STATISTICAL ANALYSIS PLAN

Protocol title:	**A randomized, Phase 3, open label study evaluating subcutaneous versus intravenous administration of isatuximab in combination with pomalidomide and dexamethasone in adult patients with relapsed and/or refractory multiple myeloma (RRMM)**
Protocol number:	**EFC15951**
Compound number (INN/Trademark):	**SAR650984 isatuximab/SARCLISA®**
Study phase:	**Phase 3**
Short Title:	**SC versus IV isatuximab in combination with pomalidomide and dexamethasone in RRMM**
Statistician:	[redacted]
Statistical project leader:	[redacted]
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VERSION HISTORY

The initial statistical analysis plan (SAP) was approved on 06-Jun-2022 before the first participant was enrolled. The below SAP history table gives the timing, rationale, and key details for major changes to the statistical analysis features in the statistical analysis plan.

Table 1 - Major changes in statistical analysis plan

SAP Version	Approval Date	Changes	Rationale
1	06-Jun-2022	Not Applicable	Original version
2	29-Nov-2023	Added in Section 2 analysis population set for the co-primary PK endpoint with the following conditions: • at least 11 isatuximab dose from Cycle 1 day 1 to Cycle 5 Day 15 (one dose omission permitted at Cycle 1 only) are administered, • actual isatuximab dose received at each schedule visit up to Cycle 5 Day 15 (equivalent to Cycle 1 Day 1 to Cycle 5 Day 15) is between $0.8 \times$ planned dose and $1.2 \times$ planned dose, • isatuximab predose plasma concentration results from PK samples on Cycle 6 Day 1 are collected within per protocol defined time window with adequate documentation of dosing and sampling dates and times. That is to say, predose isatuximab Cycle 6 Day 1 concentration results should be collected between 12 days and 16 days after Cycle 5 Day 15 isatuximab dose, and within 4 hours prior to the planned Cycle 6 Day 1 dose if administered.	Updated
		Added in Section 2 analysis population set for the key secondary PK endpoint with following conditions: • all 4 isatuximab doses for Cycle 1 are administered, • actual isatuximab dose received at each schedule visit of Cycle 1 (equivalent to Cycle 1 Day 1 to Cycle 1 Day 22) is between $0.8 \times$ planned dose and $1.2 \times$ planned dose, • isatuximab predose plasma concentration results from PK samples on Cycle 2 Day 1 are collected within per protocol defined time window with adequate documentation of dosing and sampling dates and times. That is to say, predose isatuximab Cycle 2 Day 1 concentration results should be collected between 6 days and 8 days after Cycle 1 Day 22 isatuximab dose, and within 4 hours prior to the planned Cycle 2 Day 1 dose if administered.	Updated
		Updated in Section 2 analysis population set for analyses	Updated and clarified
		Updated in Section 3.1 timepoint wise (or sequential) confirmed disease response criteria	Updated to align with other isatuximab studies
		Updated in Section 3.3.2.1 censoring rule for overall survival as, if death is not observed before the analysis data cut-off date, overall survival will be censored at the last date that the participant is known to be alive or at the cut-off date, whichever comes first.	Clarified

SAP Version	Approval Date	Changes	Rationale
		Added in Section 3.3.1.2 information about the non-inferior margin for the key secondary endpoint VGPR and better rate	Provided assumption
		Added in Section 3.4 additional exploratory endpoints	Updated
		Updated in Section 3.6.3.1 for neutropenia and neutropenic complications analyses	Updated to align with other isatuximab studies
		Added in Section 3.6.3.2 Cycle 6 Day 15 onward analyses for Arm SC	Clarified to focus on patient level safety review
		Updated in Section 3.7.2 subgroups for efficacy and safety analyses	Updated
		Clarified in Section 5.2 protocol deviations	Updated to align with other isatuximab studies
		Clarified in Section 5.3 and 5.4 for handling missing or partial end date	Updated to align with other isatuximab studies
		Minor editorial and typographical error corrections throughout the document	Minor, therefore, have not been summarized
3	24-Oct-2024	Section 1.2: Addition of exploratory endpoints	Exploratory endpoints were missing in previous version
		Section 2: Per protocol population modified to include all treated participants who have measurable disease at baseline and have no major protocol deviations with respect to eligibility	Clarified to align with protocol definition
		Section 3.1: Derivation of confirmed overall response updated to add derivation for participants with non-measurable disease at baseline and add clarification on overall response categories	Updated and clarified
		Sections 3.2.2 and 3.3.1.3: Stratified analyses by stratification factors added as sensitivity analyses for ORR and VGPR or better response rate	Added following FDA's recommendation
		Section 3.3.2.1: EQ-5D-5L utility index analyses removed from SAP	Analyses will be done by Health Economics and Value Assessment department
		Section 3.3.2.2: Device performance analyses and time-to-event analyses	Updated and clarified
		Section 3.3.2.2: PFS analyses as per investigator ignoring and including symptomatic deterioration added	Updated to align with other isatuximab studies
		Section 3.4.1: Renal response definition and analyses	Updated to align with other isatuximab studies
		Section 3.6.1.2: Isatuximab exposure reviewed and description of duration by gender added	Updated to align with other isatuximab studies
		Section 3.6.1.5: At home administration section added	Need to describe the exposure for administration performed at home for CSR purpose
		Section 3.6.2: General rules and planned analyses updated	Updated to align with other isatuximab studied and CSR needs

SAP Version	Approval Date	Changes	Rationale
		Section 3.6.3.1: Laboratory variable, vital signs and ECGs analyses updated	Updated to align with other isatuximab studies and CSR needs
		Section 3.6.4: Product complaints: Clarified that analyses will be performed by a different department	Analyses will be done by Specialty Care Device department
		Section 3.7.1.1: Rules for LLOQ imputation updated	Updated to align with other isatuximab studies
		Section 3.7.2: Subgroups analyses by R-ISS, R2-ISS and frailty score added for efficacy, and by number of prior lines as per eCRF for safety	Updated for CSR needs according to previous isatuximab studies
		Section 5.2: Participant disposition	Updated to align with other isatuximab studies
		Section 5.3: Demographics and baseline characteristic, prior or concomitant medications	Updated to align with other isatuximab studies
		Section 5.4: Data handling convention: Removal of time-window and addition of partial dates handling rules	Updated to align with other isatuximab studies
		Section 5.5: EORTC QLQ-C30 and QLQ-MY20 items, scales and scores Section 5.6: Description of censoring rules for primary and supportve analyses of PFS Section 5.7: Description of PFS2 analyses Section 5.8: Geographical region definition Section 5.9: List of countries for which national and/or local regulations does not permit at home administration	Added to detail derivation rules
		Minor editorial and typographical error corrections throughout the document	Minor, therefore, have not been summarized

1 INTRODUCTION

1.1 STUDY DESIGN

This is a randomized, multicenter, Phase 3, open-label study evaluating SC versus IV administration of isatuximab in combination with pomalidomide and dexamethasone in adult RRMM patients (study participants) who have received at least 1 prior line of therapy including lenalidomide and a PI. The objective of this study is to demonstrate that the efficacy and pharmacokinetics of isatuximab SC are not inferior to those for isatuximab IV.

The randomization will be stratified by MM isotype (IgG versus non-IgG), body weight (≤65 kg, >65 to ≤85 kg, and >85 kg), and number of prior lines (1-2 versus ≥3). Eligible participants (approximately 534) will be randomized 1:1 into 1 of 2 study arms:

- Arm SC (N=267): Isatuximab SC at 1400 mg with device injector+Pomalidomide(P)+ Dexamethasone(d)
- Arm IV (N=267): Isatuximab IV 10 mg/kg+ Pomalidomide(P)+ Dexamethasone(d)

Isatuximab IV and SC will be administered weekly for 4 weeks (Cycle 1) and on Day 1 and Day 15 of each subsequent cycles, in combination with pomalidomide and dexamethasone. Pomalidomide will be administered from Day 1 to Day 21 of each 28 days cycles and dexamethasone will be administered every week.

1.2 OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
Demonstrate the efficacy non-inferiority between isatuximab SC and isatuximab IV in combination with Pd	Overall response rate (ORR): defined as the proportion of participants with stringent complete response (sCR), complete response (CR), very good partial response (VGPR), and partial response (PR) according to the 2016 International Myeloma Working Group (IMWG) criteria assessed by Independent Review Committee (IRC).
Demonstrate the pharmacokinetic (PK) non-inferiority between isatuximab SC and isatuximab IV in combination with Pd	Observed concentration before dosing (C_{trough}) at steady state (corresponding to predose at C6D1)
Secondary: Key Secondary	
Demonstrate the efficacy non-inferiority between isatuximab SC and isatuximab IV in combination with Pd	Very Good Partial Response or better rate: defined as the proportion of participants with sCR, CR, and VGPR according to the 2016 International Myeloma Working Group (IMWG) criteria assessed by IRC.
Demonstrate the PK non-inferiority between isatuximab SC and isatuximab IV in combination with Pd	Observed concentration before dosing (C_{trough}) at 4 weeks (ie, CT4W corresponding to predose at C2D1)

Objectives	Endpoints
Assess safety of isatuximab SC and IV in combination with Pd	Incidence rate of infusion-reactions (IRs)
Assess patient satisfaction with isatuximab SC and IV	Percentage of participants satisfied or very satisfied with the injection method used to administer study medication based on the patient experience and satisfaction questionnaire (PESQ) at Cycle 5 Day 15
Secondary: Other Secondary	
Assess efficacy of isatuximab SC compared to isatuximab IV in combination with Pd	Duration of response (DOR): defined as the time from the date of the first response to the date of first occurrence of progressive disease (PD) as determined by IRC or death from any cause, whichever happens first. DOR is determined only for participants who have achieved a response (PR or better). In the absence of PD or death before the analysis cut-off date, the DOR will be censored at the date of the last valid disease assessment performed prior to initiation of a further anti-myeloma treatment or the analysis cut-off date, whichever is earlier. Patients with two or more consecutive missed assessments prior to PD or death will be censored at the last valid disease assessment. Time to first response (TT1R): defined as the time from randomization to the date of first IRC determined response (PR or better) that is subsequently confirmed. Time to best response (TTBR): 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. Progression free survival (PFS): defined as the time from the date of randomization to the date of first documentation of PD as determined by IRC or the date of death from any cause, whichever comes first. Responses will be determined according to IMWG criteria. Progression based on paraprotein will be confirmed based on two consecutive assessments. PFS 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 (if any) or the analysis cut-off date, whichever comes first. Patients with two or more consecutive missed assessments prior to PD or death will be censored at the last valid disease assessment. Overall survival (OS): defined as the time from the date of randomization to death from any cause. Participants without death prior to the analysis cut-off date will be censored at the last date the participant was known to be alive or the cut-off date, whichever is first. PFS2: defined as time from the date of randomization to the date of first documentation of PD (as assessed by investigator) after initiation of further anti-myeloma treatment or death from any cause, whichever happens first. Same censoring rule applies as in the PFS endpoint.

Objectives	Endpoints
Assess safety of isatuximab SC and IV and local tolerability of isatuximab SC in combination with Pd	Treatment-emergent adverse events (TEAEs)/serious adverse events (SAEs). Treatment-emergent adverse events (TEAEs) are defined as adverse events (AEs) that develop, worsen (according to the Investigator opinion), or become serious during the treatment period. The treatment period is defined as the time from first dose of study treatment up to 30 days after last dose of study treatment. Laboratory parameters Injection site reactions (ISRs) – SC arm only Adverse events and laboratory parameters will be graded using NCI CTCAE v5.0.
Characterize PK of isatuximab SC and IV in combination with Pd	PK concentrations
Assess the delivery performance of the (investigational) device injector	Number of successful injections with (investigational) isatuximab injector device defined as completion of administration per provided instructions for use with no use errors or technical issues, divided by the total number of injections.
Assess the potential immunogenicity of isatuximab SC and IV in combination with Pd	Incidence of participants with anti-drug antibodies (ADA) against isatuximab
Assess the clinical outcome of isatuximab SC and IV in combination with Pd	Patient expectation at baseline and experience/satisfaction with Isatuximab will be assessed using the patient expectation questionnaire (PEQ), the patient experience and satisfaction PESQ and the patient's assessment of treatment (PAT) questionnaires Health Resources Utilization will be assessed using the Health Resource Utilization and Productivity Questionnaire (HRUPQ) Health-related quality of life will be assessed using the European Organization for Research and Treatment of Cancer (EORTC) myeloma module with 20 items (QLQ-MY20) and EORTC quality of life questionnaire with 30 questions (QLQ-C30). Health status will be assessed using the European Quality of Life Group questionnaire with 5 dimensions and 5 levels per dimension (EQ-5D-5L).
Explore chromosomal abnormalities (mainly but not limited to t(4;14), t(14;16), del(17p) and gain(1q21+)), and potential association with clinical outcomes	Impact of abnormal cytogenetic subtypes on participant outcome.
Exploratory	
Assess Minimum Residual Disease (MRD) negativity rate of isatuximab SC compared to isatuximab IV in combination with Pd.	Minimum residual disease (MRD) negativity rate: Defined as the proportion of participants for whom MRD is negative; threshold for negativity will be at least 10^-5. MRD negative CR rate (MRD[-]CR): defined as the proportion of participants with best overall response as sCR/CR and for whom MRD is negative; threshold for negativity will be at least 10^-5.
Explore PK and Pharmacodynamics (PDy) relationship.	Relationship between isatuximab PK exposure and safety endpoints of interest may be investigated as well as between

Objectives	Endpoints
	isatuximab PK exposure and efficacy endpoints (eg, ORR, VGPR) if possible (SC arm only).
Explore genomic and genetic profiling at screening and at disease progression.	Characterization of bone marrow (BM) genomic and genetic profiles to explore mechanism of drug resistance.
Explore new methods for measuring serum M Protein such as mass spectrometry	Impact of new serum M-protein measurement methods on disease response assessment.
Explore frailty and potential association with clinical outcome.	Impact of frailty on participant clinical outcome.

1.2.1 Estimands

Primary estimand defined for primary and key secondary endpoints are summarized in below Table 2.

Table 2 - Summary of primary estimand for main endpoints

Endpoint Category (estimand)	Estimands			
	Endpoint	**Population**	**Intercurrent event(s) handling strategy**	**Population-level summary (Analysis and missing data handling)**
Primary objective: Demonstrate the efficacy and PK non-inferiority between isatuximab SC and isatuximab IV in combination with Pd				
Co-primary endpoint	ORR per IRC assessment (sCR, CR, VGPR, and PR)	ITT	While on-treatment strategy: The start of new anti-MM treatment will be handled with while on treatment strategy. The endpoint will be assessed based on all disease assessments prior to the start of new anti-MM treatment. Treatment policy strategy: Study treatment discontinuation will be handled with treatment policy strategy. Regardless of study treatment discontinuation, the endpoint will be assessed based on all disease assessments.	The ORR will be estimated and its two-sided 95% confidence interval (CI) will be provided using the Clopper-Pearson method. The relative risk for Arm SC vs Arm IV will be estimated along with its two-sided 95% CI and p-value will be calculated using the Farrington-Manning method. The lower limit of the 95% CI of the relative risk will be compared with the pre-defined non-inferiority margin of 0.839 (ie, lower limit of 95% CI ≥0.839). In addition, the odds ratio for Arm SC vs Arm IV and its two-sided 95% CI will be provided. Participants who have missing disease response or have no confirmed disease response of PR or better will be counted as non-responders.
Co-primary endpoint	C_{trough} at steady state (predose at Cycle 6 Day 1)	PK-PP	Principal stratum strategy: Doses, administration scheme, sample collection, processing and result, time window of collection and adequate documentation	The geometric mean, coefficient of variation, median and range for C_{trough} at steady state will be provided. The ratio of the geometric means for C_{trough} at steady state of SC/IV and its two-sided 90% CI (under the logarithm scale then converting back to its original scale) will be calculated. The lower limit of the 90% CI will be compared with the non-inferiority margin of 0.80 (ie, lower limit of 90% CI ≥0.80).
Key secondary objective: Demonstrate the efficacy and PK non-inferiority between isatuximab SC+Pd and isatuximab IV+Pd, and assess the safety and patient satisfaction of isatuximab SC and IV in combination with Pd				
Key secondary endpoint	VGPR or better rate per IRC assessment (sCR, CR, VGPR)	ITT	While on-treatment strategy: The start of new anti-MM treatment will be handled with while on treatment strategy. The endpoint will be assessed based on all disease assessments prior to the start of new anti-MM treatment.	The VGPR or better rate will be estimated and its two-sided 95% CI will be provided using the Clopper-Pearson method. The relative risk for Arm SC vs Arm IV will be estimated along with its two-sided 95% CI and p-value will be calculated using the Farrington-Manning method.

Endpoint Category (estimand)	Estimands			
	Endpoint	**Population**	**Intercurrent event(s) handling strategy**	**Population-level summary (Analysis and missing data handling)**
			Treatment policy strategy: Study treatment discontinuation will be handled with treatment policy strategy. Regardless of study treatment discontinuation, the endpoint will be assessed based on all disease assessments.	The lower limit of the 95% CI of the relative risk will be compared with the pre-defined non-inferiority margin of 0.6312 (ie, lower limit of 95% CI ≥0.6312). In addition, the odds ratio for Arm SC vs Arm IV and its two-sided 95% CI will be provided. Participants who have missing disease response or have no confirmed disease response of VGPR or better will be counted as non-responders.
Key secondary endpoint	C_{trough} at 4 weeks	CT4W-PK population	Principal stratum strategy: Doses, administration scheme, sample collection, processing and result, time window of collection and adequate documentation	The geometric mean, coefficient of variation, median and range for C_{trough} at 4 weeks will be provided. The ratio of the geometric means for C_{trough} at 4 weeks of SC/IV and its two-sided 90% CI (under the logarithm scale then converting back to its original scale) will be calculated. The lower limit of the 90% CI will be compared with the non-inferiority margin of 0.80 (ie, lower limit of 90% CI ≥0.80).
Key secondary endpoint	Incidence rate of infusion reactions	Safety	While on treatment strategy: Study treatment discontinuation will be handled with while on treatment strategy. The endpoint will be assessed based on all available visit assessments up to the end date of study treatment +30 days.	The rate will be estimated and its two-sided 95% CI will be provided using the Clopper-Pearson method. The relative risk and odds ratio for Arm SC vs Arm IV will be estimated and its two-sided 95% Wald CI will be provided. P-value will be provided using the Fisher's exact test.
Key secondary endpoint	Patient satisfaction rate based on PESQ questionnaire at Cycle 5 Day 15	ITT	Composite strategy: Study treatment discontinuation will be handled with composite strategy. Participants who discontinue study treatment before Cycle 5 Day 15 will be counted as non-satisfied.	The rate will be estimated and its two-sided 95% CI will be provided using the Clopper-Pearson method. The odds ratio will be estimated for SC arm vs IV arm and its two-sided 95% Wald CI will be provided. The p-value will be provided using the stratified the Cochran-Mantel-Haenszel (CMH) test. Participants who have not responded as satisfied or as very satisfied with the injection method used to administer study medication will be counted as non-satisfied.

2 ANALYSIS POPULATIONS

The following populations for analyses are defined.

Table 3 - Populations for analyses

Population	Description
Screened	All participants who signed the ICF
Intent-to-treat (ITT)	The intent-to-treat (ITT) population is the randomized population. All participants who have given their informed consent and for whom there is confirmation of successful allocation of a randomization number by the IRT will be included in this population. Participants will be analyzed according to the treatment group allocated by IRT, regardless of whether the participants received any study treatment or received a different study treatment from that to which they were randomized. This population will be used for the analysis of all efficacy endpoints.
Per Protocol-PK (PP-PK) population	The Per Protocol PK population will include all randomized participants who meet the following conditions: a) at least 11 isatuximab dose from Cycle 1 day 1 to Cycle 5 Day 15 (one dose omission permitted at Cycle 1 only – Rational for dose omission is provided below the table) are administered, b) actual isatuximab dose received at each schedule visit up to Cycle 5 Day 15 (equivalent to Cycle 1 Day 1 to Cycle 5 Day 15) is between $0.8 \times$ planned dose and $1.2 \times$ planned dose, c) isatuximab predose plasma concentration results from PK samples on Cycle 6 Day 1 are collected within per protocol defined time window with adequate documentation of dosing and sampling dates and times. That is to say, predose isatuximab Cycle 6 Day 1 concentration results should be collected between 12 days and 16 days after Cycle 5 Day 15 isatuximab dose, and within 4 hours prior to the planned Cycle 6 Day 1 dose if administered. This population will be used for the analysis of the co-primary PK endpoint.
CT4W-PK population	The CT4W-PK population for CT4W endpoint will include all randomized participants who meet the following conditions: a) all 4 isatuximab doses for Cycle 1 are administered, b) actual isatuximab dose received at each schedule visit of Cycle 1 (equivalent to Cycle 1 Day 1 to Cycle 1 Day 22) is between $0.8 \times$ planned dose and $1.2 \times$ planned dose, c) isatuximab predose plasma concentration results from PK samples on Cycle 2 Day 1 are collected within per protocol defined time window with adequate documentation of dosing and sampling dates and times. That is to say, predose isatuximab Cycle 2 Day 1 concentration results should be collected between 6 days and 8 days after Cycle 1 Day 22 isatuximab dose, and within 4 hours prior to the planned Cycle 2 Day 1 dose if administered. This population will be used for the analysis of the CT4W PK endpoint.
Per Protocol Population	The PP is defined as all treated participants who have measurable disease at baseline and have no major protocol deviations with respect to eligibility. This population will be used for sensitivity analysis of ORR and VGPR or better rate in the context of a non-inferiority design
Safety	The safety population will include ITT participants who have received at least 1 dose or a part of a dose of the study intervention. All analyses using this population will be based on the treatment actually received. All safety analysis will be performed on this population.

Population	Description
Pharmacokinetic (PK)	The PK population will include all participants with at least 1 available isatuximab concentration post-baseline (whatever the cycle and even if dosing is incomplete) with adequate documentation of dosing and sampling dates and times. This population will be used for the analysis of all PK related analyses, except PK related coprimary and key secondary endpoints.
ADA	The immunogenicity population will include all participants from safety population with at least 1 ADA result (negative, positive or inconclusive) post-baseline.

Participants exposed to study intervention before or without being randomized will not be considered randomized and will not be included in any analysis population. The safety experience of these participants will be reported separately.

Randomized participants for whom it is unclear whether they took the study intervention will be considered as exposed and will be included in the safety population as randomized.

For any participant 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 reported separately.

Rational for dose omission allowed in PP-PK population definition:

Considering the median time to reach steady-state (18 weeks, POH0503) and the long terminal half-life of isatuximab (ie 28 days for a typical patient, POH0503), it was anticipating that missing one dose at the beginning of the treatment (ie, during Cycle 1) , would have a limited impact on steady-state exposure. Therefore, various simulations from a preliminary PK model were performed to support and illustrate this assumption.

First, based on typical predicted PK profiles, it was shown that missing one dose during Cycle 1 led to a maximal decrease of 6% in trough levels after 20 weeks of treatment (Cycle 6, Day 1, [Week 20], CT20W).

Then, full trial simulations intended to support SC dose selection were conducted to assess the probability of success to reach non-inferiority (NI) for Isa-SC vs Isa-IV, based on CT20W (co-primary endpoint of study EFC15951). One thousand (1000) replicate trial were simulated per scenario tested and the probability of success of each scenario was defined as number of trials with the lower bound of the 90% CI for the SC/IV ratio being at least 0.80.

In that context, simulations were performed allowing one dose omission during the first Cycle for up to 10% of participants, as a worst-case scenario, based on actual observed compliance in previous ICARIA study.

In all tested scenarios at 1400 mg SC, including worst ones (bioavailability of 60%, 10% of patients with one missing dose during Cycle 1 and 40% of eligible patients for PK assessment (ie, total number of participants 534 with 40% eligible 214 (107 IV, 107 SC)), the probabilities of success were evaluated to be higher than 90%.

Therefore, one dose omission (only during cycle 1) is allowed in the definition of the per protocol population of eligible PK participants for the assessment of the coprimary PK endpoint.

3 STATISTICAL ANALYSES

3.1 GENERAL CONSIDERATIONS

All analyses will be performed by Arm SC: Isa SC+Pd and by Arm IV: Isa IV+Pd (and by overall, for baseline and demographics characteristics). Unless otherwise stated, efficacy analyses and baseline and demographics characteristics will be performed on the ITT population.

In general, continuous variables will be summarized using the number of observations available, mean, standard deviation (SD), median, Q1, Q3, minimum, and maximum. Categorical and ordinal and binary variables will be summarized using the count and percentage of participants.

Study treatment for Arm SC is isatuximab SC in combination with pomalidomide and dexamethasone, and for Arm IV is isatuximab IV in combination with pomalidomide and dexamethasone. The start date of study treatment for Arm SC and Arm IV, respectively, is defined as the first administration date with non-zero dose for at least one of the study interventions (isatuximab, pomalidomide and dexamethasone).

The baseline value is defined as the last non-missing value collected on or before the start date of study treatment (or the date of randomization for non-treated participants). For serum M-protein and urine M-protein, an unscheduled assessment performed on the start date of study treatment (corresponding to Cycle 1 Day 1) will be considered as the baseline value. For other parameters, unscheduled assessments or repeated tests (such as vital signs) performed on the day of first study treatment administration will be considered as post baseline. This definition applies for all variables unless otherwise specified.

Participants with measurable disease at baseline for disease assessment will be defined if at least one of the following conditions meets:

- Serum M-protein ≥0.5 g/dL measured using serum protein immunoelectrophoresis
- Urine M-protein ≥200 mg/24 hours measured using urine protein immunoelectrophoresis
- Serum free light chain (FLC) assay: Involved FLC assay ≥10 mg/dL (≥100 mg/L) and an abnormal serum FLC ratio (<0.26 or >1.6).

For all analyses, efficacy and safety data will be included up through the analysis cut-off date. The primary and the key secondary endpoints related to disease response will be analyzed according to the Independent Review Committee (IRC) assessment. Myeloma disease response assessments will be performed every 28 days (day 1 of each cycle) by the investigators using the IMWG 2016 response criteria.

IMWG response assessment will be performed from the date of randomization to the date of confirmed disease progression, start of new anti-MM treatment or death, whichever occurs first.

The category of response (sCR, CR, VGPR, PR, minimal response (MR) and PD) evaluated by the central laboratory M protein, radiological exam when required, and BM plasma cell count when required will be confirmed based on the sequential assessment visits. PD based on radiographic imaging does not require a confirmation on the subsequent time point.

For participants without measurable disease at baseline, 3 categories of overall response are possible: Non-PD, PD and CR.

In general, the following rule will be applied to consider the category of response at each visit or each timepoint wise:

Confirmed overall response based on sequential assessments for participants with measurable disease at baseline

Overall response at timepoint n	Overall response at timepoint n+1	Confirmation assessment for Overall response at timepoint n
sCR	sCR	sCR
CR	sCR	sCR
sCR	CR	sCR
CR	CR	CR
VGPR	sCR/CR/VGPR	VGPR
sCR/CR	VGPR	VGPR
PR	sCR/CR/VGPR/PR	PR
sCR/CR/VGPR	PR	PR
MR	sCR/CR/VGPR/PR/MR	MR
sCR/CR/VGPR/PR	MR	MR
sCR/CR/VGPR/PR/MR/SD	No further evaluation/NE	Confirmed assessment (if available) of timepoint (n-1), otherwise SD (if no confirmed assessment at timepoint n-1)
SD	sCR/CR/VGPR/PR/MR/SD/PD/no further evaluation/NE	SD
sCR/CR/VGPR/PR/MR	SD	SD
PD	PD	PD
PD	Any except PD	PD (if radiological assessment PD), otherwise uPD
NE	PD	NE
sCR/CR/VGPR/PR/MR/SD	PD	SD
NE	sCR/CR/VGPR/PR/MR/SD	SD
NE	No further evaluation/NE	NE

Note: uPD= unconfirmed PD, NE= not evaluable

Confirmed overall response based on sequential assessments for participants without measurable disease at baseline

Confirmed Overall Time Point Response at Subsequent Time Points		
Overall Time Point Response at Time Point n	**Overall Time Point Response at Time Point n+1**	**Confirmed Overall Time Point Response[1,2] at Timepoint n**
Biochemical PD	Biochemical PD	PD
Radiographic PD	ANY	PD
Biochemical PD	CR/NPD	NPD
Biochemical PD	No further evaluation	Unconfirmed PD (PDu)
CR/NPD	Biochemical PD	NPD
UE	Biochemical PD	UE
ANY except PD	Radiographic PD	NPD
CR	CR	CR
CR	NPD/UE/No further evaluation	NPD
NPD	CR/NPD/UE/ No further evaluation	NPD
Any Except PD	UE	Confirmed assessment (if available) of timepoint (n-1), otherwise NPD (if no confirmed assessment at timepoint n-1)
UE	CR/NPD	UE
UE	UE/No further evaluation	UE

NPD = Non Progressive disease, UE = Unevaluable

1. A Confirmed Overall Response of NPD or better can only be made after the subject is on-study for a minimum of four (4) weeks (28 days). If the subject is on-study less than four (4) weeks (28 days), any assessment indicating NPD or better before this time period will have a Confirmed Response of UE unless PD is identified.
2. A Time Point Response of CR is not applicable for patients with both serum and urine protein levels equal to zero (0) and negative by IFX at baseline.

The best overall response (BOR) is derived across all confirmed disease response assessments, and the ordering of evaluations from best to worse is: sCR, CR, VGPR, PR, MR, SD, PD, not evaluable (NE). NE for BOR also represents missing disease response. For randomized participants with no disease assessments the BOR is set to NE.

A valid disease assessment corresponds with a timepoint where IMWG disease response is not missing or not NE. Disease assessment with missing date will also not be considered as valid assessment. If several exams (laboratory or radiology) are performed at different dates without showing PD, the date of last valid disease assessment is the latest date of response assessment. If PD is based on radiology, the date of PD will be the date of the first radiological exam showing PD. If PD is based on laboratory, the date of PD will be the date of first PD that is subsequently confirmed.

The following stratification factors collected on the date of randomization through the Interactive Response Technology (IRT) system will be used for analysis:

- MM isotype (IgG versus non-IgG).
- Body weight (≤65 kg, >65 to ≤85 kg, and >85 kg).
- Number of prior lines (1-2 versus ≥3).

The observation period will be divided into 3 segments:

- The **pre-treatment** period is defined as the time the informed consent form (ICF) is signed until the first dose of the study treatment administration.
- The **treatment-emergent (TE) period** is defined as the period from the start date of study treatment to the end date of study treatment +30 days.
- The **post-treatment period** is defined as the time starting 31 days after the end date of study treatment to study closure or death, whichever comes first.

3.2 PRIMARY ENDPOINT(S) ANALYSIS

The co-primary endpoints detailed in this section are ORR per IRC assessment and C_{trough} at steady state.

ORR per IRC assessment:

ORR per IRC assessment is defined as the proportion of participants who have BOR of PR or better as assessed by IRC. Participants who have missing disease response or have no confirmed disease response of PR or better will be counted as non-responders.

C_{trough} at steady state:

C_{trough} at steady state is the observed plasma concentration collected on predose at Cycle 6 Day 1 (equivalent to prior to Cycle 6 Day 1) of isatuximab administration dose. Participants will be included in the analysis as defined in PP-PK population.

3.2.1 Main analytical approach

The co-primary endpoints will be analyzed with the estimands defined according to the following attributes:

Co-primary endpoint: ORR per IRC assessment

- Endpoint: ORR per IRC assessment
- Treatment condition: isatuximab SC+Pd will be compared to isatuximab IV+Pd
- Analysis population: ITT population
- Intercurrent events (IE):
  - While on-treatment strategy: The start of new anti-MM treatment will be handled with while on treatment strategy. The endpoint will be assessed based on all disease assessments prior to the start of new anti-MM treatment.
  - Treatment policy strategy: Study treatment discontinuation will be handled with treatment policy strategy. Regardless of study treatment discontinuation, the endpoint will be assessed based on all disease assessments.

- Population-level summary:
  - The ORR will be estimated and its two-sided 95% confidence interval (CI) will be provided using the Clopper-Pearson method.
  - The relative risk for Arm SC vs Arm IV will be estimated along with its two-sided 95% CI and p-value will be calculated using the Farrington-Manning method.
  - The lower limit of the 95% CI of the relative risk will be compared with the pre-defined non-inferiority margin of 0.839 (ie, lower limit of 95% CI ≥0.839).
  - Additionally, the odds ratio for Arm SC vs Arm IV and its two-sided 95% CI (using the Miettinen-Nurminen score method) will be provided.
  - Participants who have missing disease response or have no confirmed disease response of PR or better will be counted as non-responders.

Co-primary endpoint: C_{trough} at steady state

- Endpoint: C_{trough} at steady state
- Treatment condition: isatuximab SC+Pd will be compared to isatuximab IV+Pd
- Analysis population: PK-PP
- Intercurrent events (IE):
  - Principal stratum strategy: Doses, administration scheme, sample collection, processing and result, time window of collection and adequate documentation
- Population-level summary:
  - The geometric mean, coefficient of variation, median and range for C_{trough} at steady state will be provided for isatuximab SC and isatuximab IV.
  - The ratio of the geometric means for C_{trough} at steady state of SC/IV and its two-sided 90% CI (under the logarithm scale then converting back to its original scale) will be calculated.
  - The lower limit of the 90% CI will be compared with the non-inferiority margin of 0.80 (ie, lower limit of 90% CI ≥0.80).

3.2.2 Sensitivity analyses

The following sensitivity analyses of the co-primary endpoint ORR will be conducted:

- ORR per IRC assessment based on per protocol population as defined in Table 3
- ORR per investigator assessment based on per protocol population as defined in Table 3
- ORR per investigator assessment based on ITT population as defined in Table 3

The same estimands (that is to say, IE handling and population level summary) as for the co-primary endpoint ORR per IRC assessment will be used for these sensitivity analyses.

As sensitivity analyses, stratified analyses on ORR per IRC assessment and ORR per investigator assessment will be performed: stratified odds ratio, stratified relative risk along with their 95% CI based on Mantel-Haenszel estimator will be provided. The lower limit of the 95% CI of the stratified relative risk will be compared with the pre-defined non-inferiority margin of 0.839 (ie, lower limit of 95% CI ≥0.839)

3.2.3 Supplementary analyses

Refer to Section 3.7.2 on Subgroup analysis, which will constitute the supplementary analysis.

3.3 SECONDARY ENDPOINT(S) ANALYSIS

The secondary endpoints detailed in this section are VGPR or better rate, C_{trough} at 4 weeks, incidence rate of infusion-reactions, patient satisfaction rate based on PESQ questionnaire at Cycle 5 Day 15, DOR, TT1R, TTBR, PFS, PFS2, OS, successful injections rate, incidence rate of participants with anti-drug antibodies, and the change from baseline type endpoints as measured by PEQ, PESQ, PAT, HRUPQ, QLQ-MY20 (2), QLQ-C30 (3), EQ-5D-5L (4). Other secondary endpoints analyses are defined in Section 3.6.2 (AE, SAE), Section 3.6.3.1 (laboratory abnormalities), Section 3.7.1.1 (PK) and Section 3.7.1.2 (immunogenicity).

3.3.1 Key/Confirmatory secondary endpoint(s)

The key secondary endpoints are in following orders:

1. VGPR or better rate per IRC assessment
2. C_{trough} at 4 weeks
3. Incidence rate of infusion-reactions
4. Patient satisfaction rate based on PESQ questionnaire at Cycle 5 Day 15

3.3.1.1 Definition of endpoint(s)

VGPR or better rate per IRC assessment:

VGPR or better rate per IRC assessment is defined as the proportion of participants who have BOR of VGPR or better assessed by IRC. Participants who have missing disease response or have no confirmed disease response of VGPR or better will be counted as non-responders.

C_{trough} at 4 weeks:

C_{trough} at 4 weeks is the observed plasma concentrations collected on predose at Cycle 2 Day 1 (equivalent to prior to Cycle 2 Day 1) of isatuximab administration dose. Participants will be included in the analysis as defined in CT4W-PK population.

Incidence rate of infusion-reactions:

Incidence rate of infusion-reactions is defined as the proportion of participants who have observed AE of infusion reactions collected through the electronic case report form (eCRF) AE IR as assessed by investigators after the start date of study treatment and before the end date of study treatment+30 days.

Patient satisfaction rate based on PESQ questionnaire at Cycle 5 Day 15:

Patient satisfaction rate based on PESQ questionnaire is defined as the proportion of participants who have responded as satisfied or as very satisfied with the injection method used to administer study medication (corresponding with the response of the question-8 of the PESQ-FU questionnaire as specified in the study protocol) at Cycle 5 Day 15. Participants who have not responded as satisfied or as very satisfied with the injection method used to administer study medication will be counted as non-satisfied. Participants who discontinue study treatment before Cycle 5 Day 15 will be counted as non-satisfied.

3.3.1.2 Main analytical approach

The key secondary endpoints will be analyzed with the estimands defined according to the following attributes:

Key secondary endpoint: VGPR or better rate per IRC assessment

- Endpoint: VGPR or better rate per IRC assessment
- Treatment condition: isatuximab SC+Pd will be compared to isatuximab IV+Pd
- Analysis population: ITT
- Intercurrent events (IE):
  - While on-treatment strategy: The start of new anti-MM treatment will be handled with while on treatment strategy. The endpoint will be assessed based on all disease assessments prior to the start of new anti-MM treatment.
  - Treatment policy strategy: Study treatment discontinuation will be handled with treatment policy strategy. Regardless of study treatment discontinuation, the endpoint will be assessed based on all disease assessments.
- Population-level summary:
  - The VGPR or better rate will be estimated and its two-sided 95% Cl will be provided using the Clopper-Pearson method.
  - The relative risk for Arm SC vs Arm IV will be estimated along with its two-sided 95% CI and p-value will be calculated using the Farrington-Manning method.
  - The lower limit of the 95% CI of the relative risk will be compared with the pre-defined non-inferiority margin of 0.6312 (ie, lower limit of 95% CI ≥0.6312), which was calculated as 40% retention of the observed historical clinical benefit of VGPR or better ratio 0.4645 (upper bound of the 95% CI of rate ratio for Pd over CD38+Pd as demonstrated in ICARIA-MM trial) under the logarithm scale then converting back to its original scale,.

- Additionally, odds ratio for Arm SC vs Arm IV and its two-sided 95% CI will be provided.
- Participants who have missing disease response or have no confirmed disease response of VGPR or better will be counted as non-responders.

Key secondary endpoint: C_{trough} at 4 weeks

- Endpoint: C_{trough} at 4 weeks
- Treatment condition: isatuximab SC+Pd will be compared to isatuximab IV+Pd
- Analysis population: CT4W-PK
- Intercurrent events (IE):
  - Principal stratum strategy: Doses, administration scheme, sample collection, processing and result, time window of collection and adequate documentation
- Population-level summary:
  - The geometric mean, coefficient of variation, median and range for C_{trough} at 4 weeks will be provided for isatuximab SC and isatuximab IV.
  - The ratio of the geometric means for C_{trough} at 4 weeks of SC/IV and its two-sided 90% CI (under the logarithm scale then converting back to its original scale) will be calculated.
  - The lower limit of the 90% CI will be compared with the non-inferiority margin of 0.80 (ie, lower limit of 90% CI $\geq$0.80).

Key secondary endpoint: Incidence rate of infusion reactions

- Endpoint: Incidence rate of infusion reactions
- Treatment condition: isatuximab SC+Pd will be compared to isatuximab IV+Pd
- Analysis population: Safety
- Intercurrent events (IE):
  - While on treatment strategy: Study treatment discontinuation will be handled with while on treatment strategy. The endpoint will be assessed based on all available visit assessments up to the end date of study treatment +30 days.
- Population-level summary:
  - The rate will be estimated and its two-sided 95% Cl will be provided using the Clopper-Pearson method.
  - The relative risk and odds ratio will be estimated for Arm SC vs Arm IV and its two-sided 95% Wald Cl will be provided.
  - P-value will be provided using the Fisher's exact test.

Key secondary endpoint: Patient satisfaction rate based on PESQ questionnaire at Cycle 5 Day 15

- Endpoint: Patient satisfaction rate based on PESQ questionnaire at Cycle 5 Day 15
- Treatment condition: isatuximab SC+Pd will be compared to isatuximab IV+Pd
- Analysis population: ITT
- Intercurrent events (IE):
- Composite strategy: Study treatment discontinuation will be handled with composite strategy. Participants who discontinue study treatment before Cycle 5 Day 15 will be counted as non-satisfied.Population-level summary:
  - The rate will be estimated and its two-sided 95% Cl will be provided using the Clopper-Pearson method.
  - The odds ratio will be estimated for Arm SC vs Arm IV and its two-sided 95% Wald CI will be provided.
  - P-value will be provided using the CMH test stratified by the randomization stratification factors collected through IRT system.
  - Participants who have not responded as satisfied or as very satisfied with the injection method used to administer study medication will be counted as non-satisfied. Participants who discontinue study treatment before Cycle 5 Day 15 will be counted as non-satisfied.

3.3.1.3 Sensitivity analysis

The following sensitivity analysis of the key secondary endpoint VGPR or better rate will be conducted:

- VGPR or better rate per IRC assessment based on per protocol population as defined in Table 3
- VGPR or better rate per investigator assessment based on per protocol population as defined in Table 3
- VGPR or better rate per investigator assessment based on ITT population as defined in Table 3

The same estimands (that is to say, IE handling and population level summary) as for the VGPR or better rate per IRC assessment will be used for the sensitivity analysis.

As a sensitivity analyses, stratified analyses on VGPR or better rate per IRC assessment and VGPR or better rate per investigator assessment will be performed: stratified odds ratio, stratified relative risk along with their 95% CI based on Mantel-Haenszel estimator will be provided. The lower limit of the 95% CI of the stratified relative risk will be compared with the pre-defined non-inferiority margin of 0.6312 (ie, lower limit of 95% CI ≥0.6312)

3.3.1.4 Supplementary analysis

No supplementary analysis will be performed.

3.3.2 Supportive secondary endpoint(s)

3.3.2.1 Definition of endpoint(s)

Time to first response (TT1R):

TT1R is defined as the time from the date of randomization to the date of first confirmed disease response of PR or better. Participants who are non-responders for ORR per IRC assessment analysis with ≥1 post baseline disease assessments will be censored at the date of last valid disease assessment before confirmed PD, start of new anti-MM treatment, death, or analysis cut-off date, whichever occurs first. Participants who are non-responders for ORR without any post baseline disease assessments will be censored at the date of randomization.

Time to best response (TTBR):

TTBR is defined as the time from the date of randomization to the date of first BOR of PR or better. The same censoring rule for TTBR will be applied as in the TT1R.

Duration of response (DOR):

Only participants who are responders for ORR will be included in this analysis.

DOR is defined as the time from the date of the first response (PR or better) to the date of first occurrence of PD as determined by IRC or death from any cause, whichever occurs first. In the absence of DOR event (confirmed PD or death), DOR is censored at the date of the last valid disease assessment prior to the analysis cut-off date. For participants with start of new anti-MM treatment, DOR will be censored at the date of the last valid disease assessment not showing PD performed prior to the start of new anti-MM treatment. For participants with two or more consecutive missed disease assessments (corresponding to at least 63 days between the date of the last disease assessment prior to the missed visit and the date of PD or death, whichever occurs first) prior to PD or death, DOR will be censored at the date of last valid disease assessment performed prior to the missed assessments.

Progression free survival (PFS):

PFS is defined as the time from the date of randomization to the date of first documentation of PD or death from any cause, whichever occurs first. In absence of PFS event (confirmed PD or death), PFS will be censored at the date of the last valid disease assessment prior to the analysis cut-off date. For participants with start of new anti-MM treatment, PFS will be censored at the date of the last valid disease assessment not showing PD performed prior to the start of new anti-MM treatment. For participants with two or more consecutive missed assessments (corresponding to at least 63 days between the date of the last disease assessment prior to the missed visit and the date of PD or death, whichever occurs first) prior to PD or death, PFS will be censored at the last valid disease assessment performed prior to the missed assessments. For participants without any post baseline disease assessments in absence of PFS event PFS will be censored at the date of randomization.

Detailed censoring rules are available in Appendix 5.6.

PFS2:

PFS2 is defined as time from the date of randomization to the date of first documentation of PD after the start of new anti-MM treatment or death from any cause, whichever occurs first. In absence of PFS2 event (confirmed PD or death), PFS2 will be censored at the date of the last valid disease assessment prior to the analysis cut-off date. For participants without any post baseline disease assessments and who did not die, PFS2 will be censored at the date of randomization.

Detailed censoring rules are available in Appendix 5.7.

Overall survival (OS):

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

Device performance:

Rate will be calculated as the total number of successful injections with isatuximab injector device, defined as completion of administration per provided instructions for use with no use errors or technical issues, divided by the total number of actual injections. The dose actually administered is not considered in the definition of successful injection. The total number of actual injections will be calculated as the total frequency of isatuximab SC used between the start date of study treatment and up to the end date of study treatment. The total number of successful injections will be derived by subtracting the total number of unsuccessful injections related to device or users from the total number of actual injections. That is to write as,

Total number of successful injections= Total number of actual injections− Total number of unsuccessful injections.

At least one of the following conditions collected through the electronic case report form (eCRF) at each isatuximab SC dose schedule visit for each participant will be used to determine the unsuccessful injections used, and the period to meet these conditions is after the start date of study treatment and before the end date of study treatment:

1. injections interrupted/stopped with the reason of injector dysfunction
2. injections interrupted/stopped with the reason of unintentional interruption/stop due to human error
3. injections not interrupted/not stopped but with the reported device issues collected through eCRF-Device Event as: needle did not retract; button did not work correctly; or others specified by investigators.

Total number of unsuccessful injections= total number of injections interrupted/stopped with the reason of injector dysfunction+ total number of injections interrupted/stopped with the reason of

unintentional interruption/stop due to human error+ total number of injections not interrupted/not stopped but with the reported device issues.

In addition, an injection with full dose administered will be defined as an injection where the actual dose is equal to the planned dose of 1400 mg, regardless of whether a device event is reported or if there is any interruption due to injector dysfunction or human error.

Anti-drug-antibodies (ADA) incidence:

Anti-drug-antibodies (ADA) are biologic drug-reactive antibody, including pre-existing host antibodies that are cross-reactive with the administered biotherapeutic (baseline ADA).

Definition of the incidence is provided in Section 3.7.1.2.

Change in score from baseline for patient reported outcomes (PRO):

Change in score from baseline as measured by EORTC QLQ-C30: The change in score at each post baseline assessment visit measured by EORTC QLQ-C30 version 3 will be calculated from baseline. The score for global health status/QoL, functional scales, and symptom scales/items will be calculated according to the scoring manual, available at https://www.eortc.org/app/uploads/sites/2/2018/02/SCmanual.pdf (detailed in Appendix 5.5). A higher score for global health status/QoL and functional scales represents better outcomes, whereas a lower score for symptom scales/items represents for better outcomes.

Change in score from baseline as measured by EORTC QLQ-MY20: The change in score at each post baseline assessment visit measured by EORTC QLQ-MY20 will be calculated from baseline. The score for functional scales (consisting of body image [item number: 47], future perspective [item number: 48 to 50]) and symptoms scales (consisting of disease symptoms [item number: 31 to 36] and side-effects of treatment [item number: 37 to 46]) will be calculated. The scoring rule of these two scales is the same as the scoring rule of the EORTC QLQ-C30 functional scales and the symptoms scales (detailed in Appendix 5.5). A higher score for body image and future perspective represents better outcomes, whereas a lower score for disease symptoms and side-effects of treatment represents better outcomes.

The EQ-5D-5L comprises the EQ-5D 5 dimensions (mobility, self-care, usual activities, paint/discomfort and anxiety/depression) and a visual analogue scale (VAS). EQ-5D-5L health utility index score will be derived and analyzed under the responsibility of the Health Economics and Value Assessment (HEVA) department at Sanofi.

Change in score from baseline as measured by EQ-5D-5L: The change in score at each post baseline assessment visit measured by EQ-5D-5L will be calculated from baseline for VAS. A higher score for VAS represents better outcomes.

In addition, clinically meaningful improvement and deterioration will be separately determined by (1) EORTC QLQ-C30 symptom score, (2) EORTC QLQ-MY20 symptoms score (disease symptoms and side-effects of treatment), and (3) health status EQ VAS score. Clinical improvement (or deterioration) for EORTC QLQ-C30 symptom score and EORTC QLQ-MY20

symptoms score, respectively, is defined as the change in score from baseline at each post baseline visit decreased (or increased) by at least 10 units in any scale/item. Clinical improvement (or deterioration) for health status EQ VAS is defined as the change in score from baseline at each post baseline visit increased (or decreased) by at least 7 units.

3.3.2.2 Main analytical approach

For the analysis of device performance on the safety population, the successful injection rate and two-sided 95% CI will be provided for Arm SC using the Clopper-Pearson method. For Arm SC, the number (%) of unsuccessful injections will be summarized, by condition as defined above (injection interrupted/stopped due to injector dysfunction, injection interrupted/stopped due to unintentional/stop due to human error and injection not interrupted/not stopped but device event reported in eCRF). Among each category, the number (%) of injections with full dose administered will be provided. A summary of device events will also be provided.

The number (%) of injections with the full dose administered and associated two-sided 95% CI will be provided for Arm SC.

Number (%) or participants with at least one unsuccessful injection will be summarized and reasons for unsuccessful injection will be provided. Number (%) of participants with at least one device event will be summarized and reasons for device events will be provided.

Summary of device events will be performed for the administration done at home.

For the analysis of each time to event endpoint (TT1R, TTBR, DOR, PFS, PFS2 and OS), the quantiles and probabilities of being event free at different time points (calculated using the Kaplan-Meier methods) as well as the corresponding two-sided 95% CIs including the Kaplan-Meier curve will be presented. Except for DOR, the HR for Arm SC vs Arm IV and the associated two-sided 95% CI will be estimated using the Cox proportional hazard model stratified by the randomization factors as specified in Section 3.1. Reason and time of censoring will be described for TT1R, TTBR. Type of events and reason for censoring and time of censoring will be described for DOR, PFS, PFS2 and OS.

In addition, median follow-up duration (months) at time of data cut-off will be estimated using the Kaplan-Meier method. The 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 died will be censored at the date of death whatever the cause of death and the alive patients will be counted as event at the date of last contact.

For the analysis of the change from baseline in score as measured by each PRO on ITT population, descriptive statistics for score and for the mean change in score from baseline along will be presented for each scale/item within each PRO instrument. Additional analysis will be conducted based on the clinical improvement and the clinical deterioration, respectively, as determined by the EORTC QLQ-C30 symptom score, EORTC QLQ-MY20 symptoms score, and health status VAS score. And descriptive statistics for the score and the mean change in score from baseline at each time point will be presented. For the Health Resource Utilization and Productivity Questionnaire (HRUPQ), the descriptive statistics of the response of each

question/item will be provided at baseline visit [item number: 1-16] and at each post baseline visit [item number: 17-47]. Missing data will be handled according to the procedure as specified in each PRO instrument score manual. In addition, number (%) of participants will be provided for the response of each item (or question) collected through the questionnaires PAT, PEQ, HRUPQ and PESQ, respectively, at each timepoint.

For the analysis of ADA incidence will be based on ADA population as defined in Table 3. The incidence rate will be calculated.

Additionally, the following supportive analysis for PFS will be performed:

- PFS analyses based on investigator assessment ignoring symptomatic deterioration
- PFS analyses based on investigator assessment including symptomatic deterioration
- PFS analysis as per IRC without censoring for use of new anti-MM therapy and missed two or more consecutive disease assessments: Confirmed PD or death occurring after the use of new anti MM therapy or after missed ≥2 consecutive disease assessments will be considered as PFS events.

The same analysis as the main analytical approach for PFS will be used for this supportive analysis based on ITT population.

3.4 TERTIARY/EXPLORATORY ENDPOINT(S) ANALYSIS

The tertiary endpoints detailed in this section are MRD negativity rate, MRD negative CR rate, complete renal response rate, partial renal response rate, minor renal response rate and durable renal response rate for additional clinical benefits. Other tertiary endpoints analyses are defined in Section 3.6.2 (AE, SAE), Section 3.6.3.1 (laboratory abnormalities), Section 3.7.1.1 (PK) and Section 3.7.1.2 (immunogenicity).

3.4.1 Definition of endpoint(s)

MRD negativity rate:

Rate is defined as the proportion of participants for whom MRD is negative by threshold for negativity will be at least 10^-5.

MRD negative CR rate:

Rate is defined as the proportion of participants with BOR as sCR/CR per IRC assessment and for whom MRD is negative by threshold for negativity will be at least 10^-5.

Renal response:

- A **complete renal response** is defined as an improvement in eGFR from <50 mL/min/1.73 m^2 at baseline to ≥60 mL/min/1.73 m^2 in at least 1 assessment during the on-treatment period.

- A **partial response** is defined as an improvement in eGFR from <15 mL/min/1.73 m2 at baseline to at least 1 one post-baseline eGFR ≥30 mL/min/1.73m^2 to <60 mL/min/1.73m^2.
- A **minor response** is defined as an improvement in eGFR:
  (a) from <15 mL/min/1.73 m^2 at baseline to at least one post-baseline eGFR ≥15 mL/min/1.73m^2 to <30 mL/min/1.73m^2
  (b) or from eGFR ≥15 mL/min/1.73 m^2 to < 30 mL/min/1.73m^2 at baseline to at least one post-baseline eGFR ≥30 mL/min/1.73m^2 to <60 mL/min/1.73m^2
- A **durable renal response** is defined as a response that lasted ≥60 days.

3.4.2 Main analytical approach

For the analysis of binary endpoint (MRD negativity rate, MRD negative CR rate), the response rate and two-sided 95% CI will be provided using the Clopper-Pearson method based on the ITT population. For the analysis of MRD related endpoints, participants who enrolled from China (according to the study protocol, China participants will not participate to the MRD sample collections for the exploratory analysis) will be excluded.

For renal response, number (%) of participants within each response category will be described by treatment group. Duration of renal response will be described by treatment group.

3.5 MULTIPLICITY ISSUES

The non-inferiority of ISA- SC+ Pd relative to Isa- IV + Pd will be concluded if both the efficacy and PK co-primary endpoints achieve non-inferiority.

To adjust for multiple testing of the key secondary endpoints, a fixed sequence testing procedure will be used to control overall study-wise Type I error rate. The hierarchical procedure for testing the key secondary endpoints will be performed according to the following order only if both co-primary endpoints achieve the non-inferiority as specified in Section 3.2:

1. VGPR or better rate per IRC assessment
2. C_{trough} at 4 weeks
3. Incidence rate of infusion-reactions
4. Patient satisfaction rate based on PESQ questionnaire at Cycle 5 Day 15

Hypothesis testing of the key secondary endpoints (VGPR or better rate per IRC assessment and C_{trough} at 4 weeks) for non-inferiority, and the key secondary endpoints (incidence rate of infusion-reactions and Patient satisfaction rate based on PESQ questionnaire at Cycle 5 Day 15) for superiority will be conducted. The PK endpoints (C_{trough} at steady state, C_{trough} at 4 weeks) will be evaluated at 1-sided 0.05 alpha level (ie, the lower limit of the 90% CI of geometric mean ratio of SC/IV will be compared with the non-inferiority margin of 0.80). The rest of the endpoints (ORR, VGPR or better, incidence rate of infusion-reactions and Patient satisfaction rate) will be evaluated at 1-sided 0.025 alpha level.

3.6 SAFETY ANALYSES

All safety analyses will be performed on the safety population as defined in Section 2. Descriptive statistics will be presented for safety variables by Arm SC: Isa SC+Pd and Arm IV: Isa IV+Pd. No statistical testing is planned.

Study intervention for Arm SC is isatuximab SC, pomalidomide and dexamethasone, and for Arm IV is isatuximab IV, pomalidomide and dexamethasone. For Arm SC isatuximab uses as injection with injector device and thus is considered as injection, and for Arm IV isatuximab uses as IV infusion and thus is considered as infusion.

Regarding treatment discontinuation, following definitions will be used:

- **Permanent partial** treatment discontinuation is defined as the discontinuation of at least one of the study interventions but at least one is continued.
- **Permanent full** treatment discontinuation is defined as the discontinuation of all the study interventions.

3.6.1 Extent of exposure

The extent of exposure will be summarized within the safety population. Exposure related data for each study intervention by Arm SC and Arm IV will be collected through eCRF per protocol schedule timepoints.

3.6.1.1 Overall exposure

The dose information will be assessed by the following variables:

- Overall number of cycles started, defined by the number of cycles in which at least one dose of study treatment is administered.
- Cumulative exposure to treatment (in patient-years), derived by summing the duration of treatment exposure for all participants.
- Duration of study treatment (in weeks) is defined as (last day of treatment exposure - first day of treatment exposure)/7.
- Duration will also be converted in months.
- The first day of treatment exposure is defined as the first administration date with non-zero dose for at least one of the study interventions (isatuximab, pomalidomide and dexamethasone).

The last day of treatment exposure is the date of last administration of any study intervention. The last administration date is the maximum date using the following conditions:

- Date of last administration of isatuximab +7 days if last cycle is Cycle 1 or Date of last administration of isatuximab +14 days if last cycle is Cycle 2 or later for isatuximab,
- Date of last administration of pomalidomide +8 days for pomalidomide,

- Date of last administration of dexamethasone +7 days for dexamethasone.

Number of cycles started is defined as the number of cycles in which at least one dose of any study interventions is administered. Each cycle is length of 28 days or 4 weeks.

The total number of cycles started, number of cycles started by participant will be summarized as a quantitative variable and by category (number (%) of participants receiving at least 1 cycle, at least 2 cycles, etc). The duration of overall exposure will be summarized as descriptive statistics.

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 participant (with number of participants used as denominator) and cycle (with number of cycles used as denominator) levels, as follows:

Number (%) of participants with at least 1 cycle delayed

- Number (%) of participants with a cycle delayed between 4 and 7 days (using maximum delay across all cycles)
- Number (%) of participants with a cycle delayed >7 days (using maximum delay across all cycles)

Number (%) of cycles delayed

- Number (%) of cycles delayed between 4 and 7 days
- Number (%) of cycles delayed >7 days

Participants with at least one cycle delayed due to Covid-19 or any major pandemic, and cycles delayed will be also displayed, if applicable.

3.6.1.2 Isatuximab exposure

The dose information will be assessed as follows:

- Total number of cycles started
- Number of cycles started per participant.
- Duration of isatuximab exposure (in weeks) is defined depending on the isatuximab administration schedule as follows:
  - (date of last administration of isatuximab +7 days - date of first administration of isatuximab)/7 if last cycle is Cycle 1
  - (date of last administration of isatuximab +14 days - date of first administration of isatuximab)/7 if last cycle is Cycle 2 or greater.

- Duration will also be converted in months.
- Actual dose (mg/kg for IV and mg for SC): for a given cycle and day of IV infusion, the actual dose in mg/kg corresponds to the actual dose in mg administered at each time point divided by the actual body weight as measured at each time point (cycle and day). The actual dose for SC injection will be reported as 1400 mg. Because no partial dose will be administered through the injector device, in case of missing dose the value for the actual dose for SC injection will be imputed to 0 mg for analysis.
- Cumulative dose (mg/kg for IV and mg for SC): the cumulative dose is the sum of all actual doses of isatuximab, expressed in mg/kg for IV infusion and mg for SC injection, given from first to last administration.
- Actual dose intensity (ADI) in mg/kg/week for IV and mg/week for SC: defined as the cumulative dose (in mg/kg and mg) divided by the duration of isatuximab exposure (in weeks) for IV infusion and SC injection, respectively.
- Planned dose intensity in mg/kg/week for IV and mg/week for SC: corresponds to sum of the planned doses (per protocol: isatuximab SC- 1400 mg and isatuximab IV- 10 mg/Kg) multiplied by the theoretical total number of doses during the started cycles (4 doses for Cycle 1 and 2 doses from Cycle 2 and onwards) and divided by the theoretical cycle duration expressed in weeks (ie, 4 weeks per started cycle).
- Relative dose intensity (RDI, in %):
  - For Isatuximab SC: $100 \times \frac{\text{ADI (mg/week)}}{\text{PDI (mg/week)}}$
  - For Isatuximab IV: $100 \times \frac{\text{ADI (mg/Kg/week)}}{\text{PDI (mg/Kg/week)}}$

The total number of doses, total number of cycles started, number of cycles started by participant will be summarized as a quantitative variable and by category (number [%] of participants receiving at least 1 cycle, at least 2 cycles, etc). Duration of exposure, cumulative dose, ADI and RDI will be summarized by descriptive statistics. Number (%) of participants will be summarized by RDI category as: <80%, ≥80% - < 90% and ≥90%.

The following variables will be derived to describe dose modifications (combination of dose delay and dose omission) and dose interruptions:

- Dose delay (within cycle): a dose is deemed to have been delayed if the actual start of IV infusion or SC injection is >1 day beyond the theoretical day of treatment for weekly dose of Cycle 1, and >2 days beyond the theoretical day of treatment after Cycle 1. Dose delay does not apply to the first infusion/injection of each cycle. However, it will be considered as cycle delay.
- Dose omission is defined as a dose not administered at the scheduled visit but administered afterwards.
- Dose interruption for IV and SC administration: A dose will be considered to be interrupted if the isatuximab administration is stopped during an infusion/injection before it is completed regardless it is further restarted or not.

- Dose reduction: Although not allowed in the study protocol for isatuximab IV, potential dose reduction as defined in Table 4 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.
- Dose reduction for isatuximab SC is not possible through the injector device.

Table 4 - Dose levels for isatuximab IV dose reduction

Actual dose level	Dose level interval
Dose level -2 (low dose)	>0 mg/kg and ≤2.5 mg/kg
Dose level -1 (5 mg/kg)	>2.5 mg/kg and ≤7.5 mg/kg
Initial dose (10 mg/kg)	>7.5 mg/kg

Dose modifications and dose interruptions will be analyzed by participant, cycle and dose as follows:

Participant (number of participants treated will be used as denominator)

- Number (%) of participants with at least 1 dose modification
  - Number (%) of participants with at least 1 dose delayed
  - Number (%) of participants with at least 1 dose omission
  - Number (%) of patients with at least one dose omission due to Covid-19 (if applicable)
  - Number (%) of participants with at least 1 dose reduction (not applicable for isatuximab SC)
- Number (%) of participants with a least 1 dose interruption
  - Number (%) of participants with at least 1 dose interruption and restarted
  - Number (%) of participants with at least 1 dose interruption and not restarted (definitively stopped)
- Number (%) of participants with at least 2 dose modifications
  - Number (%) of participants with at least 2 doses delayed
  - Number (%) of participants with at least 2 dose omissions
- Participants with at least 1 infusion/injection interrupted
  - Participants with at least 1 infusion/injection interrupted and re-started
  - Participants with at least 1 infusion/injection interrupted and not re-started
- Participants with at least 2 infusions/injections interrupted

Cycle (number of cycles started will be used as denominator)

- Number (%) of cycles with at least 1 dose modification

  - Number (%) of cycles with at least 1 dose delayed
  - Number (%) of cycles with at least 1 dose omission
  - Number (%) of cycles with at least 1 dose reduction
- Number (%) of cycles with at least 1 dose interruption (not applicable for isatuximab SC)
  - Number (%) of cycles with at least 1 dose interruption and restarted
  - Number (%) of cycles with at least 1 dose interruption and not restarted (definitively stopped)

Dose (number of doses started will be used as denominator)

- Number (%) of isatuximab infusions/injections interrupted,
  - Number (%) of isatuximab infusions/injections interrupted more than once
  - Number of infusions/injections interrupted and re-started
  - Number of infusions/injections interrupted and not re-started
- Number of infusions/injections interrupted at (with % calculated using the total number of infusions/injections interrupted): 1st infusion/injection, 2nd infusion/injection, subsequent infusions/injections,
- Time from infusion/injection start to first interruption in minutes (quantitative and qualitative: 5-10, 11-30, 31-40, 41-50, 51-60, 61-90, 91-120, >120).

Additionally, duration of infusion for isatuximab IV and duration of injection for isatuximab SC will be calculated. Duration of infusion/injection (in minutes) is defined as the period from the start time of infusion/injection to the end time of infusion/injection. It will be summarized for all infusions/injections, as well as for first and subsequent infusions/injections by Arm SC and Arm IV. Duration of infusions/injections will be analyzed by gender and by body weight as well. Descriptive statistics will be provided that include n, mean, median, standard deviation, first quartile (Q1) and third quartile (Q3), where n represents total number of doses. Categorical summary (≤ 20 minutes vs > 20 minutes) will be done for the durations of SC injections.

3.6.1.3 Pomalidomide exposure

The dose information will be assessed by the following:

- Total number of cycles started
- Number of cycles started per participant
- Duration of pomalidomide exposure (in weeks) is defined by (date of last administration +8 days – date of first administration of pomalidomide)/7
- Duration will also be converted in months.
- Cumulative dose ([mg]): the cumulative dose is the sum of all actual doses of pomalidomide, given from first to last administration

- Actual dose intensity (ADI) in mg/week: defined as the cumulative dose divided by the duration of pomalidomide exposure (in weeks)
- Planned dose intensity (PDI) in mg/week: corresponds to the sum of the planned dose (per protocol: 4 mg) multiplied by the theoretical total number of doses during the started cycles (ie, 21 doses for each cycle) and divided by the theoretical cycle duration expressed in weeks (ie, 4 weeks per cycle started)
- Relative dose intensity (RDI, in %): $100 \times \frac{\text{ADI (mg/week)}}{\text{PDI (mg/week)}}$

The total number of doses, total number of cycles started, number of cycles started by participant will be summarized as a quantitative variable and by category (number [%] of participants receiving at least 1 cycle, at least 2 cycles, etc). Duration of pomalidomide exposure, cumulative dose, ADI and RDI will be summarized by descriptive statistics for Arm SC and Arm IV (and overall).

The following variables will be derived to describe dose modifications:

- Dose omission is defined as a dose not administered at the scheduled visit but administered afterwards.
- Dose reduction: The first administration will not be counted as a dose reduction. For the second and subsequent pomalidomide administrations, a dose will be 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 5 - Pomalidomide dose reduction criteria

Starting dose	Dose level -1	Dose level -2	Dose level -3
4 mg	3 mg	2 mg	1 mg

Dose modifications will be analyzed by participant and cycle as follows:

Participant (number of participants treated will be used as denominator)

- Number (%) of participants with at least 1 dose reduction
- Number (%) of participants with at least 2 dose reductions
- Number (%) of participants with at least 3 dose reductions
- Number (%) of participants with at least 1 dose omission

Cycle (number of cycles started will be used as denominator)

- Number (%) of cycles with at least 1 dose reduction
- Number (%) of cycles with at least 2 dose reductions
- Number (%) of cycles with at least 3 dose reductions
- Number (%) of cycles with at least 1 dose omission

3.6.1.4 Dexamethasone exposure

The dose information will be assessed by the following:

- Total number of cycles started
- Number of cycles started per participant
- Duration of dexamethasone exposure (in weeks) is defined by (date of last administration +7 days) - date of first administration of dexamethasone)/7
- Duration will also be converted in months.
- Cumulative dose ([mg]): the cumulative dose is the sum of all actual doses of dexamethasone, given from first to last administration
- Actual dose intensity (ADI) in mg/week: defined as the cumulative dose divided by the duration of dexamethasone exposure (in weeks)
- Planned dose intensity (PDI in mg/week): corresponds to the sum of the planned dose (per protocol: 20 mg for participants ≥75 years and 40 mg for participants <75 years) multiplied by the theoretical total number of doses during the started cycle (ie, 4 doses for each cycle) and divided by the theoretical cycle duration expressed in weeks (ie, 4 weeks per cycle started)
- Relative dose intensity (RDI, in %): $100 \times \frac{\text{ADI (mg/week)}}{\text{PDI (mg/week)}}$

The total number of doses, total number of cycles started, number of cycles started by participant will be summarized as a quantitative variable and by category (number [%] of participants receiving at least 1 cycle, at least 2 cycles, etc). Duration of dexamethasone exposure, cumulative dose, ADI and RDI will be summarized by descriptive statistics for Arm SC and Arm IV (and overall).

The following variables will be derived to describe dose modifications:

- 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 is defined as a dose not administered at the scheduled visit but administered afterwards
- Dose reduction: The first administration will not be counted as a dexamethasone reduction. For the second and subsequent dexamethasone administrations, dose reduction will be determined using the dose level intervals provided in the following table, by comparing the current dose level to the previous dose level. If the current dose level is below the dose level interval of the previous dose administration, then the current dose level is considered reduced.

Table 6 - Dexamethasone dose reduction criteria

Actual dose level (starting dose of 40/20 mg)	Dose level interval if starting dose is 40 mg[a]	Dose level interval if starting dose is 20 mg[b]
Dose level 1 (low dose)	>0 mg and ≤4 mg	>0 mg and ≤2 mg
Dose level 2 (8 mg[a]/4 mg[b])	>4 mg and ≤10 mg	>2 mg and ≤6 mg
Dose level 3 (12 mg[a]/8 mg[b])	>10 mg and ≤16 mg	>6 mg and ≤10 mg
Dose level 4 (20 mg[a]/12 mg[b])	>16 mg and ≤30 mg	>10 mg and ≤16 mg
Dose level 5 (40 mg[a]/20 mg[b])	>30 mg	>16 mg

a in participants <75 yr;
b in participants ≥75 yr

Dose modifications will be analyzed by participant and cycle as follows:

Participant (number of participants treated will be used as denominator)

- Number (%) of participants with at least 1 dose reduction
- Number (%) of participants with at least 1 dose delay
- Number (%) of participants with at least 1 dose omission

Cycle (number of cycles started will be used as denominator)

- Number (%) of cycles with at least 1 dose reduction
- Number (%) of cycles with at least 1 dose delay
- Number (%) of cycles with at least 1 dose omission

3.6.1.5 At home administration

As defined in Section 4.2 of the study protocol, home administration may be possible where permitted by national and local regulation. After the first 5 cycles, at home administration by an health care professional may be proposed to the participants in the SC arm on D15 from Cycle 6 onwards. Day 1 administration, on the other hand, from C6 onwards will always be done at clinic.

At home administration will be analyzed by participant and by injection in the SC arm as follows:

Participant (number of participants treated in the SC arm will be used as denominator)

- Number (%) of participants with at least one at home administration overall and by country
- Number (%) of participants who definitely switched to D15 at home administration
- Number (%) of participants who had at least one D15 at home administration, but return to hospital for the D15 visit at any future cycle.
- Number (%) of participants with at home administration by cycle

- Number (%) of participants with consecutive D15 administration done at home (at least 2, at least 3,…)
- Cycle of first occurrence D15 at home administration will be described with number of participants with at least one at home administration as denominator.

Injections (total number of injections will be used as denominator)

- Number (%) of D15 injections administrated at home
- Same analyses will be provided based on the safety population, excluding all participants from countries for which national and/or local regulation does not permit at home IMP administration. List of countries are defined in appendix 5.9.
- Analyses on isatuximab dose modification and duration of isatuximab injections will be provided in participants with all isatuximab SC administered at site versus participants with at least one D15 administered at home. Same analyses will be provided selecting only the D15 visit done at home.
- A listing of reasons for administration not performed at home as per eCRF whereas it was planned at home will be provided.

3.6.2 Adverse events

General common rules for adverse events

All adverse events (AEs) will be 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 Medical Dictionary for Regulatory Activities (MedDRA) version currently in effect at Sanofi at the time of database lock.

All AEs will be graded according to National cancer institute common terminology for adverse events (NCI-CTCAE version 5.0) 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 Medical Dictionary for Regulatory Activities (MedDRA) version currently in effect at Sanofi at the time of database lock.

The AEs will be analyzed in the following observation period defined in Section 3.1:

- Pre-treatment AEs: AEs that developed, worsened or became serious during the pre-treatment period.
- Treatment-emergent adverse events (TEAE)s: AEs that developed, worsened or became serious during the treatment-emergent period.
- Post-treatment AEs: AEs that developed, worsened or became serious during the post-treatment period.

Similarly, the deaths will be analyzed in the pre-treatment, treatment-emergent and post-treatment periods.

The primary AE analyses will be on TEAEs. Pre-treatment and post-treatment AEs will be described separately.

If an adverse event date of onset (occurrence, worsening, 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 date of onset 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 Appendix 5.4.

If the assessment of the relationship to study treatment is missing for an AE, this AE will be assumed as related to study treatment. Missing grade will be left as missing.

Multiple occurrences of the same event in the same participant will be counted only once in the tables within a treatment phase.

Multiple occurrences of the same event in the same participant will be counted only once in the tables, using the worst grade. Summaries will be provided for all grades combined and for grade ≥3 (including Grade 5). 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. Missing grades, if any, will be included in the "all grades" category.

The AE tables will be sorted as indicated in Table 7.

Table 7 - Sorting of AE tables

AE presentation	Sorting rules
SOC and PT	By the internationally agreed SOC order and decreasing frequency of PTs[a,b]
PT	By decreasing frequency of PTs[a]

a Sorting will be based on Arm SC
b The table of all TEAEs presented by primary SOC and PT will define the presentation order for all other tables (eg, treatment-emergent SAE) presented by SOC and PT, unless otherwise specified.

Analysis of all adverse events

The overview of TEAE with the details below will be generated:

- TEAE of any grade
- TEAE of grade ≥3
- TEAE of Grade 3 or 4
- TEAE of Grade 5 (any TEAE with a fatal outcome during the treatment period)
- Any treatment-emergent SAE
- Any TEAE leading to permanent full discontinuation
- Any TEAE leading to permanent partial discontinuation of isatuximab

- Any TEAE leading to permanent partial discontinuation of pomalidomide
- Any TEAE leading to permanent partial discontinuation of dexamethasone
- Any treatment-emergent AESI
- Any grade ≥3 treatment-emergent AESI
- Study treatment related TEAE of any grade
- Study treatment related TEAE of grade ≥3
- Any treatment-related SAE
- Any TEAE related to non-investigational medicinal product (NIMP)
- Wearable injector device related TEAE of any grade
- Wearable injector device related TEAE of grade ≥3

The AE summaries of Table 8 will be generated with number (%) of participants experiencing at least one event. The analyses will be performed for all grades combined and for grades ≥3.

Table 8 - Analysis of adverse events

Type of AE	MedDRA levels
All TEAE	Primary SOC, HGLT, HLT and PT
	Primary SOC and PT
Common TEAE (≥5% in any arm)	Primary SOC and PT
	PT (with and without details of grade ≥3)
TEAE related to study treatment	Primary SOC and PT
TEAE related to study treatment with incidence ≥5% in any arm	Primary SOC and PT
	PT
TEAE related to OBDS	Primary SOC and PT
TEAE related to non-IMP	Primary SOC and PT
Treatment emergent SAE	Primary SOC, HGLT HLT and PT
	Primary SOC and PT
Treatment emergent SAE (incidence ≥2% in any arm)	Primary SOC and PT
	PT
Treatment emergent SAE related to study treatment	Primary SOC and PT
TEAE leading to permanent full discontinuation	Primary SOC, HGLT, HLT and PT
	Primary SOC and PT
TEAE leading to permanent partial discontinuation of isatuximab	Primary SOC, HGLT, HLT and PT
	Primary SOC and PT
TEAE leading to permanent partial discontinuation of pomalidomide	Primary SOC, HGLT, HLT and PT
	Primary SOC and PT
TEAE leading to permanent partial discontinuation of dexamethasone	Primary SOC, HGLT, HLT and PT

Type of AE	MedDRA levels
	Primary SOC and PT
TEAE leading to death[a] regardless of relationship and related to study treatment	Primary SOC, HGLT, HLT and PT
TEAE leading to death[a] during the treatment-emergent period regardless of relationship and related to study treatment	Primary SOC, HGLT, HLT and PT
TEAE leading to death[a]	Primary SOC and PT
Grade ≥ 5 TEAE	Primary SOC and PT
TEAE related to study treatment leading to death	Primary SOC and PT
AE leading to death	Primary SOC and PT
- In context of disease progression[b]	
- In context other than disease progression[c]	
Pre-treatment AE	Primary SOC and PT
Post-treatment AE	Primary SOC and PT
Post-treatment SAE	Primary SOC and PT
TEAE leading to dose modification (including dose reduction and dose omission) of any drugs, and of each drug separately	Primary SOC and PT
TEAE leading to dose interruption for isatuximab	Primary SOC and PT

a Death as an outcome of the AE as reported by the Investigator in the AE page
b Death within 30 days from last study treatment administration and the cause of death is disease progression
c Death within 30 days from last study treatment administration and the cause of death is not disease progression

Listings of treatment-emergent SAEs, TEAEs leading to permanent full discontinuation, TEAEs leading to permanent partial discontinuation of isatuximab, pomalidomide and dexamethasone will be provided.

Analysis of deaths

In addition to the analyses of deaths included in Table 8 the number (%) of participants in the following categories will be provided:

- Deaths during the treatment-emergent and post-treatment periods by main reason for death collected through eCRF.
- An overview of Grade 5 AEs will be provided with the following categories:
  - Grade 5 AE (TEAE and post-treatment).
  - Fatal TEAE (regardless of date of death/period).
    - Grade 5 TEAE with a fatal outcome during the treatment-emergent 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).
- Deaths in randomized participants but not treated participants or in non-randomized participants will be listed.
- A listing of all deaths will be provided.

Analysis of adverse events of special interest (AESIs)

Adverse events of special interest (AESIs) will be selected for analyses as indicated in Table 9. Number (%) of participants experiencing at least one event will be provided for each event of interest, by PT if applicable. Tables will be sorted as indicated in Table 8.

Table 9 - Selections for AESIs and other AEs of interest

AESIs	Selection
Infusion reactions: Grade ≥3	e-CRF AE form and safety complementary form
Injection site reactions: Grade 1 lasting >24 hours, Grade 2 or higher	e-CRF AE form and safety complementary form
Pregnancy	e-CRF AE form and safety complementary form
Symptomatic overdose (serious or nonserious) with study treatment	e-CRF AE form and safety complementary form
Second Primary Malignancy	e-CRF AE form and safety complementary form

Listings of participants with reported overdose and reported pregnancy will be provided separately. Other AESI will be analyzed as described in the following sections.

Analysis of infusion reactions

The following summaries will be provided:

- Number (%) of participants experiencing IRs presented by primary SOC and PT will be summarized by grades (all grades and grade ≥3).
- Number of participants with symptoms of IRs presented by primary SOC and PT will be summarized by grades
- Number (%) of participants with TEAEs related to study treatment and occurring within 24 hours after isatuximab administration by primary SOC and PT
- Number of participants with TEAEs related to study treatment from ‘Hypersensitivity and CRS’ CMQ starting within 24 hours after isatuximab administration by primary SOC and PT
- Number of participants with TEAEs related to study treatment from ‘Hypersensitivity and CRS’ CMQ by primary SOC and PT
- Description of the IRs:
  - Analysis by participant
    - Number (%) of participants with at least one IR
    - Number (%) of participants by worst grade of IR
    - Number (%) of participants by action taken with isatuximab
    - Number (%) of participants with corrective treatment given
    - Number (%) of participants experiencing only 1, ≥1, ≥2, ≥3, ≥4 and ≥5 episodes,

- Number (%) of participants experiencing first onset of IR at first infusion/injection and at second/subsequent infusions/injections
- Number (%) of participants experiencing IR leading to permanent full discontinuation at first infusion/injection, and at subsequent infusions/injections
- Number (%) of participants experiencing IR leading to permanent partial isatuximab discontinuation at first infusion/injection, and at subsequent infusions/injections
- Number (%) of participants with IR at the first, second, third, fourth, and subsequent infusions/injections,
- Number (%) of participants with at least 2 episodes of IR at the same infusion/injection

- Analysis by episode
  - Number of episodes
  - Grade of IR
  - Number (%) of IR occurring on infusion/injection day, 1 day after infusion/injection, 2 days after infusion/injection, 3 days after infusion/injection, >3 days after injections
  - Time (in hours) from start of isatuximab infusion/injection to onset of IR episodes (defined as the start time of the first symptom of IR)
  - Duration of IR (in days)
  - Number (%) of infusions with IR out of total number of isatuximab infusions/injections
  - Number (%) of IR by infusion/injection 1, infusion/injection 2, infusion/injection 3, infusion/injection 4, infusion/injection 5, and infusion/injection >5

A listing of participants with IR occurring during home administration will also be provided.

Analysis of injection site reactions

The following summaries will be provided:

- Number (%) of participants experiencing ISRs presented by primary SOC and PT will be summarized by grades (all grades and Grade ≥3)
- Number (%) of participants with symptoms of ISRs presented by primary SOC and PT will be summarized by grades
- Description of the ISRs:
  - Analysis by participant
    - Number (%) of participants with ≥1 ISR
    - Number (%) of participants by worst grade of ISR

- Number (%) of participants experiencing only 1, ≥1, ≥2, ≥3, ≥4 and ≥5 ISR episodes
- Number (%) of participants experiencing the first occurrence of ISR at first injection and at second or subsequent injections
- Number (%) of participants experiencing ISR at first injection and at second or subsequent injections
- Number (%) of participants with at least 2 episodes of ISRs at the same injection

- Analysis by episodes
  - Number of episodes
  - Grade of ISR
  - Number (%) of injections with ISR out of total number of isatuximab injections
  - Number (%) of ISR occurring at injection 1, injection 2, injection 3, injection 4, injection 5, and injection >5
  - Number (%) of ISR duration within same day (or, 1 day) and until next day or beyond (or, >1 day)
  - Duration of ISR from start of study treatment (in days)
  - Number (%) of day onset of ISR after isatuximab injection by 1 day after, 2 day after, 3 day after and >3 day after

- Description of ISRs will also be provided separately for visits performed at home and visits performed on site.

Tumor Lysis Syndrome (TLS)

Tumor lysis syndrome will be identified using the TEAEs from the CMQ 'Tumor lysis syndrome' (CMQ000081).

A listing of participants with TLS will be provided.

Embolic and thrombotic AEs

Analysis of embolic and thrombotic adverse events will focus on the SMQ "Embolic and thrombotic events, venous" (narrow) and the SMQ "Embolic and thrombotic events, arterial" (narrow). Embolic and Thrombotic will be presented by SMQ and by decreasing incidence of PT.

Second primary malignancies

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

A listing of participants who reported second primary malignancy during the study will be provided.

The description of AEs in the CMQ 'Second primary malignancies' CMQ (worst grade) will be provided by sub-category ('haematological', 'non-hematological skin tumors', 'non-hematological non-skin tumors' and 'other tumors') and by decreasing incidence of PT for:

- All treatment-emergent and post-treatment AEs
- All TEAEs

Analysis of Covid-19 illness

AE related to Covid-19 illness (if available) will be identified using the TEAEs from the CMQ COVID-19 specific list.

3.6.3 Additional safety assessments

3.6.3.1 Laboratory variables, vital signs and electrocardiograms (ECGs)

The following laboratory variables, vital signs and electrocardiogram (ECG) variables will be analyzed by Arm SC and Arm IV (and overall). They will be converted into standard international units and conventional unit, if applicable.

Hematology:

- Red blood cells and platelets and coagulation: hemoglobin, hematocrit, red blood cell (RBC) count, platelet count, prothrombin time (expressed as international normalized ratio), activated partial thromboplastin time
- White blood cells: white blood cell count, neutrophils, lymphocytes, monocytes, basophils, eosinophils

Clinical chemistry:

- Metabolism: glucose, total protein, albumin
- Electrolytes: sodium, potassium, chloride, calcium/calcium corrected/ionized calcium, phosphorus, bicarbonate, magnesium
- Calcium Corrected (mmol/L) = Total calcium (mmol/L) +0.8 * 0.25 * [4 – Serum albumin (g/L) * 0.1]
- Renal function: creatinine, estimated glomerular filtration rate (eGFR). eGFR will be derived using the Modification of the Diet in Renal Disease (MDRD) equation from study protocol.
- Liver function: alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, lactate dehydrogenase (LDH), total and direct bilirubin
- Pregnancy test: Serum β-human chorionic gonadotropin (all female participants)
- Thyroid function tests: thyroid-stimulating hormone (TSH) and free thyroxine (T4).

Urinalysis:

- Urinalysis for quantitative analysis: RBC, leucocytes, pH, ketones, proteins, glucose, bilirubin, sodium, potassium, creatinine

Vital signs: heart rate, systolic and diastolic blood pressure according to position (sitting, standing, supine), weight, respiratory rate, temperature, ECOG performance status

ECG variables: ECG assessments will be described as normal or abnormal. A listing of abnormalities and analysis of AEs in appropriate SMQs (eg, Cardiac) will be provided if relevant.

For hematological parameters and some selected biochemistry parameters, Sanofi sponsor generic ranges (LLN, ULN) will be used for grading. For other biochemistry parameters, grading will be derived using local laboratory normal ranges.

Quantitative analyses

For vital signs, mean with the corresponding standard deviation will be plotted over time (at predose of any visit) by treatment group.

No urinalysis will be performed.

Analyses according to PCSA and NCI grading

For laboratory variables, analyses according to NCI grading will be made based on NCI-CTCAE version 5.0. In addition, for parameters for which NCI-CTCAE scale is not applicable such as vital signs and ECG variables, the potentially clinically significant abnormality (PCSA) analyses will be performed based on the PCSA list currently in effect at Sanofi at the time of the database lock.

Analyses according to PCSA and NCI grading will be performed based on the worst value during the treatment-emergent period, using all central (otherwise local) measurements.

For participants with multiple occurrences of the same laboratory variable during the treatment, the worst value per participant will be used. The denominator used for percentage (%) calculation is the number of participants with at least 1 evaluation of the laboratory test during the considered observation period.

For laboratory variables, vital signs, ECOG and ECG variables above, the incidence of participants with at least one PCSA during the treatment-emergent period will be summarized regardless of the baseline level and according to the following baseline status categories by Arm SC and Arm IV:

For laboratory variables graded by NCI-CTCAE,

- The number (%) of participants with abnormal laboratory tests at baseline will be presented by grade.

- The number (%) of participants with abnormal laboratory tests during the treatment-emergent period will be summarized by grade.
- Shift tables showing the number of patients by worst grade during the treatment period will be provided according to the grade at baseline of selected parameters (eg, thrombocytopenia, neutropenia, lymphopenia, anemia and other tests as appropriate) by treatment group.
- Neutropenia and neutropenic complications

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

  If relevant, duration of grade 3 or higher neutropenia episode, cumulative duration of grade 3 or higher neutropenia by patient and time to first onset grade 3 or higher neutropenia will be analyzed using laboratory data.

  The start date of grade 3 or higher laboratory neutropenia episode is defined as the date of first onset grade 3 or higher assessment for that episode. The end date of grade 3 or higher neutropenia episode is defined as the first date of neutropenia assessment afterwards of grade 1/2 or with no abnormality 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 grade 3 or higher 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, then the duration of the episode will be censored at the last neutrophil assessment of grade 3 or higher, or the cutoff date, whichever comes first.

  Time to first onset grade 3 or higher neutropenia (in days) is defined as: date of the first on-treatment grade 3 or higher neutropenia assessment – date of first treatment +1. If a patient does not have grade 3 or higher neutropenia, time to first onset grade 3 or higher neutropenia will be censored at the last assessment of neutropenia of grade 1/2 or with no abnormality, 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 Cycle 1 Day 1.

For laboratory tests for which NCI-CTCAE v5.0 scale is not applicable, the PCSA values are defined as abnormal values considered medically important by the Sponsor according to predefined criteria/thresholds based on literature review. For eGFR, uric acid, blood urea nitrogen glucose and chloride, PCSAs values will be derived. PCSA criteria will determine which patient had PCSA at baseline and which patients had at least 1 PCSA during the treatment period, taking into account all evaluations performed during the treatment period, including nonscheduled or repeated evaluations. The incidence of PCSA at baseline and at any time during the treatment period, will be summarized by treatment arm irrespective of the baseline level in the safety population.

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

For ECG, the incidence of participants with at least one abnormal ECG during the treatment-emergent period will be summarized regardless of the baseline level and according to the following baseline status categories:

- Normal/missing
- Abnormal

A shift table of baseline ECOG performance status vs best and worst ECOG performance status, respectively, on treatment will be provided. A summary of best and worst ECOG performance status on treatment will also be provided.

For indirect Coombs test, a summary of participants with indirect Coombs test performed at baseline and during the on-treatment period will be provided, including the number (%) of patients with:

- All tests negative
- At least one positive test

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

- Positive indirect Coombs test at baseline
- Negative indirect Coombs test at baseline
- Missing indirect Coombs test at baseline
- Panagglutination (resolved by DTT and not resolved by DTT)

And among participants with Coombs test negative at baseline

- Participants with all Coombs test negative during study treatment
- Participants with at least one Coombs test positive during study treatment
    - Panagglutination positive/negative/not done
        - resolved by DTT and not resolved by DTT and DTT not done

For blood pressure/heart rate parameters, the 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 for vital signs during the TEAE period will be summarized according to the following baseline categories:

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

As vital signs are measured several times on Cycle 1 Day 1 (just before starting infusion, 1 hour after starting infusion for IV arm and 30 minutes after starting infusion for SC arm, and at end of infusion for at home administration), only the values corresponding to the assessment done before starting infusion will be considered for the definition of baseline.

The incidence of PCSA taking into account assessment done during and after isatuximab administration at any cycle during the treatment period will also be summarized in the safety population.

3.6.3.2 Cycle 6 Day 15 onwards analyses for Arm SC

Listing for AEs and injection site reactions linked to the At Home visit collected through eCRF will be provided for participants who have safety related measurements observed at each Day 15 visit of Cycle 6 onwards. This listing will not include any safety related measurements that are observed at each Day 1 visit of Cycle 6 onwards or that are not linked to the At Home visit.

3.6.4 Product complaints

All product complaint (related to the medical device used for isatuximab SC) summaries for Arm SC during the on-treatment period (see Section 3.1) will be generated in the safety population with number (%) of participants who experience any product complaint. Product complaints will be provided in a separate report by Specialty Care Device department at Sanofi.

3.7 OTHER ANALYSES

3.7.1 Other variables and/or parameters

3.7.1.1 PK analyses

C_{trough} will be kept for the descriptive statistics if sampling occurs within 7 days ± 1 day after the previous infusion date for sampling done during Cycle 1 and within 14 days ± 2 days after the previous infusion date for sampling done for subsequent cycles. However, C_{trough} drawn outside time collection window described in the protocol PK flowchart or collected after a dose deviation higher than ±20% from intended dose will be excluded from the analyses.

C_{eoi} collected after significant infusion interruption, drawn outside collection of time window described in the PK flowchart of the protocol or collected after a dose deviation higher than ±20% from intended dose will be excluded from the analyses.

96h sample post first and 4th dose drawn outside time collection window described in the protocol PK flowchart or collected after a dose deviation higher than ±20% from intended dose will be excluded from the analyses.

All concentration values below the lower limit of quantitation (LLOQ) will be kept as “LLOQ” in listing and will be replaced by 0 in all summary statistics, except for calculation of ratios and geometric mean where values < LLOQ will be replaced by LLOQ numerical value.

Individual predose observed concentrations (C_{trough}) for isatuximab IV and SC, concentrations at end of infusion (C_{eoi}) for isatuximab IV only, 96 h post first and 4th dose for isatuximab SC only, will be listed by arm (IV and SC) and summarized with standard descriptive statistics by visit.

Mean (+/- SE) C_{trough} by treatment arm (SC and IV) will be superimposed graphically as function of sampling time (day/cycle) over the treatment phase to visualize the steady state achievement.

Ratio of the geometric means and 90% CI of C_{trough} (SC vs IV) as function of sampling time (day/cycle) will be tabulated and presented graphically over the treatment phase.

3.7.1.1.1 Descriptive statistics

Not applicable.

3.7.1.1.2 Dose effect

Not applicable.

3.7.1.1.3 Accumulation

Accumulation ratio by treatment arm (IV and SC) will be calculated with C_{trough} (Cycle 2 Day 1 vs Cycle 1 Day 8, Cycle 4 Day 1 vs Cycle 1 Day 8 and Cycle 6 Day 1 vs Cycle 1 Day 8) and additionally for the IV only with C_{eoi} (Cycle 2 Day 1 vs Cycle 1 Day 1, Cycle 4 Day 1 vs Cycle 1 Day 1 and Cycle 5 Day 1 vs Cycle 1 Day 1). They will be listed and summarized by standard descriptive statistics.

The PK variables will be summarized using the following standard descriptive statistics: arithmetic mean, geometric mean, median, standard deviation, standard error of the mean (SEM), coefficient of variation, minimum, and maximum.

PK parameters including exposure parameters will be estimated by population PK modeling. Details of the analysis plan will be provided in a separate document.

Population PK analysis will be performed under the responsibility of Sanofi, Pharmacokinetic, Dynamic and Metabolism (PKDM), Translational Medicine and Early Development (TMED) department.

3.7.1.1.4 Dose proportionality

Not applicable.

3.7.1.1.5 Food effect

Not applicable.

3.7.1.1.6 Variance components

Not applicable.

3.7.1.1.7 Drug-drug interaction

Not applicable.

3.7.1.1.8 Batch/formulation effect

Not applicable.

3.7.1.1.9 Day xx versus Day 1 4β-hydroxycholesterol ratio

Not applicable.

3.7.1.1.10 Immunogenicity impact on PK

Immunogenicity impact on PK analysis may be explored, depending on the ADA prevalence.

A standard descriptive statistic of C_{trough} as described above will be provided at each cycle in the subset of negative patients by treatment arm (IV and SC) where positive or inconclusive patients will be observed.

A graphical representation of individual C_{trough} profile with ADA positive patients highlighted (eg, color or bold) and the concentration at the same time as ADA positive result notified, along with mean (+/-SD) C_{trough} profile of ADA negative participants will be provided throughout the course of treatment, by treatment arm. Descriptive statistics of C_{trough} of ADA negative participants will be provided by Cycle at the bottom of the plot.

3.7.1.2 Immunogenicity analyses

Human anti-drug antibodies (ADAs) to isatuximab will be assessed during the study as described in the protocol and will be summarized on the ADA population by treatment arm (SC and IV).

ADA attributes

- Pre-existing ADA is defined as ADA reactive with the biotherapeutic present in subjects before treatment (or before initiation of the clinical study)..
- Treatment-induced ADA: is defined as ADAs developed de novo (seroconversion) following administration of the biotherapeutic (ie, formation of ADAs any time after the initial drug administration in a subject without pre-existing ADAs). If the baseline ADA sample is missing or non-reportable and at least one reportable ADA sample is available during the treatment (including follow-up period) the baseline sample will be considered as “negative” for data analysis. This is considered being a conservative approach for ADA assessment.
- Treatment-boosted ADA: is defined as pre-existing ADAs that were boosted to a higher level following administration of biotherapeutic (ie, any time after the initial drug administration) the ADA titer is significantly higher than the baseline titer. A low serial dilution schema (2-fold or 3 fold) should be applied during titration. A difference in titer

values of two titer steps between an on treatment or follow-up sample and its baseline sample is considered significant. For example, at least a 4-fold increase in titers for 2-fold serial dilution schema (or 9–fold increase in titers for 3- fold serial dilution schema). If no titer could be determined for a positive sample, the titer will be reported as the minimal required dilution (MRD) of the assay.

- Neutralizing ADA (NAb): ADA that inhibits or reduces the pharmacological activity of the biotherapeutic, regardless of its in vivo clinical relevance (ie, whether or not test method results relate to clinical impact in the subject).
- Non-neutralizing ADA (non-neutralizing antibody, non-NAb): ADA that binds to the biologic drug molecule but does not inhibit its pharmacological activity in an in vitro test, regardless of its in vivo clinical relevance (ie, whether or not test method results relate to clinical impact in the subject).

- ***Participant status***
- Among evaluable population for immunogenicity, following participant status will be defined:

- ADA-positive participants are defined as patients with at least 1 treatment-induced or treatment-boosted ADA positive sample at any time during the treatment or follow-up observation period.
- ADA-negative participants are defined as patients without any treatment induced or treatment boosted ADA-positive sample during the treatment or follow-up observation period.
- ADA-inconclusive participants are defined as patients who cannot irrefutably be classified as ADA-negative (eg, all post baseline samples inconclusive).

Kinetics of ADA response

- Onset of ADA: refers to the time period between the initial drug administration and the first instance of treatment-induced ADAs. The use of real-elapsed days should be used for the calculations. The “median time to ADA development” and the quartiles Q1 and Q3 should be reported.
- Duration of ADA: ADA duration will be calculated as the date of last treatment-induced ADA sample minus date of first treatment-induced or treatment-boosted ADA sample +1; ADA duration will be calculated only for patients with at least two ADA-positive samples. Median duration of an induced ADA response and the quartiles Q1 and Q3 should be reported.
- Transient ADA response is defined by:
  - Treatment-induced ADA detected only at 1 sampling time point during the treatment or follow-up observation period (excluding the last sampling time point), OR
  - Treatment-induced ADA detected at 2 or more sampling timepoints during the treatment (including follow-up period if any), 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 patient’s last sampling time point is ADA negative.

- Persistent ADA response is defined by: Treatment-induced ADA detected at 2 or more sampling timepoints during the treatment (including follow-up period if any), where the first and last ADA-positive samples (irrespective of any negative samples in between) are separated by at least 16 weeks.
- Indeterminate ADA response is defined by:
  - Treatment-induced ADA detected only in the last sampling time point, OR,
  - The last two samples being ADA-positive and separated by a period of less than 16 weeks.

Treatment-boosted ADAs are excluded from the analysis of ADA kinetics. In instances where a high number of pre-existing ADAs are detected, it may be useful to separately describe the kinetics of boosting.

For NAb, the same analysis will be applied when applicable.

ADA response variable:

Followings are the ADA response variables:

- ADA prevalence is defined as the proportion of all participants tested positive for ADAs (including pre-existing antibodies, treatment boosted ADAs and treatment induced ADAs) at any timepoint.
- ADA incidence is defined only as the proportion of participants found to either have seroconverted (treatment induced ADAs) or boosted their pre-existing ADA response during the study.
- Neutralizing ADA: When applicable, report pre-existing Nab, boosting, and incidence as described above. If all ADA are neutralizing in all participants, a separate analysis is obviously redundant.

A summary table by treatment arm (IV and SC) with the number (%) of pre-existing ADA and negative participants at baseline, number (%) of boosted and induced participants (either transient, persistent or indeterminate) will be reported, along with descriptive statistics of titer (median, IQR). Prevalence and incidence will also be presented.

In addition, for positive ADA patients, time to onset, duration of ADA response, and the characterization of the immune response (transient, persistent, indeterminate) will be provided using a summary table by treatment arm (IV and SC).

An individual data listing with ADA samples status (positive, negative or inconclusive), the titer if applicable, date of first/last dose, duration of exposure, study period (cycle), day, time point and date/time of sampling along with C_{trough} value of the drug will be provided for positive and inconclusive ADA participants.

The impact of positive immune response on efficacy, PK and safety variables may be further explored, depending on ADA incidence.

3.7.1.3 Quality of life analyses

Analyses of PEQ, PAT, HRUPQ, QLQ MY20, QLQ C30, EQ 5D 5L are described in Section 3.3. No additional quality of life analyses will be performed.

3.7.1.4 Biomarker analyses

Tumoral genomic and genetics profiles will be described separately at baseline (screening) and at progression, by arm and in the total population. The number and percent of patients with each genomic alteration per timepoint and will be tabulated per arm and in total. Sankey plots could be used to compare profiles between baseline and progression. A table and a stacked bar chard will report, for each alteration, the number and percent of patients which moved from *not- detected* to *detected* and vice versa between baseline and progression. The patient-wise differences in profile at progression as compared to baseline will be used to generate hypotheses regarding the possible patterns linked to drug resistance.

3.7.1.5 Concentration-QT analyses

Not applicable.

3.7.2 Subgroup analyses

The following subgroups collected at baseline will be performed:

- Age (<65, 65 to <75, ≥75 yrs)
- Race (White, Other)
- Gender (Male, Female)
- Region (Europe, North America, Asia, Other)
- MM isotype per IRT (IgG, Non-IgG)
- Body weight per IRT (≤65 kg, >65 to ≤85 kg, >85 kg)
- Number of prior lines of MM therapy per IRT (1-2, ≥3)
- Number of prior lines of MM therapy per eCRF (1, >1; 1-2, ≥3)
- Refractory to lenalidomide during any regimen (Yes, No)
- Refractory to lenalidomide during last regimen (Yes, No)
- ECOG grade (≤1, >1)
- ISS Staging at study entry (I, II, III) [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]
- R-ISS at study entry
- R2-ISS at study entry
- eGFR (<60 mL/min/1.73m², ≥60 mL/min/1.73m²)

- At least one R-ISS chromosomal abnormality (del(17p) and/or t(4;14) and/or t(14;16)) (Yes, No)
- At least one chromosomal abnormality by [del(17p)] or [gain 1q21+ and t(4;14) or t(14;16)] (Yes, No)

If number of categories for a given subgroup is >2, then the category with fewer than 5 participants may be combined with its next category. Fewer than 10 participants within a subgroup in Arm SC or Arm IV will not be performed the subgroup analysis.

For the analysis of binary endpoints (ORR per IRC assessment and VGPR or better rate per IRC assessment), the rate and the corresponding 95% CI will be estimated for Arm SC and Arm IV by each subgroup. The odds ratio for Arm SC vs Arm IV and the corresponding two-sided 95% Miettinen-Nurminen score CI, the relative risk with its two-sided 95% CI will be provided for each subgroup. The evaluation of interaction between treatment group and each of pre-specified subgroup on these binary endpoints will be performed using a logistic regression model including treatment group, subgroup and and their interaction as factors. The test of the interaction will be evaluated at the 10% alpha level. Forest plots will be provided.

The following subgroups will be used for treatment emergent adverse events (all grades and Grade ≥ 3) assessments:

- Age (<65, 65 to <75, ≥75 yrs)
- Gender (Male, Female)
- Race (Caucasian, Non-Caucasian)
- MM isotype per IRT (IgG, Non-IgG)
- Body weight per IRT (≤65 kg, >65 to ≤85 kg, >85 kg)
- Number of prior lines of MM therapy per IRT (1-2, ≥3)
- Number of prior lines of MM therapy per eCRF (1-2, ≥3)
- Number of prior lines of MM therapy per eCRF (1, >1)
- eGFR (<60 mL/min/1.73m², ≥60 mL/min/1.73m²)
- Hepatic status (Normal, Abnormal); abnormal hepatic status defined as mild impairment or moderate impairment or severe impairment

Descriptive statistics will be presented for safety variables. No statistical testing is planned.

3.8 INTERIM ANALYSES

No formal interim analyses with alpha spending are planned.

The analysis cutoff date for the primary analysis is approximately 6 months after the last participant in (LPI), which includes analysis on the primary endpoint and secondary endpoints

when applicable. An update of PFS and OS will be performed approximately 15 months after LPI. The cutoff date for final OS analysis will be approximately 30 months after LPI.

3.9 CHANGES TO PROTOCOL-PLANNED ANALYSES

No change in the study protocol is implemented that will impact the planned analysis.

4 SAMPLE SIZE DETERMINATION

A total sample size of 534 participants (randomization ratio 1:1, ie, 267 randomized participants in the SC arm, and 267 randomized participants in the IV arm) was determined to demonstrate non-inferiority of SC arm versus IV arm on the proportion ratio of participants who achieved ORR, and the geometric mean ratio of C_{trough} at steady state (corresponding to predose at C6D1).

For the co-primary efficacy endpoint of ORR, the non-inferiority test for non-unity null according to Farrington and Manning (1990) (1) was implemented. With 2.5% one sided Type I error rate, and a non-inferiority margin of 0.839 which was calculated as 40% retention of the observed historical clinical benefit of ORR ratio 0.7463 (upper bound of the 95% CI of rate ratio for Pd over CD38+Pd as demonstrated in ICARIA-MM trial) under the logarithm scale then converting back to its original scale, 534 randomized participants provide approximately 80% power for this efficacy co-primary endpoint assuming that ORR for IV arm is 60.4% and the true response rate ratio is 1.02 for SC arm over IV arm.

For the PK co-primary endpoint of C_{trough} at steady state, assuming C_{trough} at steady state follows log normal distribution with a true geometric mean ratio of 1 and a CV of 75%, and an assumed drop-out rate of no more than 50% to the PK per-protocol population, 534 randomized participants will provide at least an 86% power to show the lower bound of the 90% CI of the geometric mean ratio of C_{trough} at steady state is at least 80% (a non-inferiority margin of 80%).

Calculations were made based on SAS 9.4.

5 SUPPORTING DOCUMENTATION

5.1 APPENDIX 1 LIST OF ABBREVIATIONS

AE:	adverse event
AESIs:	adverse events of special interest
ECG:	electrocardiogram
e-CRF:	electronic case report form, electronic case report form
HLT:	high level term
LDH:	lactate dehydrogenase
LLT:	lower-level term
MedDRA:	medical dictionary for regulatory activities
NCI-CTCAE:	National cancer institute common terminology for adverse events
PCSA:	potentially clinically significant abnormality
PESQ:	patient experience and satisfaction questionnaire
PT:	preferred term
RDI:	relative dose intensity
SD:	standard deviation
SOC:	system organ class
TEAE:	treatment-emergent adverse event
VAS:	visual analogue scale
WHO-DD:	World Health Organization-drug dictionary

5.2 APPENDIX 2 PARTICIPANT DISPOSITION

The number (%) of participants included in each of the analysis populations listed in Table 3 will be summarized.

Screen failures are defined as participants who consent to participate in the study but are not subsequently randomized. The number (%) of screen failures and reasons for screen failures will be provided in the screened population.

The number (%) of participants in the following categories will be provided by Arm SC and Arm IV (and overall):

- Randomized participants
- Randomized but not treated participants
- Randomized and treated participants
- Participants still on treatment
- Participants with permanent full study treatment discontinuation and main reason for permanent full intervention discontinuation

- Participants still on study intervention-isatuximab
- Participants still on study intervention-pomalidomide
- Participants still on study intervention-dexamethasone
- Participants with permanent partial discontinuation of isatuximab and main reason for discontinuation
- Participants with permanent partial discontinuation of pomalidomide and main reason for discontinuation
- Participants with permanent partial discontinuation of dexamethasone and main reason for discontinuation
- Participants still on the study and who discontinued the study
- Main reason for study discontinuation
- Status at last contact (alive, death)

In addition, the number (%) of participants screened, screened-failed, randomized, with intervention discontinuation and with study discontinuation will be provided by country and site. In case of, main reason for study intervention discontinuation and study discontinuation is "Other" related to Covid-19 pandemic situation will be presented, when applicable.

A listing of exposed and not randomized participants and listing of participants randomized but not treated will be provided.

Listing of the reasons for treatment discontinuation and participants still on treatment at time of the analysis will be provided, when applicable.

A summary of the reasons for end of study by treatment group will be provided. Listing of participants who ended the study for other reason will be provided.

In addition, the number and percentage of randomized patients will be presented by stratification factor as per eCRF and as per IRT, as well as for each of the 12 stratification levels and by treatment group, as per eCRF and as per IRT.

Population without study impact or disruption due to Covid-19 or any major pandemic illness is defined as all randomized participants who have no critical or major protocol deviation related to Covid-19/any major pandemic illness, who do not discontinue study treatment due to Covid-19/any major pandemic illness, and who do not discontinue study due to Covid-19/any major pandemic illness. Reasons for exclusion from the population without study impact (disruption) due to Covid-19 or any major pandemic illness will be summarized (if applicable).

Protocol deviations

Protocol deviations (critical or major) related to inclusion and exclusion criteria, related to randomization procedures, and related to Covid-19 pandemic situation (if available) will be separately summarized in the randomized population.

5.3 APPENDIX 3 DEMOGRAPHICS AND BASELINE CHARACTERISTICS, PRIOR OR CONCOMITANT MEDICATIONS

The following demographics and baseline characteristics, medical and surgical history and disease characteristics at baseline will be summarized using descriptive statistics in the randomized population. In addition, smoking habits will be summarized separately.

Demographic and other baseline characteristics are:

- Age in [years] as quantitative variable and in categories (<65, 65 to <75, ≥75)
- Race (Asian, White, Black or African American, Other)
- Gender (Male, Female)
- Ethnicity (Hispanic, Not Hispanic)
- Geographical region (America, Asia, Europe and Other countries, see definition in appendix 5.8)
- Body weight at baseline per eCRF (as quantitative variable and in categories ≤65 kg, >65 to ≤85 kg, >85 kg)
- Extreme body weight at baseline per eCRF (≤50 kg, >50 to ≤100 kg, >100 kg)
- Body surface area (m^2)
- ECOG grade
- The following MM characteristics at initial diagnosis will be described:
- Initial diagnosis
- Time from initial diagnosis of MM to randomization (in months)
- MM subtype (heavy and light chain component)
- Biclonal status at diagnosis
- ISS Staging at diagnosis
- The following MM characteristics at study entry will be described:
- MM subtype (heavy and light chain component, as per eCRF data)
- Biclonal status at study entry (as per eCRF data)
- ISS stage derived from β2-microglobulin level in mg/L and albumin in g/L (see definition in Table 10). In addition, 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) and albumin in g/L (quantitative results and by category: <35 g/L and ≥35 g/L) will be provided.
- R-ISS stage derived as defined in Table 11 from β2-microglobulin, albumin, serum LDH and chromosomal abnormalities [CA] as described below. In addition, serum LDH (quantitative results and by category: ≤ULN, >ULN) will be provided.

- R2-ISS stage defined according to total score based on score for each risk features (details in Table 12 and Table 13)
- CA determined from central FISH assessment: number and percentage of participants
  - By chromosomal abnormality such as del(17p), t(4;14), t(14;16) and 1q21+ (Present, Absent, Unknown/missing).
  - Abnormality is defined as at least 30% of abnormal plasma cells for t(4;14), t(14;16), and 1q21+, and at least 50% of abnormal plasma cells for del(17p). 1q21+ includes gain 1q21 (only 3 copies) and amplification 1q21 (≥4 copies).
  - By type of risk as defined for R-ISS (standard risk vs high-risk [defined as presence of del(17p) and /or translocation t(4;14) and /or translocation t(14;16) abnormality] vs unknown/missing).
  - By number of abnormalities (no chromosomal abnormality vs only 1 chromosomal abnormality vs 2 chromosomal abnormalities vs ≥ 3 chromosomal abnormalities vs unknown/missing).
  - By multiple chromosomal abnormalities:
    - del(17p) and t(4;14) only
    - del(17p) and t(14;16) only
    - 1q21+ and del(17p) only
    - 1q21+ and t(4;14) only
    - 1q21+ and t(14;16) only1q21+, del(17p) and t(4;14)
    - 1q21+, del(17p) and t(14;16)
    - 1q21+ and t(4;14) or t(14;16)
    - 1q21+ and del(17p) and t(4;14) or t(14;16)
- Measurable disease (derived according to Table 14 from central laboratory results: Serum M-protein only, urine M-protein only, both serum and urine protein, sFLC only and not measurable)
- Serum free light chain at baseline (in randomized participants and in sFLC measurable only participants): involved FLC assay in serum (quantitative results and by category: > or = 10 to < 20 mg/dL, 20 to 100 mg/dL, ≥100 mg/dL), kappa/lambda free light chain ratio (quantitative results and by category: <0.26, [0.26; 1.65], >1.65)
- % of plasma cells in bone marrow at baseline (quantitative and qualitative variables: <5%, [5-20%[, [20-50%[and ≥50%).
- Participants with plasmacytoma (as per investigator and independent response committee (IRC)): Only extramedullary disease, only paramedullary disease, both extra and paramedullary disease. For paramedullary disease, distinction with soft tissue part ≥ 2 cm and soft tissue part < 2 cm will be presented.
- Organs involved at baseline according to IRC in participants with extramedullary disease.

- Participants with bone lesions (and number of lesions: 1to 4, 5 to 10, more than 10) (as per investigator and IRC).
- A listing of pre-treatment M-protein values for participants with results below level of eligibility at baseline for both serum, urine M-protein and FLC will be provided (ie, not measurable participants).

Table 10 - 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 11 - 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 in LDH and β2-microglobulin

High-risk CA by iFISH: Presence of del(17p) and /or translocation t(4;14) and /or translocation t(14;16) abnormalities
CA: Chromosomal abnormalities
iFISH: interphase fluorescence in situ hybridization
LDH: lactate dehydrogenase

Table 12 – R2-ISS Risk feature score

Risk feature	Score
ISS Stage 2	1
ISS stage 3	1.5
del(17p) present	1
LDH > ULN	1
t(4;14) present	1
1q21+ present	0.5

Table 13 – R2-ISS staging definition

Total score	R2-ISS classification
0	Stage 1
0.5-1.0	Stage 2
1.5-2.5	Stage 3
3-5	Stage 4
Not classified	At least one missing risk feature

Table 14 - Derivation of measurable paraprotein type at baseline

Measurable paraprotein at baseline	Criteria
Serum M-Protein Only	Serum M-protein ≥0.5 g/dL
Urine M-Protein Only	Urine M-protein ≥200 mg/24 hours
Both serum and urine M-protein	Serum M-protein ≥0.5 g/dL and urine M-protein ≥200 mg/24 hours
Only Free Light chain	Serum immunoglobulin free light chain ≥10 mg/dL and abnormal serum immunoglobulin kappa lambda free light chain ratio <0.26 or >1.65
Not measurable	Missing or neither serum, nor urine, nor FLC criteria

Demographics characteristics and baseline characteristics, disease characteristics at initial diagnosis and at study entry and chromosomal abnormality will be described by the following subgroup:

- Prior lines as per eCRF: One prior line vs > 1 prior lineBody weight as per eCRF: ≤ 65 kg vs > 65kg to ≤ 85kg, > 85kg
- MM isotype per IRT (IgG, Non-IgG)
- Body weight per IRT (≤65 kg, >65 to ≤85 kg, >85 kg)
- Number of prior lines of MM therapy per IRT (1-2, ≥3)

Laboratory characteristics

The following laboratory baseline parameters will be described:

- Hemoglobin (g/L) (continuous; <100, ≥100)
- Lymphocytes (10^9/L)
- Neutrophils (10^9/L)
- White blood cells ((10^9/L)
- Platelet count (10^9/L)
- Serum calcium level (mmol/L) (<2.25, ≥2.25)
- eGFR by MDRD (mild, moderate, severe impairment)
  - mild impairment: ≥60 - <90 mL/min/1.73m2
  - moderate impairment: ≥30-<60 mL/min/1.73m2
  - severe impairment: ≥15 - <30 mL/min/1.73m2
- eGFR by MDRD (≥60 mL/min/1.73m2, <60 mL/min/1.73m2)

Anticancer therapies

The following anti-myeloma therapies will be described:

- *Prior anti-myeloma treatments*:

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

  - Number of prior regimens (quantitative and qualitative variable: 1, 2, 3, 4, 5, 6, 7, ≥8),

- Number of prior lines (a line of therapy consists of ≥1 complete cycle of a single agent or a regimen consisting of a combination of several drugs, or a planned sequential therapy of various regimens) (quantitative and qualitative variable: 1, 2, 3, 4, 5, 6, 7, ≥8 and one prior line only: Yes vs No),
- Number of prior lines as per eCRF (1-2 vs ≥3)
- Main anti-myeloma therapies by class and agent:
  - Alkylating agents: such as cyclophosphamide, melphalan, bendamustine,
  - Proteasome inhibitors: such as bortezomib, carfilzomib, ixazomib,
  - Immunomodulators: such as lenalidomide, thalidomide, pomalidomide,
  - Monoclonal antibodies: such as elotuzumab (anti SLAMF7 agent), daratumumab (anti CD 38 agent) and anti CD38 agents other than daratumumab (including MOR202),
  - Anthracyclines,
  - Vinca alkaloids,
  - Corticosteroids,
  - HDAC inhibitors,
  - Antimetabolites,
  - Anti-BMCA
  - FcRH5 targeting agents,
  - GPRC5D targeting agents,
  - Anti-CD47 agents,
  - Cellmod agents,
  - Anti-PD1 agents and anti PDL1 agents,
  - CAR T cells,
  - KSP inhibitors,
  - Anti-Bcl2 antibody
  - BTK inhibitors
  - Topoisomerase inhibitors
  - Platinum compound
- The refractory status to immunomodulators, proteasome inhibitors and to both immunomodulators and proteasome inhibitors will be derived. A participant 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 stable disease (SD) or PD,
  - Reason for treatment discontinuation is “Progressive disease”.
- Description of last regimen given prior to study entry:
  - Time from completion of last regimen of treatment to first study treatment administration (months),
  - Main treatments,
  - Best response to last regimen,
  - Duration of last regimen of therapy (months),
  - Refractory status as defined above,
  - Reason for treatment discontinuation.

- *Prior transplant*: number (%) of participants with at least one transplant, number (%) of participants with at least two transplants, number of transplants by participant, type of transplant (autologous, allogenic).
- *Prior surgery*: number (%) of participants with any prior surgery related to MM, type of procedure and time from last surgery to first study treatment administration (weeks)
- *Prior radiotherapy*: number (%) of participants with any prior radiotherapy related to MM, analgesic intent and time from last radiotherapy to first study treatment administration (weeks)

Prior anti-myeloma treatments and prior transplants will be described by the following subgroups:

- Prior lines as per eCRF: One prior line vs > 1 prior line,
- Body weight as per eCRF: ≤ 65 kg vs > 65kg to ≤ 85kg, > 85kg.
- MM isotype per IRT (IgG, Non-IgG)
- Body weight per IRT (≤65 kg, >65 to ≤85 kg, >85 kg)
- Number of prior lines of MM therapy per IRT (1-2, ≥3)

Further anti-myeloma therapies

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

For further therapies, a summary table, including the number of different regimens, will be provided for further anti-myeloma treatments based on WHO-DD coding.

Time to Next Treatment (TNT):

TNT is defined as the time from randomization to the start of further anti-myeloma treatment. Participants who do not receive any further anti-myeloma treatment before the cut-off date will be censored at the date of their last follow-up visit or the cut-off date, whichever comes first.

Participants with no follow-up visit will be censored at their last study treatment administration or the cut-off date whichever comes first.

TNT will be analyzed using Kaplan-Meier methods.

Other baseline characteristics

Other baseline characteristics including frailty score (Fit, intermediate, frail ; and frail vs non-frail), Katz index (ADL in categories >4 and ≤4), Lawton instrumental activities of daily living scale (IADL in categories >5 and ≤5) will be described.

Prior or concomitant medications (other than anti-myeloma therapies)

All medications will be coded using the World Health Organization-Drug Dictionary (WHO-DD) using the version currently in effect at Sanofi at the time of database lock.

- Prior medications are those the participant received prior to study treatment intake. Prior medications can be discontinued before first administration or can be ongoing during treatment period.
- Concomitant medications are any medications received by the participant concomitantly to any study intervention from the first administration of study treatment to the last study treatment intake +30 days.
- Post-treatment medications are those the participant received in the period running from the end of the concomitant medications period up to the end of the study.
- A given medication can be classified as a prior medication and/or as a concomitant medication and/or as post-treatment medication. If it cannot be determined whether a given medication was taken prior or concomitantly or post, it will be considered as prior, concomitant, and post-treatment medication.

The prior and concomitant and post-treatment medications will be summarized for the randomized population, by anatomic and therapeutic level. Participants will be counted once in each ATC category (anatomic or therapeutic) linked to the medication. The analysis of concomitant medications will include the infusion reaction (IR) medications.

In addition, analyses including number (%) of participants with concomitant red blood cells transfusions, with concomitant platelets transfusions, with concomitant use of granulocyte colony stimulating factor/ granulocyte-macrophage colony stimulating factor (prophylaxis andcurative intent) will be provided for the safety population.

IR medications

As defined in Section 6.1.2 of the study protocol, participants will receive premedication to prevent or reduce the risk and severity of isatuximab-related IRs.

Analysis of IR medications will focus on those given for prophylactic intent on the days of isatuximab administrations.

Medication given in curative intent of IR will be also analyzed.

IR medications given when administration is at home will also be described separately.

Any technical details related to computation, dates, imputation for missing dates are described in Appendix 5.4.

5.4 APPENDIX 4 DATA HANDLING CONVENTIONS

Unscheduled visits

Unscheduled visit measurements of laboratory data, vital signs, ECG and ADA will be used for computation of baseline, the last on-treatment value, analysis according to PCSAs/NCI grades/PCSAs and NCI grades, and the shift summaries for safety. They will also be included in the by-visit summaries if they are re-allocated to scheduled visits.

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.

Hepatic function

- Normal: Total bilirubin ≤ Upper limit of normal (ULN) and aspartate aminotransferase (AST) ≤ ULN
- Mild impairment: ULN < Total bilirubin ≤1.5 x ULN and AST=Any; or Total bilirubin ≤ ULN and AST > ULN
- Moderate impairment: 1.5 x ULN < Total bilirubin ≤3 x ULN and AST=any

Severe impairment: Total bilirubin >3 x ULN and AST=any

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.

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 further anti-myeloma treatment start date

For further 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 date will be set equal to the treatment end date +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.

5.5 APPENDIX 5 EORTC QLQ-C30 AND QLQ-MY20 ITEMS, SCALES AND SCORES

For QLQ-C30:

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**:

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

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

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

- **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

For QLQ-MY20:

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

- **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

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.

5.6 APPENDIX 5.6 DESCRIPTION OF CENSORING RULES FOR PRIMARY AND SUPPORTVE ANALYSES OF PFS

General rules for censoring for all PFS analysis:

Participant is censored:

- At the last valid disease assessment if this one is done on or before the cut-off date,
- At randomization if there is no valid disease assessment after randomization

Initiation of further anti-myeloma therapy must be considered or not for the selection of the last valid assessment according to the analysis considered.

Table 15 - PFS primary analysis (progression based on blinded IRC disease assessment)

Situation	Date of progression or censoring	Outcome
No valid baseline or post baseline disease assessments	Date of randomization	Censored
Documented Progression according to IRC prior to initiation of new anti-myeloma treatment and prior to the cut-off date and within 9 weeks from last valid disease assessment	Earliest date among all disease assessments with evidence of progression	Event
Death without both documented progression as per IRC and initiation of new anti-myeloma treatment prior to the cut-off date and within 9 weeks from last valid disease assessment	Date of death	Event
Both documented progression as per IRC prior to initiation of new anti-myeloma treatment and death prior to the cut-off date, and within 9 weeks from last valid disease assessment	Date of progression	Event
No documented progression according to IRC prior to initiation of new anti-myeloma treatment and no death prior to the cut-off date	Date of last valid disease assessment with no evidence of progression before initiation of new anti-myeloma treatment	Censored

Situation	Date of progression or censoring	Outcome
Initiation of new anti-myeloma treatment before documented progression according to IRC or before death	Date of last valid disease assessment with no evidence of progression before initiation of new anti-myeloma treatment	Censored
Earliest of Death or progression occurring more than 9 weeks[a] after the last valid disease assessment	Date of last valid disease assessment with no evidence of progression before initiation of new anti-myeloma treatment	Censored

a 9 weeks corresponds to >2 consecutive missed scheduled disease assessments

Table 16 - PFS supportive analysis (progression based on investigator disease assessment ignoring symptomatic deterioration)

Situation	Date of progression or censoring	Outcome
No valid baseline or post-baseline disease assessments	Date of randomization	Censored
Documented Progression according to investigator prior to initiation of new anti-myeloma treatment and prior to the cut-off date and within 9 weeks from last valid disease assessment	Earliest date among all disease assessments with evidence of progression	Event
Death without both documented progression as per investigator and initiation of new anti-myeloma treatment prior to the cut-off date and within 9 weeks from last valid disease assessment	Date of death	Event
Both documented progression as per investigator prior to initiation of new anti-myeloma treatment and death prior to the cut-off date, and within 9 weeks from last valid disease assessment	Date of progression	Event
No documented progression according to investigator prior to initiation of new anti-myeloma treatment and no death prior to the cut-off date	Date of last valid disease assessment with no evidence of progression before initiation of new anti-myeloma treatment	Censored
Symptomatic deterioration reported and no documented progression according to investigator and no death	Ignored	Ignored
Initiation of new anti-myeloma treatment before documented progression according to investigator or before death	Date of last valid disease assessment with no evidence of progression before initiation of new anti-myeloma treatment	Censored
Earliest of Death or progression occurring more than 9 weeks[a] after the last valid disease assessment	Date of last valid disease assessment with no evidence of progression before initiation of new anti-myeloma treatment	Censored

a 9 weeks corresponds to >2 consecutive missed scheduled disease assessments

Table 17 - PFS supportive analysis (progression based on investigator disease assessment with symptomatic deterioration)

Situation	Date of progression or censoring	Outcome
No valid baseline disease assessments	Date of randomization	Censored
No valid post-baseline disease assessments	Date of Randomization	Censored
Documented Progression according to investigator prior to initiation of new anti-myeloma treatment and prior to the cut-off date and within 9 weeks from last valid disease assessment	Earliest date among all disease assessments with evidence of progression	Event
Death prior to the cut off date without documented progression as per investigator or symptomatic deterioration or initiation of new anti-myeloma treatment prior to the cut-off date and within 9 weeks from last valid disease assessment	Date of death	Event
Both documented progression as per investigator prior to initiation of new anti-myeloma treatment and death prior to the cut-off date, and within 9 weeks from last valid disease assessment	Date of progression	Event
Symptomatic deterioration prior to initiation of new anti-myeloma treatment and prior to the cutoff date with no documented progression according to investigator and no death, and within 9 weeks from last valid disease assessment	Date of symptomatic deterioration	Event
Symptomatic deterioration and documented progression according to the investigator prior to initiation of new anti-myeloma treatment and prior to the cut-off date regardless of death occurrence, and within 9 weeks of last valid disease assessment	Earliest date among symptomatic deterioration and documented progression	Event
No symptomatic deterioration, no documented progression according to investigator prior to initiation of new anti-myeloma treatment and no death prior to the cut-off date	Date of last valid disease assessment with no evidence of progression before initiation of new anti-myeloma treatment	Censored
Initiation of new anti-myeloma treatment before symptomatic deterioration or before documented progression according to investigator or before death	Date of last valid disease assessment with no evidence of progression before initiation of new anti-myeloma treatment	Censored
Earliest of Death or progression or symptomatic deterioration occurring more than 9 weeks[a] after the last valid disease assessment	Date of last valid disease assessment with no evidence of progression before initiation of new anti-myeloma treatment	Censored

a 9 weeks corresponds to >2 consecutive missed scheduled disease assessments

5.7 APPENDIX 5.7 DESCRIPTION OF PFS2 ANALYSES

Table 18 - PFS2 analysis (progression based on investigator disease assessment)

Situation	Date of progression or censoring	Outcome
No valid baseline and 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 and within 9 weeks from last valid disease assessment, as per investigator including symptomatic deterioration

5.8 APPENDIX 5.8 GEOGRAPHICAL REGION DEFINITION

Europe	America	Asia	Other
Czech Republic	Argentina	China	Australia
France	Brazil	Japan	Turkey
Germany	Canada	Taiwan, Province of China	
Greece	Chile		
Hungary	United states		
Italy			
Norway			
Poland			
Spain			
Sweden			
United Kingdom			

5.9 APPENDIX 5.9 LIST OF COUNTRIES FOR WHICH NATIONAL AND/OR LOCAL REGULATIONS DOES NOT PERMIT AT HOME ADMINISTRATION

Countries in which national and/or local regulations does not permit at home administration are:

- China
- Taiwan, Province of China
- France
- Germany
- Greece

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