

PFS in the high risk cytogenetic population

PFS will be analyzed using Kaplan-Meier methods with the same censoring rules as the primary analysis of PFS.

TTP, DOR , TT1R and TTBR

These time-to-event endpoints will be analyzed using Kaplan-Meier methods.

Similarly to the primary analysis of PFS, if progression and death (excluding for TTP: only progression) are not observed before the analysis data cut-off date, TTP and DOR will be censored at the date of the last valid disease assessment not showing disease progression performed prior to initiation of further anti-myeloma treatment (if any) or the data cut-off date, whichever comes first.

If no response (PR or better) is observed before the analysis cut-off date, TT1R and TTBR will be censored at the date of the last valid disease assessment before disease progression or death, the date of the last valid disease assessment before initiation of a further anti-myeloma treatment (if any) or the analysis cut-off date, whichever comes first.

Analysis of the pre-specified secondary endpoints will be descriptive only. Any testing procedure carried out on these endpoints will be considered as exploratory.

Minimal residual disease (MRD)

The MRD status (negative, positive) will be summarized by treatment group in the ITT population using descriptive statistics. The timing (study day from first dose) of MRD negative status will also be described.

Subgroup analyses

Subgroup analyses on main prognostic factors as defined for PFS may be performed for the key secondary endpoints based on the findings, as exploratory analyses.

2.4.4.3 Analyses of exploratory efficacy endpoints

PFS2 and PFS on first line of further therapy

PFS2 and PFS on first line of further therapy will be analyzed at the time of second interim and final OS analyses. PFS2 will be analyzed using Kaplan-Meier methods, the hazard ratio and its 95% CI will be estimated using the Cox proportional hazards model stratified by stratification factors as entered in the IRT (ie, age and number of previous lines of therapy). P-value will be provided for descriptive purpose only. PFS on first line of further therapy will be summarized among patients who received at least one line of further therapy using Kaplan-Meier methods. It will be summarized separately for further therapy with daratumumab and non-daratumumab treatment.

ORR, VGPR rate and CR rate on subsequent therapy

ORR, VGPR rate and CR rate on subsequent therapy, based on investigator assessments, will be summarized by number of subsequent line and selected drug class and agent, with descriptive statistics at the time of the second interim and final OS analyses. Confidence intervals will be computed using the Clopper-Pearson method.

2.4.4.4 Multiplicity issues

Hypothesis testing of the key secondary efficacy endpoints will be carried out. A closed test procedure will be used to control the type I error rate meaning that not further testing will be performed unless the significance level had been reached on PFS. The hierarchical procedure will be then carried out at the one-sided 2.5% significance level in the following order:

- ORR at the time of the primary analysis on PFS (first cut-off date).
- OS tested both at the time of the primary analysis on PFS (at about 36% information), and at the end of the study (final analysis on OS).

No update of PFS or ORR as per IRC will be provided at the time of final OS analysis.

2.4.5 Analyses of safety data

The summary of safety results will be presented by treatment group.

General common rules

All safety analyses will be performed on the safety population as defined in Section 2.3.2, unless otherwise specified.

The analysis of the safety variables will be essentially descriptive and no systematic testing is planned. Relative risks versus placebo and their 95% confidence intervals (CIs) may be provided, if relevant.

2.4.5.1 Analyses of adverse events

Generalities

The primary focus of adverse event reporting will be on treatment-emergent adverse events. Pre-treatment and post-treatment adverse events will be described separately.

If an adverse event date of onset (occurrence or becoming serious) is incomplete, an imputation algorithm will be used to classify the adverse event as pre-treatment, treatment-emergent, or post-treatment. The algorithm for imputing the treatment emergent status will be conservative and will classify an adverse event as treatment emergent unless there is definitive information to determine it is pre-treatment or post-treatment. Details on classification of adverse events with missing or partial onset dates are provided in Section 2.5.3.

Regarding treatment discontinuation, following definitions will be used:

- **Premature** treatment discontinuation is defined as the discontinuation of at least one of the study drugs but at least one is continued.
- **Definitive** treatment discontinuation is defined as the discontinuation of all the study drugs.

The severity grade will be taken into account in the summary. For patients with multiple occurrences of the same adverse event, the maximum (worst) grade by period of observation is used. Summaries will be provided for all grades and for Grade ≥3 (including Grade 5). Missing grades, if any, will be included in the "all grades" category.

Sorting within tables ensures the same presentation for the set of all adverse events within the observation period (pre-treatment, treatment-emergent and post-treatment). For that purpose, the table of all treatment-emergent adverse events presented by SOC and PT sorted by the internationally agreed SOC order (see Appendix B) and decreasing frequency of PTs within SOCs will define the presentation order for all other tables unless otherwise specified. Sorting will be based on results for the IPd arm.

The AE incidence tables presented by primary SOC, HLGT, HLT and PT will present the number (n) and percentage (%) of patients experiencing an AE sorted by SOC internationally agreed order, then by alphabetic order of HLGT, HLT and PT.

Analysis of all treatment-emergent adverse events

The following TEAE summaries will be generated for the safety population.

- Overview of TEAEs, summarizing number (%) of patients with any
  - TEAE any grade, regardless of relationship,
  - TEAE of Grade ≥3,
  - TEAE of Grade 3-4,
  - TEAE with Grade 5 (any TEAE with fatal outcome during the treatment period),
  - Serious TEAE,
  - Serious treatment-related TEAE,
  - TEAE leading to definitive (full study treatment) discontinuation,
  - TEAE leading to premature discontinuation of isatuximab,
  - TEAE leading to premature discontinuation of dexamethasone,
  - TEAE leading to premature discontinuation of pomalidomide,
  - AESI: IRs of Grade ≥3; pregnancy, overdose and second primary malignancy, if any, will be presented separately,
  - Treatment-related TEAEs,
  - Treatment-related TEAEs of Grade ≥3.

Treatment-related TEAEs are TEAEs related to at least one drug of the combination.

Analysis of adverse events will be performed according to following domains:

- TEAEs (regardless relationship to study treatment)
- Drug related TEAEs

- Deaths, serious adverse events, adverse events leading to withdrawal (premature or definitive), and other significant adverse events (IR and IR symptoms, Selected respiratory TEAEs, Specific hematological analysis, Second primary malignancies, TEAE leading to dose modification, pre- and post-treatment AE)

The following frequency distributions of TEAEs (incidence tables) will be provided for the safety population, for all grades combined and Grade ≥3:

- All TEAEs by primary SOC, HLGT, HLT and PT, showing number (%) of patients with at least 1 TEAE sorted by the SOC internationally agreed order. The other levels (HLGT, HLT, PT) will be presented in alphabetical order.
- All TEAEs by primary SOC and PT, showing the number (%) of patients with at least 1 TEAE, sorted by the internationally agreed SOC order and by decreasing incidence of PTs within each SOC. This sorting order will be applied to all other tables, unless otherwise specified.
- Most frequent (≥5% of patients in any group) treatment emergent adverse events by primary SOC and PT.
- Most frequent (≥5% of patients in any group) treatment emergent adverse events by PT.
- All related TEAEs by primary SOC and PT, showing the number (%) of patients with at least 1 related TEAE, sorted by the sorting order defined above.

Analysis of all serious treatment emergent adverse event(s)

- All serious TEAEs by primary SOC, HLGT, HLT and PT, showing number (%) of patients with at least 1 serious TEAE sorted by the SOC internationally agreed order. The other levels (HLGT, HLT, PT) will be presented in alphabetical order.
- All serious TEAEs by primary SOC and PT, showing the number (%) of patients with at least 1 TEAE, sorted by the internationally agreed SOC order and by decreasing incidence of PTs within each SOC.
- Most frequent (≥2% of patients in any group) serious TEAEs by primary SOC and PT.
- All serious TEAEs related to treatment, by primary SOC and PT, showing the number (%) of patients with at least 1 serious TEAE, sorted by the internationally agreed SOC order.

Analysis of all treatment-emergent adverse event(s) leading to treatment discontinuation

- All TEAEs leading to treatment definitive discontinuation by primary SOC, HLGT, HLT and PT, showing the number (%) of patients sorted by the internationally agreed SOC order. The other levels (HLGT, HLT, PT) will be presented in alphabetical order.
- All TEAE leading to treatment definitive discontinuation by primary SOC and PT, showing the number (%) of patients with at least 1 TEAE, sorted by the internationally agreed SOC order and decreasing frequency of PT.
- All TEAEs leading to premature treatment discontinuation of isatuximab, by primary SOC, HLGT, HLT, and PT, showing the number (%) of patients sorted by the internationally agreed SOC order. The other levels (HLGT, HLT, PT) will be presented in

alphabetical order. Summary by primary SOC and PT will also be presented, sorted by the internationally agreed SOC order and decreasing incidence of PT.

- All TEAEs leading to premature treatment discontinuation of pomalidomide, by primary SOC, HLGT, HLT and PT, showing the number (%) of patients sorted by the internationally agreed SOC order. The other levels (HLGT, HLT, PT) will be presented in alphabetical order. Summary by primary SOC and PT will also be presented, sorted by the internationally agreed SOC order and decreasing incidence of PT.
- All TEAEs leading to premature treatment discontinuation of dexamethasone, by primary SOC, HLGT, HLT, and PT, showing the number (%) of patients sorted by the internationally agreed SOC order. The other levels (HLGT, HLT, PT) will be presented in alphabetical order. Summary by primary SOC and PT will also be presented, sorted by the internationally agreed SOC order and decreasing incidence of PT.

Analysis of all treatment-emergent adverse event(s) leading to dose modification

The following summary tables are based on the investigator's intent reported in the AE page ("action taken"):

- All TEAEs leading to dose reduction of any drug by primary SOC and PT, showing the number (%) of patients, sorted by the sorting order defined above.
- All TEAEs leading to dose reduction of isatuximab by primary SOC and PT, showing the number (%) of patients, sorted by the sorting order defined above.
- All TEAEs leading to dose reduction of pomalidomide by primary SOC and PT, showing the number (%) of patients, sorted by the sorting order defined above.
- All TEAEs leading to dose reduction of dexamethasone by primary SOC and PT, showing the number (%) of patients, sorted by the sorting order defined above.
- All TEAEs leading to dose interruption of isatuximab by primary SOC and PT, showing the number (%) of patients, sorted by the sorting order defined above.
- All TEAEs leading to any dose delay of any drug by primary SOC and PT, showing the number (%) of patients, sorted by the sorting order defined above.
- All TEAEs leading to any dose delay of isatuximab by primary SOC and PT, showing the number (%) of patients, sorted by the sorting order defined above.
- All TEAEs leading to dose delay of pomalidomide by primary SOC and PT, showing the number (%) of patients, sorted by the sorting order defined above.
- All TEAEs leading to dose delay of dexamethasone by primary SOC and PT, showing the number (%) of patients, sorted by the sorting order defined above.

Of note as per eCRF completion guideline, action taken of TEAEs leading to dose omissions were to be reported as dose reduction in the AE page of the eCRF.

Analysis of adverse events of special interest

Number (%) of patients with at least one AESI cited in Section 2.1.4.1 sorted by decreasing incidence of PT (presented separately for each category of AESI).

Analysis of infusion reactions

The following summaries will be provided:

- Number (%) of patients experiencing IRs according to investigator reported AEs presented by primary SOC and PT (both sorted by decreasing order of frequency) will be summarized by grades (all grades and by grade).
- Description of the IRs (according to investigator reporting):
  - Number (%) of patients by action taken with isatuximab,
  - Number (%) of patients with only 1, ≥1, ≥2, ≥3, ≥4 and ≥5 episodes,
  - Number (%) of patients with first occurrence of IR at the first infusion and subsequent infusions,
  - Number (%) of patients with IR at the first and subsequent infusions,
  - Number (%) of patients with at least two episodes of IRs at the same infusion,
  - Day of onset from the isatuximab infusion,
  - Duration (in days).
- Number (%) of patients experiencing TEAEs (related and regardless of causality) within 24 hours from the start of any isatuximab infusion presented by primary SOC and PT (both sorted by decreasing order of frequency) will be summarized by grades (all grades and Grades ≥3).
- Similar tables including all TEAEs within 24 hours from the start of any isatuximab infusion from the selected CMQ (see Section 2.1.4.1) will also be performed.
- Number (%) of patients experiencing TEAEs (related and regardless of causality), (not only limited to those occurring within 24h of each isatuximab administration) from the selected CMQ (see Section 2.1.4.1) presented by primary SOC and PT (both sorted by decreasing order of frequency) will be summarized by treatment groups and by grades (all grades and Grades ≥3).
- Number of patients with symptoms of IRs presented by primary SOC and PT (both sorted by decreasing order of frequency) will be summarized by grades (all grades and Grades ≥3).

Second primary malignancies

A listing of patients who reported second primary malignancies during the study will be provided (as per the CMQ). This listing will include diagnosis, study day of diagnosis (from first dose), number of days from last study treatment to diagnosis, prior exposure to anti-myeloma treatments, and whether or not patient received subsequent anti-cancer treatment.

In addition, treatment-emergent and post-treatment AEs in the CMQ 'Second primary malignancies' will be presented by sub-category ('haematological', 'non-hematological skin tumors', 'non-hematological non-skin tumors' and 'other tumors') and by decreasing incidence of PT.

COVID19

COVID19 related TEAEs will be analyzed using selection defined in Section 2.1.4.1 and will be presented by SOC and PT.

Overdose

A listing of patients who reported overdose during the study will be provided. This listing will include drug with overdose.

Neutropenia and neutropenic complications

Neutropenia (from laboratory abnormalities) will be displayed along with febrile neutropenia and neutropenic infections (see Section 2.1.4.1).

Duration of Grade 3/4 neutropenia episode, cumulative duration of Grade 4 neutropenia by patient and time to first Grade 3/4 neutropenia will be analyzed using laboratory data.

The start date of a Grade 4 laboratory neutropenia episode is defined as the date of first Grade 3/4 assessment for that episode. The end date of a Grade 4 neutropenia episode is defined as the first date of neutropenia assessment afterwards of Grade 0/1/2 for that episode assuming there will be at least 3 days between the first Grade ≤2 neutropenia and the next Grade ≥3 assessment (if any). If the start date of a new episode is within 3 days of the previous episode, then the two episodes will be considered as one episode. The worst grade of an episode is the worst grade of all assessments included in that episode.

Duration of a Grade 3/4 neutropenia episode (in days) is defined as end date of an episode – start date of an episode +1. If a patient does not have an end date before the cutoff date in an episode then the duration of the episode will be censored at the last neutrophil assessment of Grade 3/4 or the cutoff date, whichever comes first.

Time to first Grade 3/4 neutropenia (in days) is defined as: date of the first on-treatment Grade 3/4 neutropenia assessment – date of first treatment +1. If a patient does not have Grade 3/4 neutropenia, time to first Grade 3/4 neutropenia will be censored at the last assessment of neutropenia of Grade 0/1/2 or the cutoff date, whichever comes first. If a patient does not have any on-treatment assessment of neutropenia, then the patient will be censored at Day 1.

Respiratory TEAEs

Respiratory TEAEs will be analyzed using selection defined in Section 2.1.4.1 and will be presented by PT.

Thrombocytopenia and hemorrhages

The number (%) of patients will be provided for:

- On-treatment thrombocytopenia (Lab) identified through grading of laboratory data per the NCI-CTCAE 4.03, by grade
- Hemorrhages as defined in Section 2.1.4.1 by grade
- Hemorrhages following Grades 4 thrombocytopenia (Lab). The first hemorrhages event occurring within 8 days after any occurrence of the thrombocytopenia (Lab) will be used for this analysis.

Hemolytic disorders

Hemolytic disorders that occurred within 8 days after the blood cell transfusion will be analyzed using selection defined in Section 2.1.4.1 and will be presented by PT.

A listing of patients with hemolytic disorders will be provided. This listing will include the PT, study day of diagnosis (from first dose of study treatment), interval to onset from the last study treatment before the diagnosis (last drug administered), duration of AE, the cycle of occurrence, severity, seriousness, outcome, action taken on study treatment, study day of the blood transfusion, and results and sampling date of indirect anti-globulin test.

Autoimmune disorders

A listing of patients with autoimmune disorders (selected using definition in Section 2.1.4.1) will be provided. This listing will include the PT, study day of diagnosis (from first dose of study treatment), interval to onset from the last study treatment before the diagnosis (last drug administered in a combination treatment), duration of AE, the cycle of occurrence, severity, seriousness, action taken on study treatment, and outcome.

TLS

A listing of patients with TLS reported in eCRF AE forms during the study will be provided.

Exposure-adjusted analyses of TEAEs

The event rate per patient-year (the number of patients with an event divided by total patient-years) will be provided by SOC and PT for the most frequent (≥5% of patients in any group) TEAEs, most frequent (≥5% of patients in any group) Grade ≥3 TEAEs, serious TEAEs, TEAE leading to definitive discontinuation and AEs leading to death in context other than disease progression (see definition in Section 2.4.5.2). For a patient with event, patient year is censored at time of first event; for patient without event, it corresponds to length of treatment period as defined in Section 2.1.4.

Analysis of pre-treatment and post-treatment adverse events

- All pre-treatment AEs by primary SOC and PT, showing the number (%) of patients with at least 1 pre-treatment AE, sorted by the internationally agreed SOC order and decreasing incidence of PTs within each SOC.
- All pre-treatment serious adverse events by primary SOC and PT, showing the number (%) of patients with at least 1 pretreatment serious adverse event, sorted by the internationally agreed SOC order and decreasing incidence of PTs within each SOC.
- All post-treatment AEs by primary SOC and PT, showing the number (%) of patients with at least 1 post-treatment AE, sorted by the internationally agreed SOC order and decreasing incidence of PTs within each SOC.
- All post-treatment SAEs by primary SOC and PT, showing the number (%) of patients with at least 1 post-treatment SAE, sorted by the internationally agreed SOC order and decreasing incidence of PTs within each SOC.

2.4.5.2 Deaths

An overview of Grade 5 AEs will be provided summarizing number (%) of patients with any:

- Grade 5 AE (TEAE and post-treatment).
- Fatal TEAE (regardless date of death/period).
  - Grade 5 TEAE with a fatal outcome during the treatment period,
  - Any Grade TEAE with a fatal outcome during the post-treatment period.
- Post-treatment Grade 5 AE (excluding a TEAE that worsened to Grade 5 during the post-treatment period).

The following summaries of deaths will be generated for the safety population.

- Number (%) of patients who died by study period (on-treatment, post-treatment, within 60 days of first dose) and reasons for death (disease progression, AE, other) by treatment received.
- Listing of deaths in non-randomized patients or randomized but not treated patients (this listing will be generated on the screened patients).
- All TEAEs leading to death by primary SOC and PT, sorted by the internationally agreed SOC order and by decreasing incidence of PTs.
- All TEAEs related to treatment and leading to death by primary SOC and PT sorted by the internationally agreed SOC order and by decreasing incidence of PTs.
- Number (%) of patients with TEAE(s) leading to death regardless of relationship and related to IMP by Primary SOC, HLGT, HLT and PT.
- Summary of AEs leading to death, by Primary SOC and PT
  - In context of disease progression (death within 30 days from last study treatment administration and the cause of death is disease progression),

- In context other than disease progression (death within 30 days from last study treatment administration and for whom cause of death is not disease progression or the death occurred more than 30 days from last study treatment administration and the cause of death is adverse event).

2.4.5.3 Analyses of laboratory variables

Hematological and clinical biochemistry toxicities will be assessed from laboratory test parameters. Each test result will be graded by NCI-CTCAE version 4.03, whenever applicable.

For hematological parameters and for some selected biochemistry parameters, sanofi sponsor generic ranges (LLN, ULN) are defined and will be used for grading (see list of parameters in Appendix C). For other biochemistry parameters (eg, for hepatic enzymes ALT, AST, Alkaline phosphatase, total bilirubin), grading will be derived using local laboratory normal ranges.

The number of patients with abnormal laboratory tests at baseline will be presented by grade and all grades together. The frequency of patients in each grade and all grades of laboratory abnormalities during treatment will be summarized. For patients with multiple occurrences of the same laboratory variable during the treatment, the maximum grade (worst) per patient will be used.

The denominator used for percentage calculation is the number of patients with at least 1 evaluation of the laboratory test during the considered observation period.

When appropriate, the summary table will present the frequency of patients with any grade of abnormal laboratory tests and with Grade 3-4 abnormal laboratory tests.

For laboratory tests for which NCI-CTCAE V4.03 scale is not applicable, potentially clinically significant abnormalities (PCSA) values are defined as abnormal values considered medically important by the Sponsor according to predefined criteria/thresholds based on literature review. PCSA criteria will determine which patients had at least 1 PCSA during the on-treatment period, taking into account all evaluations performed during the on-treatment period, including nonscheduled or repeated evaluations. The incidence of PCSA any time during the on-treatment period will be summarized by treatment group irrespective of the baseline level.

Anemia, thrombocytopenia and neutropenia

Shift tables showing the number of patients in each grade at baseline by worst grade during the on-treatment period and the bone marrow involvement at baseline by worst grade during the on-treatment period will be provided.

Further analyses including summary of cycle of onset (all grades and Grade ≥3), duration and concomitance with other hematological abnormalities will also be provided.

2.4.5.4 Analyses of vital sign variables

A shift table of baseline ECOG PS versus best and worst ECOG PS on treatment will be provided.

For blood pressure/heart rate parameters, potentially clinically significant abnormality (PCSA) values are defined as abnormal values considered medically important by the Sponsor according to predefined criteria/thresholds based on literature review.

The incidence of PCSAs prior to study treatment administration at any cycle during the TEAE period will be summarized by treatment group whatever the baseline level and/or according to the following baseline categories:

- Normal/missing.
- Abnormal according to PCSA criterion or criteria.

The incidence of PCSA during and after study treatment administration at any cycle during the TEAE period in the IPd arm will also be summarized.

2.4.5.5 Analyses of electrocardiogram variables

The incidence of patients with at least 1 abnormal ECG at any time during the TEAE period will be summarized by treatment group irrespective of the baseline level and/or according to the following baseline status categories:

- Normal/missing
- Abnormal

A listing of abnormalities and analysis of AEs in appropriate SMQs (eg, Cardiac) will be provided if relevant.

2.4.5.6 Analyses of other safety endpoints

The summary statistics (including number, mean, median, Q1, Q3, standard deviation, minimum and maximum) of baseline values, peak values, change from baseline and relative change from baseline will be calculated for Cytokines (TNF-α, IL-1-β, IL-4, IL-6, IFN-γ), markers of complement (C3a, C4, CH50) and serum tryptase when available.

For indirect antiglobuline test (IAT), a summary of patients in experimental arm with indirect Coombs test during the on-treatment period will be provided, including number (%) of patients with:

- All tests negative
- At least one positive test

And among patients with at least one positive test during study treatment, number (%) of patients with:

- Negative indirect Coombs test at baseline
- Missing indirect Coombs test at baseline

2.4.6 Analyses of pharmacokinetic and pharmacodynamic variables

The population PK of isatuximab will be characterized in the population of patients in the experimental arm, using a nonlinear mixed effect modeling approach. Both rich and sparse sampling pharmacokinetic data available from Phase 1, 2 and 3 studies will be used for the analysis. The assessment of pomalidomide, pathophysiological and demographic covariate effects on the main PK parameters will be performed. Additional details of the analysis plan and the results will be provided in a separate document. The population estimates from this analysis will provide a prior distribution from which individual Bayesian estimates of the PK parameters for each patient in this study will be derived.

Pharmacokinetic plasma concentration of isatuximab will be summarized by theoretical sampling times using descriptive statistics (such as arithmetic mean, geometric mean, median, standard deviation, standard error of the mean (SEM), coefficient of variation (CV), minimum and maximum). Accumulation ratio will be calculated with concentration at the end of infusion (CEOI) (C2D1 vs C1D1 and C4D1 vs C1D1) and C_{trough} (C2D1 vs C1D8 and C4D1 vs C1D8) and will be summarized by descriptive statistics (such as geometric mean, arithmetic mean median, standard deviation, standard error of the mean (SEM), coefficient of variation (CV), minimum and maximum).

2.4.7 Analyses of immunogenicity variables

ADA attributes and response endpoints defined in Section 2.1.6 will be summarized in the ADA population. Titers will be also described using descriptive statistics. Further analyses may be performed, such as time to onset and duration of ADA.

The impact of positive immune response on efficacy, PK and safety endpoints may be further explored by graphical methods or descriptively, depending on ADA prevalence.

2.4.8 Analyses of biomarker variables

2.4.8.1 Immune genetic variables

2.4.8.1.1 Descriptive analysis

Each genetic biomarker will be summarized with descriptive statistics by treatment group and overall.

2.4.8.1.2 Univariate analysis

Each genetic biomarker will be tested for a potential prognostic/predictive effect for PFS.

A cox regression model will be conducted separately for each genetic biomarker with a treatment effect, a biomarker effect and a biomarker×treatment interaction.

For biomarkers coded as genotype (0, 1, 2), different coding may be investigated: additive, dominant or recessive.

Benjamini-Hochberg multiple correction procedure will be used to control the False Discovery Rate.

Additional analyses using ORR and OS instead of PFS might also be performed.

2.4.9 Analyses of quality of life/health economics variables

PRO endpoints for each of the 3 selected PRO/HRQL and health utility instruments (EORTC QLQ-C30, QLQ-MY20 and EQ-5D-5L) will be analyzed in patients from the safety population who have completed the baseline and at least 1 post baseline assessment.

For each questionnaire the compliance profile over time will be summarized on the safety population (number and percentage of forms received versus expected, and number and percentage of forms evaluable versus expected). Reasons for non-completion will be summarized on the safety population.

Descriptive statistics of the mean change scores by treatment arms (from baseline to each cycle, from baseline to EOT and from baseline to 60 days after last study treatment) will be conducted for each PRO as follows:

- QLQ-C30: global health status/QoL summary score, the five functional subscale scores (physical, emotional, cognitive, role and social), the three symptom subscale scores (fatigue, nausea/vomiting and pain) and the six additional single item scores (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties);
- MY20: future perspective, body image, disease symptoms and side effects of treatment subscale scores;
- EQ-5D-5L: health state utility value and VAS scores.

Additional analyses (eg responder analyses for each PRO summary, subscale and symptom score and EQ-5D shift tables) could be presented in a separate document.

2.4.10 Further therapy after discontinuation of investigational medicinal product administration during the study

A summary table, including the number of different regimen, will be provided for further anti-myeloma treatments based on WHO-DD coding.

Further anti-myeloma treatments will also be summarized by number of subsequent lines and drug class or agent, using selected drug classes or agents (e.g. daratumumab, elotuzumab, BCMA agents, PI, Immunomodulators [IMID]).

Time to next treatment

TNT will be analyzed using Kaplan-Meier methods.

2.5 DATA HANDLING CONVENTIONS

2.5.1 General conventions

The following formulas will be used for computation of parameters.

Renal function formulas

Creatinine clearance will be estimated using the equation of MDRD:

GFR (mL/min/1.73 m²) = 175 x (Scr*0.0113) $^{-1.154}$ x (Age) $^{-0.203}$ x (0.742 if Female) x (1.212 if African-American)

with serum creatinine in umol/L and age in years.

Corrected calcium formula

Corrected Calcium (mmol/L) = (Serum Calcium (in mmol/L) + 0.8 * 0.25 (4 - serum albumin [in g/L]*0.1)

Qol formulas

EORTC QLQ-C30 and QLQ-MY20 raw scores and scores calculation:

For all scales, raw score (RS) = mean of the component items.

For functional scales, Score = (1- ((RS-1)/range)) *100

For symptom scales/items and the global health status, Score = (RS-1)/range *100

The range is the difference between the maximum and the minimum response to individual items.

See Appendix F.

2.5.2 Data handling conventions for secondary efficacy variables

Not applicable.

2.5.3 Missing data

The analyses and summaries of continuous and categorical variables will be based on observed data only. Percentages will be calculated using as denominator the number of patients with non-missing observation in the considered population. When relevant, the number of patients with missing data is presented.

Handling of disease characteristics missing/partial dates

- If the day is missing, it will be estimated by 1.
- If the month is missing, it will be estimated by 1 (only for medical history variables).
- If the year is missing, no estimation will be performed.

Handling of medication missing/partial dates

No imputation of medication start/end dates or times will be performed. If a medication date or time is missing or partially missing and it cannot be determined whether it was taken prior or concomitantly, it will be considered a prior, concomitant, and post-treatment medication.

Imputation of incomplete date for post anti-myeloma treatment start date

For post anti-myeloma treatments, if the medication start date is missing, it will be imputed as follows:

- If the medication start day and month are missing and the medication start year is the same as treatment end year, the medication start date will be set equal to treatment end date + 1.
- If the medication start day and month are missing and the medication start year is after the treatment end year, the medication start day and month will each be set to 01.
- If the medication start day is missing and medication start year and month is the same as the treatment end year and month, the medication start day will be set equal to the treatment end day + 1.
- If the medication start day is missing and medication start month is before the treatment end month and the medication start year is the same as treatment end year, the medication start day will be set to 01.
- If the medication start day is missing and the medication start month is after the treatment end month and the medication start year is the same as treatment end year, the medication start day will be set to 01.
- If the medication start day is missing and the medication start month is not missing and the medication start year is after the treatment end year, the medication start day will be set to 01.
- If the medication start day, start month and start year is missing, the medication start date will be set equal to the treatment end date + 1.

Handling of missing/partial death dates

- If the day of the death date is missing, it will be imputed as the first day of the month, except if the date of the patient's last contact is in the same month as the death date. In this case, the death date is imputed as the date of last contact + 1 day.
- If the day and month of the death date is missing, the date of death will be imputed to the first of January of the year, except if the date of the patient's last contact is in the same year as the death date. In this case, the death date will be imputed as the date of last contact + 1 day.
- If the death date is missing, no imputation will be done and the patient will be censored at the last contact date.

Handling of adverse events with missing or partial date of onset

Missing or partial adverse event onset dates (occurrence or becoming serious) will be imputed so that if the partial adverse event onset date information or visit number does not indicate that the adverse event started prior to treatment or after the treatment-emergent adverse event period, the adverse event will be classified as treatment-emergent. In case of AEs worsening during the study, the emergence will also be based on the cycle of worsening. No imputation of adverse event end dates will be performed. These data imputations are for categorization purpose only and will not be used in listings. No imputation is planned for date of adverse event resolution.

Missing grade

If the grade is missing for one of the treatment emergent occurrences of an AE, the maximal severity on the remaining occurrences will be considered. If the severity is missing for all the occurrences, no imputation will be done and missing grades will be summarized in the "all grades" category.

Handling of missing assessment of relationship of adverse events to investigational medicinal product

If the assessment of the relationship to the regimen is missing, then the relationship to the regimen has to be assumed and the adverse event considered as such in the frequency tables of possibly related adverse events, but no imputation should be done at the data level.

2.5.4 Windows for time points

Laboratory data

An episode occurred during a cycle if the date of sampling is after (>) the first day of the cycle, but prior or equal (≤) to the first day of the next cycle.

2.5.5 Unscheduled visits

Unscheduled visit measurements of laboratory data, vital signs, and ECG will be used for computation of baseline and worst values and/or grades.

2.5.6 Pooling of centers for statistical analyses

Data from all sites will be pooled together for analyses.

2.5.7 Statistical technical issues

Not applicable.

3 INTERIM ANALYSIS

No interim analysis is planned for PFS. However, at the time of final PFS analysis, once 162 PFS events have been observed, secondary efficacy data (ORR and OS) will be reviewed (according to the outcome of the final analysis of the primary endpoint). An interim analysis on OS will be performed at that stage. An additional interim analysis on OS will be performed when approximately 90% of events have occurred.

At the time of final PFS analysis, formal comparisons of PFS, ORR and OS will be made according to a closed test procedure at the level of 2.5% one-sided:

If an improvement in median PFS is demonstrated, the analysis on ORR and interim analysis on OS will be performed. The ORR will be tested, at the one sided 2.5%-level. Then, if the improvement in ORR is also significant, OS will be tested as a formal comparison that would allow for early stopping for overwhelming efficacy. The stopping boundaries will be derived based on the O'Brien and Fleming α spending functions.

The stopping boundaries for efficacy on OS endpoint will be derived based on the O'Brien and Fleming α spending functions and will depend on the actual number of deaths observed at the time of the interim analyses.

At the first interim analysis on OS, in case where exactly 80 deaths are observed, the sponsor could stop the study for overwhelming efficacy if the p-value is ≤0.000184 (corresponding to a HR of 0.448). Under current accrual assumptions of 15 patients per month and assuming an exponential distribution of PFS in both treatment groups, the 162 PFS events milestone (and interim analysis on OS) is estimated to occur at about 18 months after FPI.

At the second interim analysis on OS, the 1-sided nominal significance level to stop the study for overwhelming efficacy at approximately 90% information fraction (198 OS events) is 0.0181 (corresponding to an HR of 0.742). This is estimated to occur at about 43 months after FPI.

The final analysis of survival, provided that the survival portion of the study is not stopped early, will take place after approximately 220 deaths have been observed, which is projected to occur approximately 51 months after the first patient is randomized. The nominal significance level for the final survival comparisons will be determined by an O'Brien and Fleming alpha spending function. It would be of 0.0200 for 220 events (corresponding to a HR of 0.758).

No update of PFS or ORR as per IRC will be provided at the time of second interim and final OS analyses. Analyses that will be provided at time of primary analysis of PFS and second interim and final OS analyses are detailed in Table 10 below.

Table 10 – Analyses that will be provided at time of primary analysis of PFS and second interim and final OS analyses

	Primary analysis of PFS	Second interim and final OS analyses
Disposition		
Analysis populations, patient disposition	X	X
Reasons for screen failure, disposition of screened patient by country and site, patients randomized but not treated	X	
Reasons for definitive and premature treatment discontinuations	X	X
Critical or major deviations related to inclusion and exclusion criteria, and to randomization procedures	X	
Other critical or major deviations	X	X
Demographics and baseline characteristics		
Demographic characteristics	X	
Medical or surgical history	X	
MM characteristics at diagnosis	X	
MM characteristics at study entry, except gain(1q21) abnormality	X	
Gain(1q21) abnormality		X
Prior anti-myeloma therapies	X	
Prior or concomitant medications (other than anticancer therapies)		
Prior medications (other than anti-myeloma therapies)	X	
Concomitant medications	X	X
IR medications	X	
Primary efficacy endpoint		
PFS	X	
Key secondary efficacy endpoints		
ORR	X	
OS	X	X
Other secondary efficacy endpoints		
BOR, VGPR rate, CBR, PFS in the high risk cytogenetic population, DOR, TT1R, TTBR	X	
MRD	X	X
PFS2		X
PFS on first line of further therapy		X
ORR, VGPR rate and CR rate on subsequent therapy		X
Further therapies, TNT	X	X

	Primary analysis of PFS	Second interim and final OS analyses
Adverse events		
TEAEs	X	X
Deaths	X	X
SAEs	X	X
AEs leading to withdrawal of study treatment, dose interruption/delay/reduction/omission	X	X
Other significant adverse events, except infusion reactions and COVID19 related TEAEs	X	X
Infusion reactions	X	
COVID19 related TEAEs		X
Exposure-adjusted analyses of TEAEs		
Pre-treatment AEs	X	
Post treatment AEs	X	X
Laboratory safety parameters		
Hematology, electrolytes, metabolic function, renal function, liver parameters	X	X
Anemia, thrombocytopenia, Neutropenia (except time to first grade 3/4 neutropenia and duration of grade 3/4 neutropenia)	X	X
Time to first grade 3/4 neutropenia and duration of grade 3/4 neutropenia	X	
Other safety endpoints		
Vital signs	X	
ECG, TEAEs in the cardiac CMQ	X	
TEAEs in the cardiac CMQ	X	X
Cytokines, markers of complement, serum tryptase	X	X
Indirect Coombs test	X	
Pharmacokinetics	X	
Immunogenicity		
ADA	X	X
Health-related quality-of-life endpoints	X	
Exploratory biomarker analysis	X	

4 DATABASE LOCK

Estimated cut-off date for primary analysis of PFS will be approximately 18 months after FPI.

The estimated cut-off date for second interim analysis on OS will be approximately 43 months after FPI and for the final analysis on OS it will be approximately 51 months after FPI.

5 SOFTWARE DOCUMENTATION

All summaries and statistical analyses will be generated using SAS version 9.4 or higher. Biomarkers analyses will be generated using R version 3.3.2.

6 REFERENCES

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7 LIST OF APPENDICES

Appendix A: Potentially clinically significant abnormalities (PCSA) criteria

Appendix B: SOC sorting order

Appendix C: Generic ranges for hematological and biochemistry parameters

Appendix D: IMWG criteria

Appendix E: Description of primary and sensitivity analyses of PFS

Appendix F: Scoring the EORTC QLQ-C30

Appendix A Potentially clinically significant abnormalities criteria

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES

Parameter	PCSA	Comments
Vital signs		
HR	≤50 bpm and decrease from baseline ≥20 bpm ≥120 bpm and increase from baseline≥20 bpm	To be applied for all positions (including missing) except STANDING.
SBP	≤95 mmHg and decrease from baseline ≥20mmHg ≥160 mmHg and increase from baseline ≥20 mmHg	To be applied for all positions (including missing) except STANDING.
DBP	≤45 mmHg and decrease from baseline ≥10 mmHg ≥110 mmHg and increase from baseline ≥10 mmHg	To be applied for all positions (including missing) except STANDING.
Orthostatic Hypotension		
Orthostatic SDB	≤-20 mmHg	
Orthostatic DBP	≤-10 mmHg	
Weight	≥5% increase from baseline ≥5% decrease from baseline	FDA Feb 2007.

Appendix B SOC sorting order

The internationally agreed order (International Conference on Harmonization (ICH)-endorsed guide for MedDRA users on data output) for SOC:

1. Infections and infestations.
2. Neoplasms benign and malignant (including cysts and polyps).
3. Blood and the lymphatic system disorders.
4. Immune system disorders.
5. Endocrine disorders.
6. Metabolism and nutrition disorders.
7. Psychiatric disorders.
8. Nervous system disorders.
9. Eye disorders.
10. Ear and labyrinth disorders.
11. Cardiac disorders.
12. Vascular disorders.
13. Respiratory, thoracic and mediastinal disorders.
14. Gastrointestinal disorders.
15. Hepato-biliary disorders.
16. Skin and subcutaneous tissue disorders.
17. Musculoskeletal, connective tissue and bone disorders.
18. Renal and urinary disorders.
19. Pregnancy, puerperium and perinatal conditions.
20. Reproductive system and breast disorders.
21. Congenital and familial/genetic disorders.
22. General disorders and administration site conditions.
23. Investigations.
24. Injury, poisoning and procedural complications.
25. Surgical and medical procedures.
26. Social circumstances.
27. Product issue.

Appendix C Generic ranges for hematological and biochemistry parameters

The current list of generic ranges for hematological parameters (for adults) is provided in the table below:

Table 11 - Generic ranges for hematological parameters

LBTESTCD	LBTEST	GENDER	LBSTRESU	LBGNNRLO
HGB	Hemoglobin	F	g/L	120
HGB	Hemoglobin	M	g/L	135
LYM	Lymphocytes		10^9/L	1
NEUT	Neutrophils		10^9/L	1,8
PLAT	Platelets		10^9/L	150
WBC	Leukocytes		10^9/L	4,5
EOS	Eosinophils		10^9/L	0
BASO	Basophils		10^9/L	0
MONO	Monocytes		10^9/L	0,18
HCT	Hematocrit	M	%	0,41
HCT	Hematocrit	F	%	0,36
RBC	Erythrocytes	F	10^12/L	4
RBC	Erythrocytes	M	10^12/L	4,5
INR	INR		Ratio	0.8

Based on NEJM (N Engl J Med 2004;351:1548-63.): “Laboratory Reference Values”, Alexander Kratz, M.D., Ph.D., M.P.H., Maryjane Ferraro, Ph.D., M.P.H., Patrick M. Sluss, Ph.D., and Kent B. Lewandrowski, M.D.

The current list of generic ranges for biochemistry parameters (for adults) is provided in the table below:

Table 12 - Generic ranges for biochemistry parameters

LBTEST	LBSTRESU	LBGNNRLO - LBGNNRHI
Albumin	g/L	35 – 55
Blood Urea Nitrogen (BUN)	mmol/L	3.6 - 7.1
Calcium	mmol/L	2,2 - 2,6
Chloride	mmol/L	80 – 115
Glucose	mmol/L	3,9 – 7
Bicarbonate (HCO3)	mmol/L	22 – 29
Carbon dioxide	mmol/L	21 – 30
Potassium	mmol/L	3,5 – 5
Magnesium	mmol/L	0,8 - 1,2
Sodium	mmol/L	136 - 145
Phosphate	mmol/L	1 - 1,4
Protein	g/L	55 - 80
Urea	mmol/L	3,6 - 7,1

Appendix D IMWG criteria

Disease response will be assessed using the updated International Myeloma Working Group Response Criteria (IMWG). A confirmation assessment for disease response within 4 weeks is required in this protocol (either PR or better, or PD).

PD cannot not be diagnosed on FLC increase only, even in patients for whom serum and urine M-protein become below level of eligibility on efficacy laboratory performed on Cycle 1 Day 1 (see below the table for assessment of overall response and progression diagnosis of these patients).

Adapted from updated International Myeloma Working Group Response Criteria

IMWG MRD criteria (requires a complete response as defined below)	
Sustained MRD-negative	MRD negativity in the marrow (NGF or NGS, or both) and by imaging as defined below, confirmed minimum of 1 year apart. Subsequent evaluations can be used to further specify the duration of negativity (eg, MRD-negative at 5 years)
Flow MRD-negative	Absence of phenotypically aberrant clonal plasma cells by NGF on bone marrow aspirates using the EuroFlow standard operation procedure for MRD detection in multiple myeloma (or validated equivalent method) with a minimum sensitivity of 1 in 10^5 nucleated cells or higher
Sequencing MRD-negative	Absence of clonal plasma cells by NGS on bone marrow aspirate in which presence of a clone is defined as less than two identical sequencing reads obtained after DNA sequencing of bone marrow aspirates using the LymphoSIGHT platform (or validated equivalent method) with a minimum sensitivity of 1 in 10^5 nucleated cells or higher
Imaging-positive MRD-negative	MRD negativity as defined by NGF or NGS plus disappearance of every area of increased tracer uptake found at baseline or a preceding PET/CT or decrease to less mediastinal blood pool SUV or decrease to less than that of surrounding normal tissue
Standard IMWG response criteria	
Response	**IMWG criteria**
CR	• Negative immunofixation on the serum and urine and • disappearance of any soft tissue plasmacytomas and • <5% plasma cells in bone marrow aspirates. • A normal FLC ratio of 0.26–1.65 is required. **Two consecutive assessments are needed. No known evidence of progressive disease or new bone lesions if radiographic studies were performed**
sCR	CR as defined above plus: • normal FLC ratio (0.26 to 1.65) and • absence of clonal cells in bone marrow by immunohistochemistry (κ/λ ratio ≤4:1 or ≥1:2 for κ and λ patients, respectively, after counting ≥100 plasma cells) **Two consecutive assessments of laboratory parameters are needed. No known evidence of progressive disease or new bone lesions if radiographic studies were performed**

VGPR	• Serum and urine M-protein detectable by immunofixation but not on electrophoresis or • ≥90% reduction in serum M-protein plus urine M-protein level <100 mg/24 h. Note: subjects who otherwise achieve a biochemical CR but are either missing bone marrow data or are positive by immunofixation will be assessed as VGPR. In addition, they will be further assessed according to the following subcategories: • Biochemical CR: negative immunofixation of both serum and urine M-protein, with missing bone marrow data. • Near CR: serum and/or urine M-component detectable by immunofixation but not on electrophoresis. **Two consecutive assessments are needed. No known evidence of progressive disease or new bone lesions if radiographic studies were performed**
PR	• ≥50% reduction of serum M-protein and reduction in 24 hours urinary M-protein by ≥90% or to <200 mg/24 h • In addition to the above listed criteria, if present at baseline, a ≥50% reduction in the size (SPD) of soft tissue plasmacytomas is also required **Two consecutive assessments are needed. No known evidence of progressive disease or new bone lesions if radiographic studies were performed**
MR	≥25% but ≤49% reduction in serum M-protein and reduction in 24h urine M-protein by 50-89%, which still exceed 200 mg/24H. In addition to the above listed criteria, if present at baseline, ≥50% reduction in size (SPD) of soft tissue plasmacytomas is also required **No known evidence of progressive disease or new bone lesions if radiographic studies were performed**
Stable Disease	• Not meeting criteria for CR, VGPR, PR, MR or progressive disease **Two consecutive assessments are needed. No known evidence of progressive disease or new bone lesions if radiographic studies were performed**
Progressive disease	Any one or more of the following criteria: Increase of ≥25% from lowest confirmed value in any one of the following criteria: • Serum M-protein (the absolute increase must be ≥0.5 g/dL) • Serum M-protein increase ≥1 g/dL if the lowest M component was ≥5 g/dL • Urine M-component (the absolute increase must be ≥200 mg/24 h) Appearance of new lesion(s), including lesions determined by physical examination, ≥50% increase from nadir in SPD of >1 lesion, or ≥50% increase in the longest diameter of a previous lesion >1 cm in short axis; ≥50% increase in circulating plasma cells (minimum of 200 cells per µL) if this is the only measure of disease **Two consecutive assessments are needed. No known evidence of progressive disease or new bone lesions if radiographic studies were performed**

Abbreviations: CR, complete response; FLC, free light chain; IMWG, International Myeloma Working Group; M, monoclonal; MRD, minimal residual disease; NGF, next-generation flow; NGS, next-generation sequencing; PD, progressive disease; PR, partial response; sCR, stringent complete response; SD, stable disease; SPD, sum of the products of the maximal perpendicular diameters of measured lesions; SUV, maximum standardized uptake value; VGPR, very good partial response.

Patients with disease only measurable by FLC are not allowed.

A plasmacytoma that has been radiated is not suitable for response assessment; however, it must be monitored to assess for progressive disease.

For patients achieving very good partial response by other criteria, a soft tissue plasmacytoma must decrease by more than 90% in the sum of the maximal perpendicular diameter (SPD) compared with baseline.

Definite increase in the size of existing bone lesions or soft tissue plasmacytomas is defined as below: ≥50% increase in the size of at least one bidimensionally measurable lesion (in comparison with the measurements at Nadir) or appearance of a new lesion. Pathological fracture or collapse of bone are not necessarily evidence of disease progression.

Reminder: definitions of Response and Progression are based on IMWG Uniform Reporting Criteria:

- Any response (sCR, CR, VGPR, PR) or progression needs to be confirmed by two consecutive disease assessments according to the Study Flow Chart. A disease assessment at one time point not matched by the same disease assessment at the next time point will be considered unconfirmed (except for progression by imaging, bone marrow PC counts, where one time point is adequate for confirmed progression).
- Urine M-protein is not needed to document partial response or minor response if baseline urine M-protein was not measurable; however, it is still required for complete response and very good partial response.
- Documentation of response requires two consecutive readings of the applicable disease parameter (serum M-protein, urine M-protein), performed at any time (no minimum interval is required, it can be done the same day); however, to confirm response or progressive disease, two discrete samples are required; testing cannot be based upon the splitting of a single sample.
- Patients will continue in the last confirmed response category until there is confirmation of progression or improvement to a higher response status; patients cannot move to a lower response category.
- Percent decreases for response calculations are from baseline values (as defined in Section 2.1.1).
- Percent increases for progression calculations are from lowest response values or baseline values, whichever is the smaller number. The lowest value does not need to be confirmed.
- The lowest confirmed value before suspected progression will be used as baseline for calculation of progression; if a serum and/or urine spike is considered too low to quantitate, this value can be assigned as zero as a baseline for documentation of subsequent progressive disease. Patients will be considered to have progressive disease if they meet the criteria for progression by a variable that was not considered measurable at baseline; however, for patients who had a measurable serum or urine M-spike at baseline, progression cannot be defined by increases in serum FLC alone.

Patients with serum and urine M-Protein below level of eligibility at baseline (eg, patients with only FLC measurable disease according to IMWG or patients without any biological measurable disease, M-protein value >0 [or IFX positive] and <0.5 g/dL):

- Patients with M-protein (urine and/or serum) below the level of measurability (M-protein value >0 [or IFX positive] and <0.5 g/dL) can have CR, non-PD or PD responses only according to the increase or decrease of M protein or extramedullary disease if applicable, following the IMWG criteria.
- Patients with FLC measurable disease only (M-protein =0 and IFX negative), can have either non-PD or PD responses (PD will be an absolute increase of >10 mg/dL in the difference between involved and uninvolved FLC).
- Patients with serum M-protein value >0 g/dL (or serum IFX positive) and <0.5 g/dL, independently of FLC can only be qualified as: CR, non-PD, or PD

  AND/OR

- Patients with urine M-protein value >0 mg/24h (or urine IFX positive) and <200 mg/24h,independently of FLC can only be qualified as: CR, non-PD, or PD

  OR

- Patients with serum M-protein value =0 g/dL and serum IFX for intact Ig negative and urine M-protein =0 mg/24h and urine IFX negative, independently of FLC can only be qualified as: non-PD or PD

Appendix E Description of primary and sensitivity analyses of PFS

Table 13 – PFS Primary analysis (based on blinded IRC)

Situation	Date of progression or censoring	Outcome
No baseline tumor assessments	Date of Randomization	Censored
No valid post-baseline tumor assessments	Date of Randomization	Censored
Documented Progression according to IRC prior to initiation of further anti-myeloma treatment and prior to the cut-off date	Earliest date among all disease assessments with evidence of progression	Event
Death without documented progression prior to initiation of further anti-myeloma treatment and prior to the cut-off date	Date of death	Event
Both documented progression and death prior to initiation of further anti-myeloma treatment and prior to the cut-off date	Date of progression	Event
No documented progression according to IRC and no death prior to initiation of further anti-myeloma treatment and prior to the cut-off date	Earliest of the date of last valid disease assessment without evidence of progression before initiation of further anti-myeloma treatment and cut-off date	Censored
Symptomatic deterioration reported and no documented progression according to IRC and no death	Ignored	Ignored
Initiation of new anti-myeloma treatment before documented progression according to IRC	Earliest of the date of last valid disease assessment without evidence of progression before the initiation of further anti-myeloma treatment and cut-off date	Censored

Table 14 - PFS sensitivity analysis #1 (based on IRC and ignoring further anti-myeloma treatment)

Situation	Date of progression or censoring	Outcome
No baseline tumor assessments	Date of Randomization	Censored
No valid post-baseline tumor assessments	Date of Randomization	Censored
Documented Progression according to IRC prior to the cut-off date	Earliest date among all disease assessments with evidence of progression	Event
Death without documented progression prior to the cut-off date	Date of death	Event
Both documented progression and death prior to the cut-off date	Date of progression	Event
No documented progression according to IRC and no death prior to the cut-off date	Earliest of the date of last valid disease assessment without evidence of progression and cut-off date[a]	Censored
Symptomatic deterioration reported and no documented progression according to IRC and no death	Ignored	Ignored
Initiation of new anti-myeloma treatment	Ignored	Ignored

[a] If the last valid assessment without evidence of progression is after the cut-off date, then the PFS will be censored at the cut-off date. If there is no valid assessment not showing progression after the cut-off date, then the PFS will be censored at the last valid assessment without evidence of progression before the cut-off date.

Table 15 - PFS sensitivity analysis #2 (based on investigator's assessment of disease and ignoring symptomatic deterioration)

Situation	Date of progression or censoring	Outcome
No baseline tumor assessments	Date of Randomization	Censored
No valid post-baseline tumor assessments	Date of Randomization	Censored
Documented Progression according to investigator prior to initiation of further anti-myeloma treatment and prior to the cut-off date	Earliest date among all disease assessments with evidence of progression	Event
Death without documented progression prior to initiation of further anti-myeloma treatment and prior to the cut-off date	Date of death	Event
Both documented progression and death prior to initiation of further anti-myeloma treatment and prior to the cut-off date	Date of progression	Event
No documented progression according to investigator and no death prior to initiation of further anti-myeloma treatment and prior to the cut-off date	Earliest of the date of last valid disease assessment without evidence of progression before initiation of further anti-myeloma treatment and cut-off date	Censored
Symptomatic deterioration reported and no documented progression according to investigator and no death	Symptomatic deterioration ignored	Ignored
Initiation of new anti-myeloma treatment before documented progression according to investigator	Earliest of the date of last valid disease assessment without evidence of progression before the initiation of further anti-myeloma treatment and cut-off date	Censored

Table 16 - PFS sensitivity analysis #3 (progression based on investigator's assessment of disease, and including symptomatic deterioration)

Situation	Date of progression or censoring	Outcome
No baseline tumor assessments	Date of Randomization	Censored
No valid post-baseline tumor assessments	Date of Randomization	Censored
Documented Progression (without symptomatic deterioration) according to the investigator prior to initiation of further anti-myeloma treatment and prior to the cut-off date	Earliest date among all disease assessments with evidence of progression	Event
Death prior to initiation of further anti-myeloma treatment and prior to the cut-off date without documented progression and without symptomatic deterioration	Date of death	Event
Symptomatic deterioration prior to initiation of further anti-myeloma treatment and prior to the cut-off date reported with no documented progression according to investigator and no death	Date of symptomatic deterioration	Event
Symptomatic deterioration and documented progression according to the investigator prior to initiation of further anti-myeloma treatment and prior to the cut-off date regardless of death occurrence	Earliest of the date of symptomatic deterioration and date of documented progression	Event
Symptomatic deterioration and death prior to initiation of further anti-myeloma treatment and prior to the cut-off date with no documented progression according to the investigator	Date of symptomatic deterioration	Event
Documented progression according to the investigator and death prior to initiation of further anti-myeloma treatment and prior to the cut-off date with no symptomatic deterioration	Date of documented progression	Event
No documented progression according to the investigator, no death, and no symptomatic deterioration prior to initiation of further anti-myeloma treatment and prior to the cut-off date	Earliest of the date of last valid disease assessment without evidence of progression before the initiation of further anti-myeloma treatment and cut-off date	Censored
New anti-myeloma treatment started	Earliest of the date of last valid disease assessment without evidence of progression before the initiation of further anti-myeloma treatment and cut-off date	Censored

Table 17 - PFS sensitivity analysis #4 (progression based on IRC and including initiation of further anti-myeloma treatment as an event)

Situation	Date of progression or censoring	Outcome
No baseline tumor assessments	Date of Randomization	Censored
No valid post-baseline tumor assessments	Date of Randomization	Censored
Documented Progression according to IRC prior to initiation of further anti-myeloma treatment and prior to the cut-off date	Earliest date among all disease assessments with evidence of progression	Event
Death without documented progression prior to initiation of further anti-myeloma treatment and prior to the cut-off date	Date of death	Event
Both documented progression and death prior to initiation of further anti-myeloma treatment and prior to the cut-off date	Date of progression	Event
No documented progression according to IRC and no death prior to initiation of further anti-myeloma treatment and prior to the cut-off date	Earliest of the date of last valid disease assessment without evidence of progression before initiation of further anti-myeloma treatment and cut-off date	Censored
Symptomatic deterioration reported and no documented progression according to IRC and no death	Ignored	Ignored
Initiation of new anti-myeloma treatment before documented progression according to IRC and before the cut-off date	Start date of further anti-myeloma treatment	Event

Table 18 - PFS sensitivity analysis #5 (based on IRC, assigning uniform progression and assessment dates and censoring late progressions and deaths)

Situation	Date of progression or censoring	Outcome
No baseline tumor assessments	Date of Randomization	Censored
No valid post-baseline tumor assessments	Date of Randomization	Censored
Documented progression according to IRC prior to the cut-off date and within 8 weeks from last valid disease assessment	Date of the scheduled visit for this time window	Event
Death without documented progression prior to the cut-off date and within 8 weeks from last valid disease assessment	Date of death	Event
Death or Progression after more than one missed disease assessment (ie, more than 8 weeks from last valid disease assessment)	Earliest of the date of last valid disease assessment without evidence of progression before initiation of further anti-myeloma treatment and cut-off date	Censored
Symptomatic deterioration reported and no documented progression according to IRC and no death	Ignored	Ignored
No documented progression according to IRC and no death	Earliest of the date of last valid disease assessment without evidence of progression before initiation of further anti-myeloma treatment and cut-off date	Censored
Initiation of new anti-myeloma treatment before documented progression according to IRC	Earliest of the date of last valid disease assessment without evidence of progression before the initiation of further anti-myeloma treatment and cut-off date	Censored

Note: 8 weeks corresponds to twice the time between two tumor assessments per protocol (every 2*4 weeks)

Date of scheduled visit will be determined by the following windows:

# Window	Window for tumor assessment	Fixed date
	No window	Baseline
1	Day 2 – Day 43	Day 29
2	Day 44 – Day 71	Day 57
3	Day 72 – Day 99	Day 85
...	...	...

In general, the window for the time point of Day 28×n +1 (where n >1) is [Day 28×n -12, Day 28×n + 15]. The number of days in the definition is determined relative to the date of C1D1.

Disease assessments of Cycle 1, Cycle 2 and Cycle 3 are planned at Day 29 (from C1D1), Day 57 and Day 85, respectively. In case of a patient with progression occurring between two theoretical date of disease assessments, for this analysis the progression date will be the theoretical date of the disease assessment of the corresponding window, for example:

- in case of progression occurring at Day 43 (ie, window #1), the progression date would be the date of Day 29 (theoretical day of disease assessment of Cycle 1 according to protocol)
- in case of progression occurring at Day 44 or Day 65 (ie, window #2), the progression date would be the date of Day 57 (theoretical day of disease assessment of Cycle 2 according to protocol)

Appendix F EORTC QLQ-C30 and QLQ-MY20 items, scales and scores

For QLQ-C30:

- Global health status:
  - Global health status/QOL (QL2): (((Q29+Q30)/2)-1)/6 * 100
- Functional scales:
  - Physical functioning (PF2): (1 - (((Q1+Q2+Q3+Q4+Q5)/5) -1)/3) * 100
  - Role functioning (RF2): (1 - (((Q6+Q7)/2)-1)/3) * 100
  - Emotional functioning (EF): (1 - (((Q21+Q22+Q23+Q24)/4)-1)/3) * 100
  - Cognitive functioning (CF): (1 - (((Q20+Q25)/2)-1)/3) * 100
  - Social functioning (SF): (1 - (((Q26+Q27)/2)-1)/3) * 100
- **Symptom scales/Items:**
  - Fatigue (FA): (((Q10+Q12+Q18)/3)-1)/3 * 100
  - Nausea and vomiting (NV): (((Q14+Q15)/2)-1)/3 * 100
  - Pain (PA): (((Q9+Q19)/2)-1)/3 * 100
  - Dyspnoea (DY): (Q8-1)/3 * 100
  - Insomnia (SL): (Q11-1)/3 * 100
  - Appetite loss (AP): (Q13-1)/3 * 100
  - Constipation (CO): (Q16-1)/3 * 100
  - Diarrhoea (DI): (Q17-1)/3 * 100
  - Financial difficulties (FI): (Q28-1)/3 * 100

Scoring the EORTC QLQ-C30 version 3.0

Table 1: Scoring the QLQ-C30 version 3.0

	Scale	Number of items	Item range*	**Version 3.0** Item numbers	Function scales
Global health status / QoL					
Global health status/QoL (revised)†	QL2	2	6	29, 30	
Functional scales					
Physical functioning (revised)†	PF2	5	3	1 to 5	F
Role functioning (revised)†	RF2	2	3	6, 7	F
Emotional functioning	EF	4	3	21 to 24	F
Cognitive functioning	CF	2	3	20, 25	F
Social functioning	SF	2	3	26, 27	F
Symptom scales / items					
Fatigue	FA	3	3	10, 12, 18	
Nausea and vomiting	NV	2	3	14, 15	
Pain	PA	2	3	9, 19	
Dyspnoea	DY	1	3	8	
Insomnia	SL	1	3	11	
Appetite loss	AP	1	3	13	
Constipation	CO	1	3	16	
Diarrhoea	DI	1	3	17	
Financial difficulties	FI	1	3	28	

* *Item range* is the difference between the possible maximum and the minimum response to individual items; most items take values from 1 to 4, giving *range* = 3.
† (revised) scales are those that have been changed since version 1.0, and their short names are indicated in this manual by a suffix "2" – for example, PF2.

For all scales, the *RawScore*, *RS*, is the mean of the component items:

$$RawScore = RS = (I_1 + I_2 + ... + I_n)/n$$

Then for **Functional scales**:

$$Score = \left[1 - \frac{(RS-1)}{range}\right] \times 100$$

and for **Symptom scales / items** and **Global health status / QoL:**

$$Score = \{(RS-1)/range\} \times 100$$

For QLQ-MY20:

- Functional scales:
  - Future perspective (MYFP): (1 - (((Q48+Q49+Q50)/3) -1)/3) * 100
  - Body image (MYBI): (1 - (Q47-1)/3) * 100
- Symptom scales:
  - Disease symptoms (MYDS): (((Q31+Q32+Q33+Q34+Q35+Q36)/6)-1)/3 * 100
  - Side effect of treatment (MYSE): (((Q37+Q38+Q39+Q40+Q41+Q42+Q43+Q44+Q45+Q46)/10)-1)/3 * 100

Scoring the QLQ-MY20 :

Scale **Subscale (abbreviation)**	No. Items	Item Number(s)
Functional scales		
Future perspective (MYFP)	3	48 to 50
Body image (MYBI)	1	47
Symptom scales		
Disease symptoms (MYDS)	6	31 to 36
Side effects of treatment (MYSE)	10	37 to 46

Handling of Missing items for QLQ-C30 and QLQ-MY20:

- Multi-item Scales

  Have at least half of the items from a given scale been answered?

  - If Yes, use all the items that were completed, and apply the standard equations given above for calculating the scale scores; ignore any items with missing values when making the calculations.
  - If No, set scale score to missing.

- Single-item Scales:

  Set to missing if no response.

Appendix G Definition of regions

1) Geographical regions

Western Europe	Eastern Europe	North America	Asia	Other countries
Belgium Denmark France Germany Greece Italy Norway Portugal Spain Sweden United Kingdom	Czech Republic Hungary Poland Slovakia	Canada United States	Japan Korea (Republic of) Taiwan (Province of China)	Australia New Zealand Turkey Russian Federation

2) Regulatory regions

Western countries	Other countries
Belgium Denmark France Germany Greece Italy Norway Portugal Spain Sweden United Kingdom Canada United States Australia New Zealand	Czech Republic Hungary Poland Slovakia Japan Korea (Republic of) Taiwan (Province of China) Russian Federation Turkey

Appendix H Description of PFS2 analysis

Table 19 - PFS2 analysis (progression based on investigator disease assessment)

Situation	Date of progression or censoring	Outcome
No valid post-baseline disease assessments	Date of randomization	Censored
Death when further anti-myeloma treatment not yet started and prior to the cut-off date	Date of death	PFS2 event
No disease progression on study treatment* but disease progression or death after initiation of further anti-myeloma treatment and prior to the cut-off date	First progression date after initiation of further anti-myeloma therapy reported as per investigator or date of death if no progression after initiation of further anti-myeloma treatment	PFS2 event
No disease progression on study treatment*, no disease progression and no death after initiation of further anti-myeloma treatment and prior to the cut-off date	Earliest of the date of the last follow-up visit after initiation of further anti-myeloma treatment and the cut-off date. If no initiation of further anti-myeloma treatment, same date of censoring as for PFS on study treatment	Censored
Disease progression on study treatment*, no disease progression and no death after initiation of further anti-myeloma treatment and prior to the cut-off date	Earliest of the date of the last follow-up visit after initiation of further anti-myeloma treatment and the cut-off date. If no initiation of further anti-myeloma treatment, censor at the date of progression on study treatment	Censored
Disease progression on study treatment*, disease progression or death after initiation of further anti-myeloma treatment and prior to the cut-off date	First progression date after initiation of further anti-myeloma therapy reported as per investigator or date of death if no progression after initiation of further anti-myeloma treatment	PFS2 event

* disease progression on study treatment or in follow-up but before initiation of further anti-myeloma treatment as per investigator including symptomatic deterioration

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