AMENDED CLINICAL TRIAL PROTOCOL 10

COMPOUND: isatuximab/SAR650984

Randomized, open label, multicenter study assessing the clinical benefit of isatuximab combined with carfilzomib (Kyprolis®) and dexamethasone versus carfilzomib with dexamethasone in patients with relapsed and/or refractory multiple myeloma previously treated with 1 to 3 prior lines

STUDY NUMBER: EFC15246

STUDY NAME: IKEMA

VERSION DATE / STATUS: 24-Nov-2022 / Approved

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NAMES AND ADDRESSES OF

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PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY

Document	Country/countries impacted by amendment	Date, version
Amended Clinical Trial Protocol 10	All	24 November 2022, version 1 (electronic 10.0)
Amended Clinical Trial Protocol 09	All	14 September 2021, version 1 (electronic 9.0)
Amended Clinical Trial Protocol 08	All	11 March 2021, version 1 (electronic 8.0)
Amended Clinical Trial Protocol 07	All	10 August 2020, version 1 (electronic 7.0)
Amended Clinical Trial Protocol 06	All	13 Nov 2019, version 1 (electronic 6.0)
Amended Clinical Trial Protocol 05	All	11 Sep 2019, version 1 (electronic 5.0)
Amended Clinical Trial Protocol 04	All	11 June 2019, version 1 (electronic 4.0)
Amended Clinical Trial Protocol 03	All	02 July 2018, version 1 (electronic 3.0)
Amended Clinical Trial Protocol 04 (GB)	Great Britain only	02 July 2018, version 1 (electronic 3.0)
Protocol Amendment 04	All	02 July 2018, version 1 (electronic 1.0)
Amended Clinical Trial Protocol 02	All	08 February 2018, version 1 (electronic 2.0)
Amended Clinical Trial Protocol 03 (GB)	Great Britain only	08 February 2018, version 1 (electronic 2.0)
Protocol Amendment 03	All	08 February 2018, version 1 (electronic 1.0)
Amended Clinical Trial Protocol 02 (GB)	Great Britain only	30 August 2017, version 1 (electronic 1.0)
Protocol Amendment 02 (GB)	Great Britain only	30 August 2017, version 1 (electronic 1.0)
Amended Clinical Trial Protocol 01	All	21 August 2017, version 1 (electronic 1.0)
Protocol Amendment 01	All	21 August 2017, version 1 (electronic 1.0)
Original Protocol		05 July 2017, version 1 (electronic 1.0)

Amended protocol 10 (24-Nov-2022)

This amended protocol 10 is considered to be substantial based on the criteria set forth in Article 2(2)(13) of the Regulation No 536/2014 of the European Parliament and the Council of the European Union.

OVERALL RATIONALE FOR THE AMENDMENT

An overwhelming treatment effect of isatuximab carfilzomib dexamethasone (IKd) arm in comparison to carfilzomib dexamethasone (Kd) arm was observed at the time of the pre-specified interim analysis performed with a data cut-off date of 07 February 2020. However, the median progression free survival (PFS) was not reached for IKd arm while it was reached for Kd arm. It was anticipated that the median PFS could be not reached at the time of the pre-specified final analysis. Therefore, a descriptive additional PFS analysis was added in the amended protocol #08 dated 11 March 2021 to increase the possibility of observing the median PFS time for the IKd arm when approximately 180 PFS events as per Independent Response Committee (IRC) are observed.

The final PFS analysis was performed with a data cut-off date of 14 January 2022 and median PFS was reached in the IKd arm at the time of this analysis. Therefore, the reason to perform additional descriptive analysis when approximately 180 PFS events are occurred is no longer necessary, and this amendment removes this analysis from the study protocol.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Title Page	ClinicalTrials.gov identifier was added.	To include the ClinicalTrials.gov identifier in the amended protocol.
Protocol Amendment Summary of Changes	"This amended protocol 09 is substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union" was replaced by "This amended protocol 10 is considered to be substantial based on the criteria set forth in Article 2(2)(13) of the Regulation No 536/2014 of the European Parliament and the Council of the European Union"	To reflect the current amendment number and for consistency with the protocol template released in September 2022.
Clinical Trial Summary: Assessment Schedule	Text related to additional descriptive PFS analysis was removed and the management of patients still on treatment or in the follow-up was updated accordingly.	Median PFS was reached at the final PFS analysis; therefore, additional descriptive PFS analysis is no longer necessary.
Clinical Trial Summary: Statistical Considerations, Primary analysis	The following sentences were removed: "An additional PFS analysis will be performed when approximately 180 events assessed by the IRC have been observed to better characterize the distribution of PFS in the IKd arm in a descriptive way. This analysis will be performed at the latest 15 months after the 159 PFS event analysis cut-off date in case of the approximately 180 PFS events are not observed at that time".	Median PFS was reached at the final PFS analysis; therefore, additional descriptive PFS analysis is no longer necessary.
Clinical Trial Summary: Statistical Considerations, Interim analysis, Planned PFS and OS cut-off dates	The following sentences were removed: "Efficacy results will be updated in a descriptive way (non-inferential analysis) at the time of the PFS additional analysis (approximately 180 events)". "The cut-off date for the additional PFS analysis will be the date when approximately 180 PFS events assessed by the IRC have occurred or 15 months after 159 PFS events analysis cut-off date, whichever comes first".	Median PFS was reached at the final PFS analysis; therefore, additional descriptive PFS analysis is no longer necessary.
Clinical Trial Summary: Duration of Study Period (per patient)	All wordings related to additional PFS analysis was removed and the management of patients still on treatment or in the follow-up was updated accordingly.	Median PFS was reached at the final PFS analysis; therefore, additional descriptive PFS analysis is no longer necessary.
Section 6.2.1 Duration of study participation for each patient	Text related to 180 additional PFS events was removed and management of patients still on treatment or in follow-up was updated accordingly.	Median PFS was reached at the final PFS analysis; therefore, additional descriptive PFS analysis is no longer necessary.

Section # and Name	Description of Change	Brief Rationale
Section 6.2.2 Determination of end of clinical trial (all patients)	The following sentences were removed: "An additional PFS analysis will be performed at approximately 180 events. The additional analysis will be performed at the latest 15 months after the 159 PFS event analysis cut-off date in case of the approximately 180 PFS events are not observed at that time".	Median PFS was reached at the final PFS analysis; therefore, additional descriptive PFS analysis is no longer necessary.
Section 6.4 Study Committees	"No IRC review will be performed after the additional PFS analysis cut-off date" was replaced by "IRC will review disease assessments until the last time point with M protein assessed by central laboratory or overall survival cut-off date, whichever comes first".	To analyze all samples drawn before implementation of amended protocol #10.
Section 10.1.6 After Implementation of Amended Protocol #10	Previous heading "Post additional PFS analysis cut-off date (approximately 180 PFS events as per IRC)" and the applicable text in this section were replaced by "After implementation of amended protocol #10".	To reflect removal of the additional PFS analysis.
Section 10.1.6 After Implementation of Amended Protocol #10	Added that following additional information will be collected during the study treatment administration after the implementation of amended protocol #10: "Hematology and biochemistry, or any other laboratory results supporting the reported AEs." "Other procedures supporting the reported AEs."	To include the additional information required to be collected after implementation of amended protocol #10.
Section 10.1.6 After Implementation of Amended Protocol #10	Updated that survival status and further anti-myeloma therapies will be collected twice a year if study treatment is stopped before the OS cut-off date.	To correct inconsistency with Section 6.2.1.
Section 10.1.7 Post OS analysis cut-off date	Added that following additional information will be collected during the study treatment administration post OS analysis cut-off date: "Hematology and biochemistry, or any other laboratory results supporting the reported AEs." "Other procedures supporting the reported AEs." "Death date and reason if occurred during study treatment."	To include the additional information required to be collected post OS analysis cut-off date.
Section 10.1.7 Post OS analysis cut-off date	Added that following additional information will be collected after the discontinuation of study treatment: "Death date and reason if occurred in follow-up period due to related AE."	To include the additional information required to be collected post OS analysis cut-off date.
Section 11.4.2.1 Analysis of primary efficacy endpoint	The following sentences were removed: "An additional PFS analysis (non-inferential analysis) will be performed when approximately 180 events assessed by the IRC have been observed to better characterize the distribution of PFS in the Ikd arm in a descriptive way. The additional analysis will be performed at the latest 15 months after the 159 PFS event analysis cut-off date in case of the approximately 180 PFS events are not observed at that time".	Median PFS was reached at the final PFS analysis; therefore, additional descriptive PFS analysis is no longer necessary.
Section 11.4.2.3 Multiplicity considerations	The following sentence was removed: "Efficacy results will be updated at the time of the PFS additional analysis (approximately 180 events) but will be only descriptive (non-inferential analysis)".	Median PFS was reached at the final PFS analysis; therefore, additional descriptive PFS analysis is no longer necessary.

Section # and Name	Description of Change	Brief Rationale
Section 11.5 Interim analysis	The following sentences were removed: “Efficacy results will be updated at the time of the PFS additional analysis (approximately 180 events) but will be only descriptive (non-inferential analysis). No α-spending or formal testing is planned for the PFS additional analysis”.	Median PFS was reached at the final PFS analysis; therefore, additional descriptive PFS analysis is no longer necessary.
Section 12.1 Ethical and Regulatory Considerations	Additional details regarding ethical and regulatory standards included as per the updated protocol template.	For consistency with the protocol template released in September 2022.
Section 14.5 Data Protection	Additional details regarding data protection methods included as per the updated protocol template.	For consistency with the protocol template released in September 2022.
Appendix O (Protocol amendment history)	Changes related to amended protocol #09 were moved to Appendix O.	History of amendment to this protocol added.

CLINICAL TRIAL SUMMARY

COMPOUND: isatuximab/SAR650984	**STUDY No: EFC15246**
TITLE	Randomized, open label, multicenter study assessing the clinical benefit of isatuximab combined with carfilzomib (Kyprolis®) and dexamethasone versus carfilzomib with dexamethasone in patients with relapsed and/or refractory multiple myeloma previously treated with 1 to 3 prior lines.
INVESTIGATOR/TRIAL LOCATION	Worldwide
PHASE OF DEVELOPMENT	Phase 3
STUDY OBJECTIVES	**Primary objective:** To demonstrate the benefit of isatuximab in combination with carfilzomib and dexamethasone in the prolongation of progression free survival (PFS) using International Myeloma Working Group (IMWG) criteria as compared to carfilzomib and dexamethasone in patients with relapsed and/or refractory multiple myeloma (MM) previously treated with 1 to 3 lines of therapy. **Secondary objectives:** Key efficacy objectives • To evaluate overall response rate (ORR). • To evaluate rate of very good partial response (VGPR) or better. • To evaluate rate of VGPR or better (IMWG criteria) with minimal residual disease (MRD) negativity in both arms. • To evaluate complete response (CR) rate in both arms (IMWG criteria). • To evaluate overall survival (OS) in both arms. Other secondary objectives • To evaluate safety in both arms. • To evaluate duration of response (DOR) in both arms. • To evaluate time to progression (TTP) in both arms. • To evaluate time from the date of randomization to the date of second PD or death from any cause, whichever happens first (PFS2) in both arms. • To evaluate time to first response in both arms • To evaluate time to best response in both arms • To determine the pharmacokinetic (PK) profile of isatuximab and carfilzomib when combined together. • To evaluate immunogenicity of isatuximab in isatuximab arm. • To evaluate generic and disease- and treatment-specific health-related quality of life (HRQL), and changes in HRQL, health state utility, and health status in both arms. **Exploratory objectives:** • To explore PK and pharmacodynamics relationship. • To explore the relationship between immune genetic determinants and efficacy endpoints. • To explore relationship between cytogenetics abnormalities not part of Revised International Staging System (R-ISS) including but not limited to del (1p) and gain (1q) and efficacy endpoints. • To explore the impact of M-protein measurement without isatuximab interference on best overall response assessment.

STUDY DESIGN	This is a prospective multicenter, multinational, randomized, open label, parallel group, 2-arm study assessing the clinical benefit of isatuximab at 10 mg/kg weekly in the first cycle (4 weeks) and then combined with carfilzomib at 56 mg/m² twice weekly 3 out of 4 weeks and dexamethasone (IKd arm) twice weekly versus carfilzomib at 56 mg/m² twice weekly 3 out of 4 weeks and dexamethasone twice weekly (Kd arm), in terms of PFS in patients with relapsed and/or refractory MM previously treated with 1 to 3 prior lines. Patients will be treated until disease progression, unacceptable adverse event (AE), patient decision to stop the study treatment, or any other reasons. Isatuximab, carfilzomib, and dexamethasone are defined in this protocol as "study treatment". Treatment allocation will be performed by an Interactive Response Technology (IRT). All eligible patients will be randomly assigned to the IKd (experimental) arm or Kd (control) arm in a 3:2 ratio. Randomization will be stratified by number of prior lines 1 vs. >1 and R-ISS I or II vs. III vs. not classified (inconclusive fluorescence in situ hybridization [FISH] unless stage can be determined on lactate dehydrogenase (LDH), albumin, and β2 microglobulin only) (see Appendix A).
STUDY POPULATION **Main selection criteria**	**Inclusion criteria:** I 01. Multiple myeloma. I 02. Measurable disease: Serum M protein ≥0.5 g/dL measured using serum protein immunoelectrophoresis; and/or Urine M protein ≥200 mg/24 hours measured using urine protein immunoelectrophoresis. I 03. Patient with relapsed and/or refractory MM with at least 1 prior line and no more than 3 prior lines. I 04. Patient has given voluntary written informed consent before performance of any study related procedures not part of normal medical care. **Exclusion criteria:** E 01. Less than 18 years (or country's legal age of majority if the legal age is >18 years). E 02. Primary refractory MM defined as patients who have never achieved at least a minimal response with any treatment during the disease course. E 03. Patient with serum free light chain (FLC) measurable disease only. E 04. Patient with prior anti-CD38 monoclonal antibody (mAb) treatment with progression on or within 60 days after end of anti-CD38 mAb treatment or failure to achieve at least minimal response to treatment (ie, refractory to anti-CD38). E 05. Any anti-myeloma drug treatment within 14 days before randomization, including dexamethasone. E 06. Patient who has received any other investigational drugs or prohibited therapy for this study within 28 days prior to randomization (Section 8.8.2). E 07. Prior treatment with carfilzomib. E 08. Known history of allergy to Captisol (a cyclodextrin derivative used to solubilize carfilzomib), prior hypersensitivity to sucrose, histidine (as base and hydrochloride salt), polysorbate 80, or any of the components (active substance or excipient) of study treatment that are

	not amenable to premedication with steroids, or H2 blockers, that would prohibit further treatment with these agents. E 09. Patients with contraindication to dexamethasone. E 10. Prior allogenic hematopoietic stem cell transplant with active graft versus host disease (any grade and/or being under immunosuppressive treatment within 2 months before randomization). E 11. Known amyloidosis or concomitant plasma cell leukemia. E 12. Pleural effusions requiring thoracentesis or ascites requiring paracentesis or any major procedures within 14 days before randomization: eg, plasmapheresis, curative radiotherapy, major surgery (kyphoplasty is not considered a major procedure). E 13. Eastern Cooperative Oncology Group (ECOG) performance status (PS) >2. E 14. Platelets <50,000 cells/µL if <50% of bone marrow (BM) nucleated cells are plasma cells and <30,000 cells/µL if ≥50% of BM nucleated cells are plasma cells. Platelet transfusion is not allowed within 3 days before the screening hematological test. E 15. Absolute neutrophil count (ANC) <1000 µ/L (1 x 10^9/L). The use of granulocyte colony stimulating factor is not allowed to reach this level. E 16. Creatinine clearance <15 mL/min/1.73 m² (Modification of Diet in Renal Disease [MDRD] Formula). E 17. Total bilirubin >1.5 x upper limit of normal (ULN), except for known Gilbert syndrome. E 18. Corrected serum calcium >14 mg/dL (>3.5 mmol/L). E 19. Aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) >3 x ULN. E 20. Ongoing toxicity (excluding alopecia and those listed in eligibility criteria) from any prior anti-myeloma therapy of Grade >1 (National Cancer Institute Common Toxicity Criteria for Adverse Events [NCI-CTCAE] v4.03). E 21. Prior malignancy. Adequately treated basal cell or squamous cell skin or superficial (pTis, pTa, and pT1) bladder cancer or low risk prostate cancer or any in situ malignancy after curative therapy are allowed, as well as any other cancer for which therapy has been completed ≥5 years prior to randomization and from which the patient has been disease-free for ≥5 years. E 22. Any of the following within 6 months prior to randomization: myocardial infarction, severe/unstable angina pectoris, coronary/peripheral artery bypass graft, New York Heart Association class III or IV congestive heart failure, Grade ≥3 arrhythmias, stroke, or transient ischemic attack. E 23. Left ventricular ejection fraction <40%. E 24. Known acquired immunodeficiency syndrome (AIDS) related illnesses or HIV disease requiring antiretroviral treatment, or to have active hepatitis A, B (defined as a known positive hepatitis B surface antigen (HBsAg) result), or C (defined as a known quantitative hepatitis C [HCV] ribonucleic acid [RNA] results greater than the lower limits of detection of the assay or positive HCV antigen) infection. E 25. Any of the following within 3 months prior to randomization: treatment resistant peptic ulcer disease, erosive esophagitis or gastritis, infectious or inflammatory bowel disease, diverticulitis, pulmonary embolism, or other uncontrolled thromboembolic event.

	E 26. Any severe acute or chronic medical condition which could impair the ability of the patient to participate in the study or interfere with interpretation of the study results (eg, systemic infection unless anti-infective therapy is employed), or patient unable to comply with the study procedures. E 27. Female patients who are pregnant or lactating. E 28. Women of childbearing potential (WOCBP) not protected by highly-effective method of birth control and/or who are unwilling or unable to be tested for pregnancy (see Appendix C). E 29. Male participant with a female partner of childbearing potential not protected by highly effective method of birth control.
Total expected number of patients	Approximately 300 (180 patients in IKd arm and 120 patients in Kd arm)
STUDY TREATMENTS	
Investigational medicinal product	**Isatuximab**
Formulation:	The drug product is presented as a concentrate for solution for infusion in vials containing 20 mg/mL (500 mg/25 mL) of isatuximab in 20 mM histidine, 10% (w/v) sucrose, 0.02% (w/v) polysorbate 80, and pH 6.0 buffer. It is packed in 30 mL glass vials fitted with elastomeric closure. Each vial contains a nominal content of 500 mg of isatuximab. The fill volume has been established to ensure removal of 25 mL.
Route of administration:	Intravenous (IV)
Dose regimen:	Isatuximab will be given at 10 mg/kg IV on Days 1, 8, 15, and 22 in Cycle 1 and then on Days 1 and 15 in subsequent cycles. The duration of each cycle is 28 days. Premedication will include acetaminophen or paracetamol, ranitidine or equivalent, and diphenhydramine or equivalent, in addition to dexamethasone. Dose omission/delay will be applied in case of toxicity.
Investigational medicinal product	**Carfilzomib (Kyprolis®)**
Formulation:	Carfilzomib for injection is presented as a lyophilized parenteral product in single-use vials. The lyophilized product is reconstituted with water for injection to a final carfilzomib concentration of 2.0 mg/mL prior to administration.
Route of administration:	IV
Dose regimen:	Carfilzomib (after appropriate hydration) will be given as a 30-minute infusion on Days 1, 2, 8, 9, 15, and 16 of 28 day cycles at the dose of 20 mg/m² on Day 1 and Day 2 in Cycle 1 and then escalated to 56 mg/m² on Days 8, 9, 15, and 16 of Cycle 1 and Days 1, 2, 8, 9, 15, and 16 for subsequent cycles. The carfilzomib infusion should follow the isatuximab infusion and should begin just after the end of the isatuximab infusion. Patients with a body surface area (BSA) >2.2 m² will use 2.2 m² for the determination of carfilzomib dose. Hydration is required for the first cycle and left to the Investigator's judgment for further administrations. Premedication will include dexamethasone. Anti-viral prophylaxis will be done according to site's/Investigator's practice. Dose modifications will be applied in case of toxicity.
Investigational medicinal product	**Dexamethasone**
Formulation:	The drug product is presented as 4 mg tablets; and 3.3 mg/mL for IV injection (8.3 mg/mL in the United States).

Routes of administration:	IV/orally (PO)
Dose regimen:	Dexamethasone will be given at 20 mg for patients on Days 1, 2, 8, 9, 15, 16, 22, and 23 in a 28-day cycle. Patients will be asked to maintain a diary to record the doses of dexamethasone PO to document all oral administrations. Dexamethasone will be administered IV on the days of isatuximab and/or carfilzomib infusions, and PO on the other days. Dose modifications will be applied in case of toxicity. Dexamethasone will have also intent of premedication for infusion acute reaction related to both isatuximab and carfilzomib.
Non-investigational medicinal products (premedication)	
Product:	**Acetaminophen or paracetamol**
Route of administration:	PO
Dose regimen:	Acetaminophen or paracetamol will be given 650 to 1000 mg 15 to 30 minutes (but no longer than 60 minutes) before isatuximab infusion.
Product:	**Ranitidine or equivalent** (other approved H2 antagonists [eg, cimetidine] or oral proton pump inhibitors [eg, omeprazole, esomeprazole]).
Route of administration:	IV
Dose regimen:	Ranitidine or equivalent will be given 50 mg 15 to 30 minutes (but no longer than 60 minutes) before isatuximab infusion.
Product:	**Diphenhydramine or equivalent** (eg, cetirizine, promethazine, or dexchlorpheniramine, according to local approval and availability). Intravenous route is preferred for at least the first 4 infusions.
Route of administration:	IV
Dose regimen:	Diphenhydramine or equivalent will be given 25 to 50 mg 15 to 30 minutes (but no longer than 60 minutes) before isatuximab infusion.
ENDPOINTS	**Primary endpoint:** The primary endpoint is PFS, defined as the time from the date of randomization to the date of first documentation of progressive disease (PD) (as determined by the Independent Response Committee [IRC]) or the date of death from any cause, whichever comes first. Response will be determined according to IMWG criteria. Progression based on paraprotein will be confirmed based on 2 consecutive assessments. **Secondary endpoints:** The key secondary efficacy endpoints are: • **ORR:** Defined as the proportion of patients with stringent complete response (sCR), CR, VGPR, and partial response (PR) as best overall response assessed by IRC using the IMWG response criteria. • **Rate of VGPR or better**: Defined as the proportion of patients with sCR, CR, and VGPR. • **Rate of VGPR or better with MRD negativity:** Defined as the proportion of patients for whom MRD assessed by sequencing is negative at any time after first dose of study treatment. Minimal residual disease will be assessed centrally by next-generation sequencing in BM aspiration samples from patients who achieve VGPR or better, to determine the depth of response at the molecular level. Threshold for negativity will be at least 10^{-5}. • **CR rate**: Defined as the proportion of patients with sCR and CR.

	• **OS:** Defined as the time from the date of randomization to death from any cause. The other secondary efficacy endpoints are: • **DOR:** Defined as the time from the date of the first IRC determined response for patients achieving PR or better to the date of first documented PD determined by IRC or death, whichever happens first. • **TTP:** Defined as time from randomization to the date of first documentation of PD (as determined by the IRC). • **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. • **Time to first response:** 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:** 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. **Safety evaluation:** The secondary safety endpoints are: • Treatment-emergent adverse events (TEAEs)/serious adverse events (SAEs). Treatment-emergent AEs are defined as 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. • Infusion associated reactions (IARs). • Laboratory parameters. • Vital signs and electrocardiogram (ECG). • Findings from physical examination. Adverse events and laboratory parameters will be graded using NCI-CTCAE v4.03.
	PK evaluation: The PK evaluation of isatuximab will be performed in all patients in the IKd arm. Among them, approximately 12 patients will be sampled for carfilzomib PK evaluation. Isatuximab: • Blood samples will be collected up to Cycle 10 from all patients treated with isatuximab using a sparse sampling strategy in order to assess the PK profile of isatuximab using population PK approach. This analysis will involve an estimation of inter-patient PK variability, the population PK parameters estimates, and the assessment of carfilzomib and pathophysiologic covariate effects on the main PK parameters. Empirical Bayesian estimation of individual parameters and of individual exposure will also be performed. Carfilzomib: • Blood samples will be collected at selected time points in a subset of 12 patients in the IKd arm at Cycle 1 Day 15. The following PK parameters will be estimated by non-compartmental analysis: • C_{eoi}, C_{max}, t_{max}, C_{last}, t_{last}, C_{trough}, AUC_{last} and AUC.

	Anti-drug antibodies (ADA): • Presence of isatuximab ADA in the IKd arm will be assessed in all patients up to Cycle 10. If ADA positive or inconclusive at Cycle 10, one additional sampling time for ADA evaluation will be collected 3 months later. No further ADA will be sampled, even if this 3-month sample is positive. **HRQL:** • Health-related quality of life will be assessed using the European Organisation 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 state utility and health status will be assessed using the European Quality of Life Group questionnaire with 5 dimensions and 5 levels per dimension (EQ-5D-5L). **Exploratory endpoints:** • Pharmacokinetic estimates will be investigated as prognostic factors for clinical outcome including safety and efficacy endpoints if possible. • Blood sample will be collected and analyzed for immune genetic determinants such as Fcγ receptor polymorphism and correlated with efficacy endpoints, including ORR, DOR, PFS, and OS. • In addition to the cytogenetic abnormalities assessed by FISH at baseline to determine R-ISS, other cytogenetic abnormalities such as but not limited to del(1p) and gain(1q) will be assessed and correlated with parameters of clinical response. • M protein measurement without isatuximab interference and impact on BOR will be assessed. Blood sample will be collected up to Cycle 30 for all patients in isatuximab arm. After Cycle 30, blood sample will be collected until disease progression only for patients who reach at least VGPR at this cycle.
ASSESSMENT SCHEDULE	The following evaluations will be performed at Screening/Baseline only: • Demographic characteristics and medical/surgical history. • Prior MM history (diagnosis, stage at diagnosis and at study entry, and prior anti-MM therapies). • Cardiac ultrasonography (multigated acquisition (MUGA) scan or MRI are accepted). • Serum β2-microglobulin. • Molecular analysis on BM samples (FISH for high risk cytogenetics [central laboratory]). The following laboratory assessments will be performed before study treatment initiation: • Blood typing: Complete blood phenotyping if not already available and antibody screening (indirect Coombs test or indirect antiglobulin test) in the IKd arm only (local laboratory). Indirect Coombs test will be repeated once after study treatment initiation. • Immune genetic determinants, such as Fcγ receptor polymorphism, will be performed prior to study treatment administration (central laboratory).

	Safety evaluation will be performed during the treatment period and will include the following: • Serum or urine pregnancy test at Screening/Baseline, before each cycle, at end of treatment (EOT), and monthly during follow-up up to the end of contraception period. • Vital signs and physical examination. • ECOG PS. • AE evaluation. Severity grade will be determined according to the NCI-CTCAE v4.03. • Concomitant medications. • Laboratory tests (including coagulation urine analysis at baseline and then if clinically indicated). • ECG. • Presence of ADA in the IKd arm will be assessed in all patients up to Cycle 10. If ADA positive or inconclusive at Cycle 10, one additional sampling time for ADA evaluation will be collected 3 months later. No further ADA will be sampled, even if this 3-month sample is positive. • Hepatitis B virus (HBV) serology in patients with unknown HBV status. The following disease assessment procedures will be performed at Screening (for eligibility) and again at Cycle 1 Day 1 prior to study treatment administration, Day 1 of every cycle during treatment up to progression, and at EOT: • M protein quantification (serum and 24-hour urine, protein immunoelectrophoresis, and immunofixation [IF]) (central laboratory). An additional sample (serum) will be collected for patients in the IKd arm to evaluate the potential isatuximab interference with the M protein assessment in immunoelectrophoresis and IF assays. This additional sample will be collected at all time points at which M protein is collected up to Cycle 30. After Cycle 30, this sample will be collected only for patients who reach at least VGPR at this cycle until disease progression. In case of isatuximab is stopped before progression, sample interference assay will be collected up to 3 months or when PD is observed, whichever comes first. • Free light chains quantification (central laboratory). • Quantitative immunoglobulins (central laboratory). • For patients who discontinue study treatment for reasons other than disease progression, serum M protein, urine M protein, and serum FLCs are to be performed every 4 weeks (central laboratory) during the follow-up period until progression even if further anti-myeloma therapy is started before PD is diagnosed. Other examinations for disease assessment include: • Bone marrow aspiration for plasma cell infiltration assessment (local laboratory) at baseline and then in case of VGPR and/or to confirm CR or as clinically indicated. **In case of VGPR**, plasma cell infiltration assessment is mandatory for patients in IKd arm with residual serum M protein of Ig G ≤0.5 g/dL and/or residual kappa IF positivity in urine, due to potential interference between isatuximab and M protein. **In case of CR on M protein**, plasma cell infiltration assessment is mandatory in IKd arm and in Kd arm, unless a previous assessment was made within 3 months and showed plasma cells ≤ 5%. Bone marrow biopsy can be done for stringent CR (sCR) assessment as per investigator decision.

	• Bone marrow aspiration for MRD assessment at baseline and in case of VGPR or better (central laboratory). If the patient presents ≥VGPR but is determined MRD positive, another BM sample will be collected 3 months (3 cycles) later, in order to identify late negativity. A third sample may be collected after another 3 months if the patient remains MRD positive and is still being treated. If a patient becomes CR after a third BM sample MRD positive performed during VGPR, up to 3 additional BM samples will be collected after CR. Therefore, a maximum of 6 BMA could be performed by patient (no more than 3 per category of response). However, because BMA is invasive procedure, the following guidance is given in the purpose to limit as much as possible the number of BMA **For patients with CR without previous documentation of VGPR**, first bone marrow for MRD assessment will be collected at time of confirmation of CR (ie, at the second time point showing CR). If patient is determined MRD positive, another BM sample will be collected 3 months (3 cycles) later, in order to identify late negativity. A third sample may be collected after another 3 months if the patient remains MRD positive and is still being treated. • For patients with VGPR: - First bone marrow will be collected when VGPR is confirmed at the second time point or at a later time point as per investigator judgement based on kinetic of M protein decrease and/or if a plateau phase is reached (plateau is defined as variation less than 20% over 12 weeks). - If MRD is positive on first BMA, a second BMA will be collected 3 months later (3 cycles) to identify late negativity. - In case of MRD is still positive on second BMA made while patient is in VGPR, the timing to perform the third BMA can be postponed until CR achievement. - In case of the patient becomes CR and patient was MRD positive on the last BMA performed during VGPR, a BMA will be done for MRD assessment at time of confirmation of CR. - After the first BMA during CR is done and in case patient was MRD positive on this BMA, the additional BMA planned by the protocol can be discussed with the patient. • Radiological disease assessment. • Skeletal survey or whole-body low-dose computed tomography (WBLDCT) scan at baseline, then once a year and anytime during the study if clinically indicated. • Plasmacytoma assessment. • If known extramedullary disease at baseline, CT scan or magnetic resonance imaging (MRI) is to be done at baseline, every 12 weeks (±1 week) until PD (even for patients who would initiate further anti-myeloma therapy without PD) and if clinically indicated. • If suspected extramedullary disease (plasmacytoma) at baseline, CT scan or MRI is to be done at baseline. In case of confirmation of existing plasmacytoma, CT or MRI will be repeated every 12 weeks (±1 week) until PD (even for patients who would initiate further anti-myeloma therapy without PD) and if clinically indicated. • CT scan or MRI to be done in case of suspicion of progression or if clinically indicated in a patient with no previous positive image for extramedullary disease.

	Note: For bone lesion or extramedullary disease assessment, the same modality should be used throughout the study for each individual patient. All imaging must be sent for central review. Carfizomib PK will be assessed on D15 cycle 1 in approximately 12 patients. Further anti-myeloma therapies, best overall response and date of progression on further anti myeloma therapies according to Investigator's assessment and survival status will be collected at every 3 months follow-up visit. In case of initiation of first further anti-myeloma therapy without PD, disease assessment will continue to be performed monthly as done during study treatment up to PD and then follow-up done as described just above. **HRQL** will be assessed electronically on Day 1 prior to first study treatment administration, on Day 1 of each cycle throughout the study treatment period, at EOT 30 ±5 days after last study treatment administration (or before further anti myeloma therapy whichever comes first), and 90 days after last study treatment administration (first or second FU visit in case of study treatment due discontinuation due to PD or without PD, respectively). The PK samples will be collected from all patients receiving isatuximab using a sparse sampling strategy (central laboratory) up to Cycle 10 (stopped at Cycle 11). For all alive patients at the implementation of amended protocol #10, survival status will be collected approximately twice a year, until death, or OS analysis cut-off date, whichever comes first. Patients still on treatment at the implementation of amended protocol #10 or OS analysis cut-off date and benefitting from the study treatment can continue the study treatment until disease progression, unacceptable AEs, patient wish to discontinue further study treatment, or any other reasons. For cycles completed after the cut-off dates, all SAEs (related or not) and all related non-serious AEs ongoing at the cut-off date, and then all new related AEs (serious or not) occurred post cut-off date, IP administration, and reason of end of treatment (EOT) will continue to be collected. If last ADA before cut-off date is positive or inconclusive, one additional sampling time for ADA evaluation should be collected 3 months later. No further ADA will be sampled, even if this 3-month sample is positive.
STATISTICAL CONSIDERATIONS	**Sample size determination:** A total of 159 PFS events will be needed to detect a hazard ratio of 0.59 using a log rank test at the 1-sided level of 0.025 and a 90% power. Assuming proportional hazards and based on an anticipated median PFS time of 19-months in the Kd arm; this is expected to correspond to a median PFS of 32-months in the IKd arm. In addition, with a total of 300 patients (180 patients in IKd arm and 120 patients in Kd arm) and assuming a uniform accrual rate of 19 patients per month, the cut-off date for the final analysis of PFS is expected to be approximately 36 months after first patient in. **Main analysis populations:** Intent-to-treat (ITT) population: This population will include all patients who have given their informed consent and for whom there is a confirmation of successful allocation of a randomization number by the IRT. This population is the primary population for all efficacy parameters. All analyses using this population will be based on the treatment assigned at randomization.

	Primary analysis: Primary analysis will consist of PFS comparison between the IKd arm versus the Kd arm through a log-rank test procedure stratified by stratification factors as entered in the IRT. The significance levels at the interim and final analyses will be determined using alpha-spending function (see below). The analysis of PFS will be based on the following censoring rules: • If progression and death are not observed before the analysis cut-off date or the date of initiation of further anti-myeloma treatment, 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. • A patient without an event (death or disease progression) and without any valid post-baseline disease assessments will be censored at the day of randomization (Day 1). The cut-off date for the final analysis of PFS will be the date when the 159th PFS event assessed by the IRC has been observed. The estimates of the hazard ratio and corresponding (1-2α)% (α being the one-sided nominal significance level: α=0.023 at final analysis and 0.005 at PFS interim analysis) confidence intervals (CI) will be provided using the Cox proportional hazard model stratified by stratification factors as entered in the IRT. The median PFS and probabilities of being progression free at different time points calculated using the Kaplan-Meier methods as well as corresponding CI will be presented by treatment arm. The Kaplan-Meier PFS curves will also be presented. Sensitivity analyses of PFS will be performed (eg, different censoring rules and PFS assessed by the Investigator). Subgroup analyses of PFS (eg, by high risk status, number of prior lines of treatment) will also be conducted. **Analysis of key secondary efficacy endpoints:** Key secondary endpoints other than OS will be analyzed at the time of the primary and/or the final analysis of PFS. The CR rate will only be tested for comparison when the antibody-capture interference assay will be available. Key secondary endpoints other than OS will be summarized with descriptive statistics per treatment arm. They will be compared between treatment arms using Cochran Mantel Haenszel stratified method. The (1-2α) % 2-sided CI will be also computed for these endpoints using the Clopper-Pearson method. The OS analysis will be similar to what is described for PFS and will be performed approximately 3 years after the primary PFS analysis cut-off date. It will be based on the following censoring rules: patients without death prior to the OS analysis cut-off date will be censored at the last date the patient was known to be alive or the OS analysis cut-off date, whichever comes first. **Analysis of other secondary efficacy endpoints:** Other secondary endpoints will be analyzed at the time of the primary and/or the final analysis of PFS. The analyses of TTP, PFS2, DOR, time to first response and time to best response will be similar to what is described for PFS and will be based on the following censoring rules: • **TTP:** If progression is not observed before the PFS analysis cut-off date or the date of initiation of further anti-myeloma treatment, TTP 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.

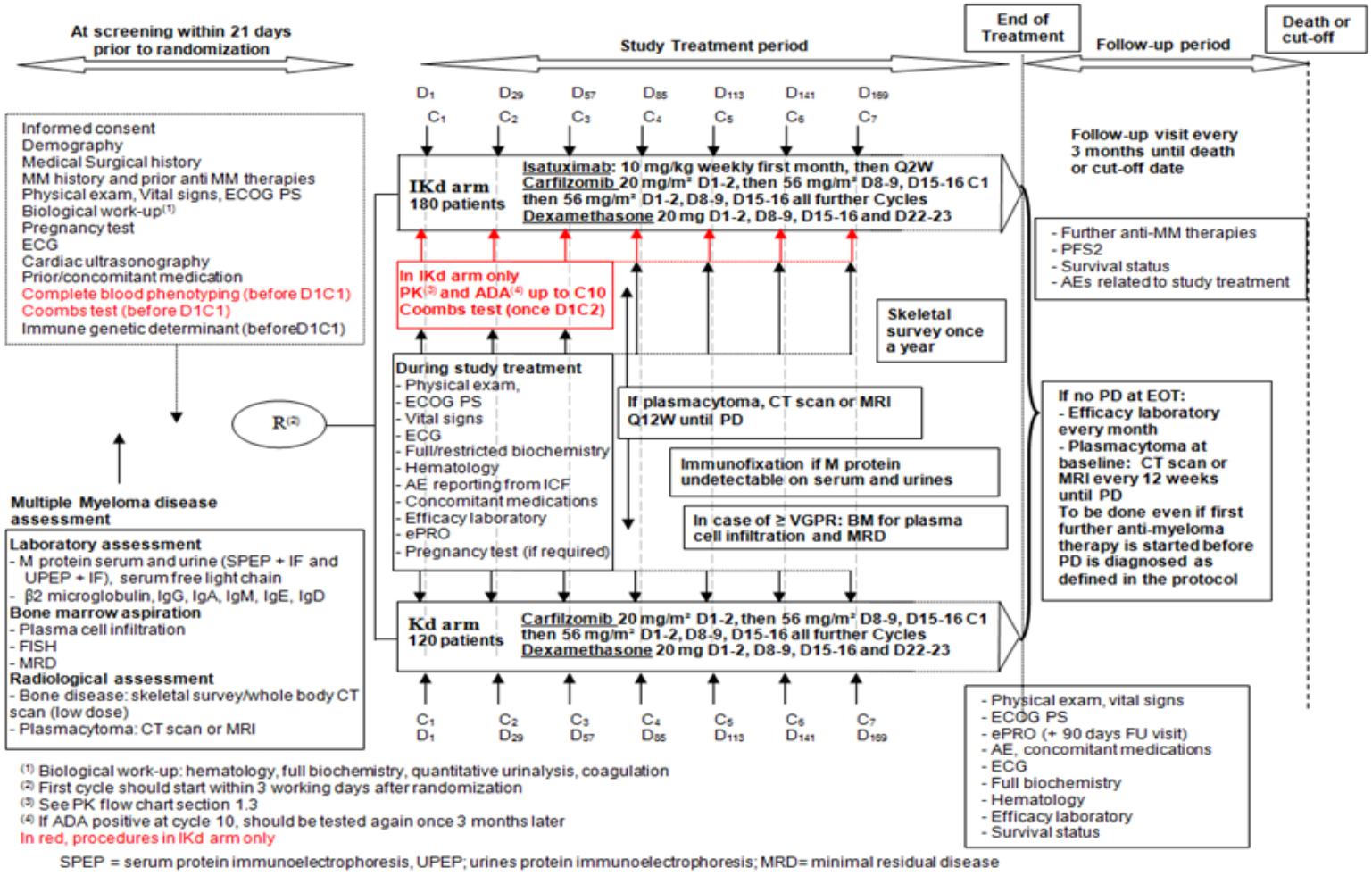
	• **PFS2:** For patients alive without a progression after initiation of further anti-myeloma treatment before the PFS analysis cut-off date, PFS2 will be censored at the date of the last follow-up visit not showing disease progression after initiation of further anti-myeloma treatment or the analysis cut-off date, whichever comes first. • **DOR:** In the absence of the confirmation of subsequent disease progression or death before the analysis cut-off date, the DOR will be censored at the date of the last valid disease assessment not showing disease progression performed prior to initiation of a further anti-myeloma treatment or the analysis cut-off date, whichever is earlier. • **Time to first response:** in the absence of response, patients will be censored at the earliest of the date of the last valid disease assessment before disease progression or death, the date of the last valid disease assessment before initiation of a further anti-myeloma treatment (if any) or the analysis cut-off date, whichever comes first. • **Time to best response:** The same censoring rules as time to first response will be used. **Multiplicity issues:** Hypothesis testing of the key secondary efficacy endpoints will be performed using a closed test procedure. The hierarchical procedure will follow the order of the list of key secondary objectives. **Analysis of safety endpoints:** Number (%) of patients experiencing TEAEs by primary system organ class and preferred term will be summarized by NCI-CTCAE v4.03 grade (all grades and Grade ≥3) for the safety population. The same summaries will be prepared for treatment-related TEAEs, TEAEs leading to premature/definitive discontinuation, TEAEs leading to dose modification, serious TEAEs, and TEAEs with fatal outcome. For patients with multiple occurrences of the same AE within treatment period, the worst grade will be used. Hematology and biochemistry results will be graded according to NCI-CTCAE v4.03, when applicable. Number (%) of patients with laboratory abnormalities (ie, all grades and by grade) using the worst grade during the treatment period will be provided for the safety population. **Analysis of HRQL endpoints:** Compliance rates (%) for completion of the EORTC QLQ-C30, QLQ-MY20, and EQ-5D-5L at each time point will be calculated via number of received assessments divided by number of expected assessments. Changes in health state utility (EQ-5D-5L) values and health status between treatment arms will be assessed by analyzing change scores from Day 1 of each cycle to EOT and 90 days after last study treatment administration. **Interim analysis:** An interim analysis for efficacy assessment of PFS is planned when 65% of the 159 PFS events have been observed. An O'Brien and Fleming α-spending function will be used to obtain the nominal significance levels for the interim and final analyses of survival. The 1-sided nominal significance level to terminate the study for efficacy at 65% information fraction (103 PFS events) is 0.005 (corresponding to a hazard ratio [HR] of 0.6). The 1-sided nominal significance level to declare superiority of IKd at the final analysis (159 events) is 0.023 (corresponding to a HR of 0.725). For key secondary efficacy endpoints, the significance levels for the interim and final analyses will be determined using alpha-spending function specific to each endpoint except if the information fraction is 100% at the interim analysis of PFS (ie, information on secondary endpoints available for every patient).

	Planned PFS and OS cut-off dates: Estimated cut-off dates will be approximately 24 months and 36 months after first patient in (FPI) for the interim PFS analysis and for the final PFS analysis, respectively. The cut-off date for analysis of OS will be 3 years after the primary PFS analysis cut-off date. The primary PFS analysis corresponds either to the positive interim PFS analysis or the final PFS analysis.
DURATION OF STUDY PERIOD (per patient)	The duration of the study for a patient will include a period for screening of up to 3 weeks. The cycle duration is 28 days. Patients will be treated until disease progression, unacceptable AE, or patient decision to stop the study treatment. After study treatment discontinuation, patients will return to the study site 30 days after the last dose of study treatment or before further anti myeloma therapy whichever comes first for EOT assessments, and 90 days after the last dose of study treatment for HRQL questionnaires. Patients who discontinue the study treatment due to PD will be followed every 3 months (12 weeks) for HRQL at first FU visit (90 days after last study treatment), further anti-myeloma therapies, second primary malignancies, PFS2 and survival until death or the implementation of amended protocol #10, whichever comes first. Patients who discontinue the study treatment prior to documentation of PD will be followed-up every 4 weeks until disease progression (even for patients who would initiate further anti-myeloma therapy without PD) and HRQL 90 days after last study treatment, and then after confirmation of disease progression, every 3 months (12 weeks) for further anti-myeloma therapies, second primary malignancies, PFS2 and survival, until death or the implementation of amended protocol #10, whichever comes first. For all alive patients in follow-up at the implementation of amended protocol #10, survival status will be collected twice a year until death, or OS analysis cut-off date, whichever comes first. If a patient is still on treatment at the implementation of amended protocol #10 or OS analysis cut-off date and benefitting from the study treatment, the patient can continue the study treatment until disease progression, unacceptable AEs, patient wish to discontinue further study treatment, or any other reason.

1 FLOW CHARTS

The sponsor collects only those data that are strictly relevant and necessary in view of the objectives of the research.

1.1 GRAPHICAL STUDY DESIGN



1.2 STUDY FLOW CHART

Evaluation[a]		Screening/ Baseline	Cycle 1[c]				Subsequent Cycles[c]				End of Treatment (EOT)	Follow-up Period
		Day -21 to 1	D1, D2	D8, D9	D15, D16	D22, D23	D1, D2	D8, D9	D15, D16	D22, D23	30 days after last study treatment administration[cc]	Every 3 months after last study treatment administration[dd]
Informed Consent[a], Inclusion/Exclusion Criteria		X										
Randomization[b]		X										
Demography, Medical/Surgical History[d]		X										
Prior anti-myeloma treatment and Myeloma history[e]		X										
Physical examination[f]		X	X	X	X	X	X				X	
Vital signs[g]		X	X	X	X	X	X	X	X		X	
Cardiac Ultrasonography[h]		X										
12-Lead ECG[h]		X	X[h]				X				X	
ECOG PS		X	X				X				X	
LOCAL LAB Assessments	Pregnancy test[i]	X	X[i]				X				X	X[i]
	Hematology[j]	X	X	X	X	X	X		X		X	
	Blood chemistry[k]	X	X[k]	X[k]	X[k]	X[k]	X[k]	X[k]	X[k]		X	
	Complete blood phenotyping (IKd arm only)[l]	X					X[l]					
	Coagulation[m]	X	As clinically indicated								As clinically indicated	
	Urinalysis[n]	X	As clinically indicated								As clinically indicated	
	Serum β2-microglobulin[o]	X										
	Hepatitis B virus serology		Once at any time if HBV status unknown before treatment started and to be repeated if clinically indicated (see Section 8.2.7)									

Evaluation[a]		Screening/ Baseline	Cycle 1[c]				Subsequent Cycles[c]				End of Treatment (EOT)	Follow-up Period
		Day -21 to 1	D1, D2	D8, D9	D15, D16	D22, D23	D1, D2	D8, D9	D15, D16	D22, D23	30 days after last study treatment administration[cc]	Every 3 months after last study treatment administration[dd]
CENTRAL LAB Assessments[p]	IKd arm only:											
	PK[q]		See PK flow chart Section 1.3									
	ADA[r]		X				X					
	Exploratory (both arms):											
	Immune genetic determinants (blood)[t]		X									
	Disease assessment labs:											
	Serum M protein[u] Immunoelectrophoresis and Immunofixation (IF)	X	X				X				X	If EOT without PD disease assessment as during study treatment up to PD[dd]
	Urine M protein (24-hour urine)[u] Immunoelectrophoresis and IF	X	X				X				X	If EOT without PD disease assessment as during study treatment up to PD[dd]
	Serum Free light chains[u]	X	X				X				X	If EOT without PD disease assessment as during study treatment up to PD[dd]
	Immunoglobulins: IgG, IgA, IgM, IgD, IgE[u]	X	X				X				X	If EOT without PD disease assessment as during study treatment up to PD[dd]

Evaluation[a]		Screening/ Baseline	Cycle 1[c]				Subsequent Cycles[c]				End of Treatment (EOT)	Follow-up Period
		Day -21 to 1	D1, D2	D8, D9	D15, D16	D22, D23	D1, D2	D8, D9	D15, D16	D22, D23	30 days after last study treatment administration[cc]	Every 3 months after last study treatment administration[dd]
Other Disease assessments												
Bone Marrow for disease assessment[s]:												
FISH (aspirate)[s]		X										
MRD assessment (aspirate)[s]		X	In case of VGPR or better								As clinically indicated	
Bone disease involvement (plasma cell infiltration)		X	In case of VGPR or better and as clinically indicated								As clinically indicated	
Radiological disease assessment:												
Skeletal survey[v]		X	Once a year and if clinically indicated								As clinically indicated	
Extramedullary disease (plasmacytoma) (CT scan or MRI)[v]		X	If present at baseline every 12 weeks, and if clinically indicated[v]								As clinically indicated	If EOT without PD disease assessment as during study treatment up to PD[dd]
Electronic HRQL[w]	QLQ-C30		X				X				X	X (90 days only)
	QLQ-MY20		X				X				X	X (90 days only)
	EQ-5D-5L		X				X				X	X (90 days only)
Study Treatments[x]:												
Isatuximab (IKd arm only)			D1, D8, D15, D22				D1, D15					
Carfilzomib			D1, D2, D8, D9, D15, D16									
Dexamethasone (IV/PO)[y]			D1, D2, D8, D9, D15, D16, D22, D23									
AE Assessment[z]		X	Continuously throughout study period								X	X (related AEs, all SAEs)
Prior/Concomitant Medication[aa]		X	Continuously throughout study period								X	
Further anti-myeloma therapy[bb]												X
Survival status												X

a **Evaluation**: Assessments to be performed prior to study treatment administration and prior to any premedication arm unless otherwise indicated. Inform consent should be signed before any study specific procedures. It can be signed more than 21 days prior to randomization. Screening time indicates in which time frame exams used to support eligibility have to be done prior to randomization.

b **Randomization**: To take place once the consented patient has completed all the necessary screening procedures and is deemed eligible (based on myeloma-specific results from the central laboratory [see footnote u]) and hematology/biochemistry local laboratory results) for study entry by the Investigator or designee. All eligible patients must be randomized using Interactive Response Technology (IRT). Every effort should be made to start treatment within 3 working days of randomization.

c **Cycle:** A cycle duration is 28 days. Day 1 of Cycle 1 refers to the day the patient receives the first study treatment administration. Day 1 of each subsequent cycle corresponds to Day 29 of the previous cycle. The time window for Days 8, 9, 15, 16, 22, and 23 is ±1 day; any delay above this time window or any omission due to AEs will be documented in the electronic case report form (eCRF).

d **Demography**: Includes age, gender, and race. Medical/Surgical History, other than MM, includes relevant history of previous/associated pathologies including respiratory function history (smoking status will be collected).

e **Prior anti-myeloma treatment and myeloma history**: Includes date of initial diagnosis of symptomatic MM, stage of the disease at diagnosis and at study entry, type of disease at diagnosis and at study entry (heavy and light chain component), and previous anti-myeloma therapy (transplant if any, drug name, start and stop dates, intent, date of progression, best response, and reason for discontinuation).

f **Physical Examination**: To be performed at screening (≤7 days prior to randomization), prior to study treatment administration on Days 1, 8, 15, and 22 of Cycle 1, and then on Day 1 of each subsequent cycle, and at the EOT visit. Consists of examination of major body systems including neurological, digestive, respiratory (signs and symptoms, respiratory rate), hepatic and spleen span, and lymph node examinations, plus weight and height (height at baseline only). Only the main diagnoses will be reported in the eCRF as AEs or medical history. Signs and symptoms related to MM ongoing at baseline will be recorded in the patient's medical history and will be reported in the AE page in case they worsen or become serious during study treatment. Laboratory abnormalities at baseline will be recorded in the laboratory pages.

g **Vital Signs**: Blood pressure, heart rate, temperature, and respiration rate will be recorded at screening, on Days 1, 2, 8, 9, 15, and 16 of Cycle 1 in both arms, and on Day 22 of Cycle 1 in IKd arm. For each subsequent cycle, vital signs are to be measured on Days 1, 2, 8, 9, 15, and 16 in both arms. In addition, in the IKd arm, vital signs are to be taken just before starting infusion, 1 hour after starting infusion, and at EOI on Days 1, 8, 15, and 22 of Cycle 1, Days 1 and 15 of each subsequent cycle up to Cycle 4, and as clinically indicated. The final measurements will be performed at the EOT visit in both arms.

h **Cardiac ultrasonography and 12-Lead ECG**: Cardiac ultrasonography (MUGA scan or MRI are accepted) to be performed at screening; 12-Lead ECG to be performed at screening and repeated within 1 day prior to Cycle 1 Day 1 if screening test >7 days of Day 1 Cycle 1, within 1 day prior each cycle administration, at EOT, and as clinically indicated.

i **Pregnancy tests (serum or urine) for WOCBP** to be performed prior to randomization (should be within 7 days prior to first study treatment administration), within 1 day before each cycle initiation, at EOT visit, and monthly during follow-up (up to 3 months in the Kd arm and up to 5 months in the Ikd arm). It can be performed at home during the follow-up period..

j **Hematology**: To be performed at screening and repeated within 1 day prior to Cycle 1 Day 1 if screening test >7 days of Day 1 Cycle 1, on Days 8, 15, and 22 of Cycle 1, on Days 1 and 15 of every subsequent cycle, at the EOT visit, and as clinically indicated. Hematology includes hemoglobin, hematocrit, red blood cells (RBC), white blood cells (WBC) with differential and platelet count. In the event of Grade 4 neutropenia, ANC is assessed every 2 to 3 days until ANC ≥0.5 x 10^9/L and at least weekly thereafter until ANC ≥1.0 x 10^9/L (test to be done prior to study treatment administration). Hematological abnormalities will be recorded as AEs only if they are serious or lead to study treatment modification or discontinuation.

k **Blood Chemistry**: Full blood biochemistry (see below) to be performed at screening and repeated within 1 day prior to Cycle 1 Day 1 if screening test >7 days of Day 1 Cycle 1. Full biochemistry will be performed prior to study treatment administration on Days 1, 8, 15, and 22 at Cycle 1, and on Day 1 for subsequent cycles. Restricted biochemistry (see below) will be performed on Days 2, 9, and 16 at Cycle 1, and then on Days 8 and 15 at Cycle 2, and then on Day 15 for subsequent cycles. Full biochemistry will be performed at the EOT visit and as clinically indicated throughout the study treatment.
Full biochemistry/blood chemistry includes AST, ALT, bilirubin (total and direct), alkaline phosphatase, LDH, sodium, potassium, chloride, bicarbonate or carbon dioxide (venous) (if bicarbonate or carbon dioxide are assessed only on arterial blood at site level, to be done only if clinically indicated), calcium, corrected serum calcium, magnesium, phosphate, uric acid, serum creatinine and estimated creatinine clearance (MDRD Formula), urea or blood urea nitrogen (BUN), fasting glucose (according to site guidelines), albumin, and total protein. Biochemistry abnormalities will be recorded as AEs only if they are serious or lead to study treatment modification or discontinuation. Restricted biochemistry includes sodium, potassium, chloride, bicarbonate/carbon dioxide, urea or BUN, serum creatinine, and estimated creatinine clearance (MDRD Formula).

l **Blood typing** (A, B, O, and Rh), **complete blood phenotyping** (C,c; E,e; Kell. Kidd; Duffy; S,s is recommended, if not available follow site's standard), and **antibody screening** (Indirect Coombs Test, Indirect Antiglobulin Test) in IKd arm only to be drawn after randomization and prior first study treatment administration if not already available. The blood type card will be kept by the patient with the study card.
Blood transfusions are to be recorded in the eCRF. The blood bank needs to be informed that the patient is receiving a treatment with an anti-CD38 and a potential interference with the Coombs test is possible.
Indirect Coombs test will be repeated once after study treatment initiation (on Day 1 at Cycle 2 or on Day 1 of a later cycle if not done at Cycle 2).

m **Coagulation**: To be performed at screening and then as clinically indicated. Coagulation includes prothrombin time or international normalized ratio, and activated partial thromboplastin time.

n **Urinalysis**: To be performed at screening and as clinically indicated. Quantitative or semi quantitative (according to site practice and if semi-quantitative method can provide with an absolute numeric value of the parameters) urinalysis (ie, RBCs, protein, glucose, pH, ketones, bilirubin, and leucocytes) at baseline and qualitative (dipstick; ie, blood, protein, glucose, pH, ketones, bilirubin, and leucocytes).

o **Serum β2-microglobulin**: To be performed at screening.

p **Central Labs**: Refer to laboratory manual for sample collection and shipping information.

q **Pharmacokinetics (PK)**: Refer to Pharmacokinetics/Pharmacodynamics Flow Chart in Section 1.3.

r **ADA** (IKd arm only): To be performed on Day 1 of every cycle prior to each isatuximab administration up to Cycle 10. If the test is positive or inconclusive at Cycle 10, additional ADA samples will be done 3 months later. If isatuximab is stopped prior to carfilzomib and dexamethasone administration, ADA will be tested 3 months later.

s **Bone marrow aspirate**:

- At screening: Bone marrow aspirate (BMA) will be collected for FISH (including, but may not be limited to, del(17p), t(4:14), t(14:16)), and MRD analyses in central laboratory. Central laboratory samples for FISH will be collected and analyzed for all patients, R-ISS used as stratification factor will be assessed with FISH central laboratory results. Central laboratory samples for MRD will be collected for all patients but will be analyzed only for patients who will reach VGPR or better. Bone marrow aspirate or core biopsy (as clinically indicated) will be collected for bone marrow involvement assessment (local laboratory). In case of randomization would be delayed due to unplanned event after BMA was done, BMA will not need to be done again if BMA remains within 8 weeks prior to randomization,
- During study treatment:
  For plasma cell infiltration assessment (local laboratory) in case of VGPR and/or to confirm CR or as clinically indicated. **In case of VGPR**, plasma cell infiltration assessment is mandatory for patients in IKd arm with residual serum M protein of Ig G ≤0.5 g/dL and/or residual kappa IF positivity in urine, due to potential interference between isatuximab and M protein. **In case of CR on M protein**, plasma cell infiltration assessment is mandatory in IKd arm and in Kd arm, unless a previous assessment was made within 3 months and showed plasma cells ≤5 %.
  Bone marrow biopsy can be done for stringent CR (sCR) assessment as per investigator decision.
  For MRD assessment in case of VGPR or better (central laboratory), and if MRD positive to be repeated 3 months later for late negativity (one additional sample can be collected if patient remains MRD positive at the second assessment). No more than 3 post-baseline samples are to be obtained unless a patient becomes CR after a third BM sample MRD positive performed during VGPR. In this case no more than 3 additional BM samples will be collected. Therefore a maximum of 6 BMA could be performed by patient (no more than 3 per category of response). However, because BMA is invasive procedure, the following guidance is given in the purpose to limit as much as possible the number of BMA.
  For patients with CR without previous documentation of VGPR, first bone marrow for MRD assessment will be collected at time of confirmation of CR (ie, at the second time point showing CR) If patient is determined MRD positive, another BM sample will be collected 3 months (3 cycles) later, in order to identify late negativity. A third sample may be collected after another 3 months if the patient remains MRD positive and is still being treated.
  For patients with VGPR:
  - First bone marrow will be collected when VGPR is confirmed at the second time point or at a later time point as per investigator judgement based on kinetic of M protein decrease and/or if a plateau phase is reached (plateau is defined as variation less than 20% over 12 weeks).
  - If MRD is positive on first BMA, a second BMA will be collected 3 months later (3 cycles) to identify late negativity.
  - In case of MRD is still positive on second BMA made while patient is in VGPR, the timing to perform the third BMA can be postponed until CR achievement.
  - In case of the patient becomes CR and patient was MRD positive on the last BMA performed during VGPR, a BMA will be done for MRD assessment at time of confirmation of CR.
  - After the first BMA during CR is done and in case patient was MRD positive on this BMA, the additional BMA planned by the protocol can be discussed with the patient.

t **Blood sample for immune genetic determinants** (such as Fcγ receptor polymorphism): To be performed on Cycle 1 Day 1 prior to study treatment administration (central laboratory).

u **Laboratory evaluation of disease assessment** (central laboratory for each planned and any unplanned time point): At screening, all laboratory assessments are to be performed within 21 days prior to randomization. Eligibility will be assessed based on central laboratory results. Results for central M protein must be available before the patient may be randomized.
All laboratory assessments to be performed **again** prior to first study treatment administration on Cycle 1 Day 1 and response evaluation will be calculated compared to Cycle 1 Day 1 assessments. In the IKd arm only, an additional blood sample will be collected at all time-points to evaluate the potential interference of isatuximab in the M protein assessment (central laboratory) up to Cycle 30. After Cycle 30, this sample will be collected only for patients who reach at least VGPR at this cycle until disease progression. In case of isatuximab is stopped before progression, sample interference assay will be collected up to 3 months or PD, whichever comes first.
Laboratory findings on Day 1 of every cycle will be used for response assessment, to confirm response, and to confirm disease progression. Efficacy analyses will be performed according to IRC assessment, which will use central laboratory data.

- Serum-Protein immunoelectrophoresis (SPEP) and IF: To be performed at screening and again at Cycle 1 Day 1 (-1 day) prior to study treatment administration, then at Day 1 (-1 day) of every subsequent cycle prior to study treatment administration, and at the EOT visit.

- Urine M protein (24-hour urine) immunoelectrophoresis (UPEP) and IF: To be performed at screening, Cycle 1 Day 1, Day 1 of every subsequent cycle prior to study treatment administration, and at the EOT visit. If urine M protein is negative at baseline and Cycle 1 Day 1, this assessment is to be repeated every 3 cycles only (Cycle 4, Cycle 7, Cycle 10, etc) to confirm CR on blood labs.
  After Cycle 1 Day 1, IF to be done if UPEP is negative in patients whose disease is evaluable in urine. The 24-hour urine collection should be completed prior new cycle initiation.
- Serum FLCs (quantification and ratio): To be performed at screening, Cycle 1 Day 1, Day 1 of every subsequent cycle, and at EOT.
- Immunoglobulins (IgG, IgA, IgM, IgD, and IgE): To be performed at screening, Cycle 1 Day 1, Day 1 of every subsequent cycle prior to study treatment administration, and at EOT (IgD or E only if the heavy chain component of the disease is known to be E or D).

For patients who discontinue study treatment for reasons other than disease progression, serum M protein, urine M protein, and serum FLCs to be performed monthly (central laboratory) during the follow-up period until progression (even for patients who would initiate further anti-myeloma therapy without PD).

In case of PD diagnosis made on laboratory criteria, this must be confirmed by 2 consecutive measures before to treatment discontinuation. Treatment should continue until confirmation of the PD.

v **Radiological assessment:**

Bone lytic disease assessment: Skeletal survey (including skull, spine, all long bones, pelvis, and chest) or low dose whole body CT scan (see Appendix M) at baseline (within 21 days prior to randomization), once a year, and anytime during the study if clinically indicated.

Extramedullary disease (plasmacytoma) assessment (including bone plasmacytoma):

- If known extramedullary disease at baseline, CT scan or MRI is to be done at baseline, repeated every 12 weeks (±1 week) until PD (even for patients who would initiate further anti-myeloma therapy without PD), and if clinically indicated.
- If suspected extramedullary disease (plasmacytoma) at baseline, CT or MRI is to be done at baseline and if plasmacytoma confirmed on the exam to be repeated every 12 weeks (±1 week) until PD (even for patients who would initiate further anti-myeloma therapy without PD) and if clinically indicated.
- To be done in case of suspicion of progression or if clinically indicated in a patient with no previous positive image for extramedullary disease.
- Note: For bone lesion assessment and extramedullary disease, the same modality (skeletal survey or low-dose whole body CT scan; CT scan or MRI) should be used throughout the study for each individual patient when radiological follow-up is needed. All imaging will be sent for central review. Intravenous contrast is recommended if not medically contra-indicated. Patients who have contra-indication to CT scan with IV contrast may have MRI exams performed instead.

w **ePRO (EORTC QLQ-C30, QLQ-MY20, and EQ-5D-5L)**: To be completed by the patient at the center prior to discussing their health/disease status, prior to study treatment administration or other study-related procedures on Day 1 of every cycle, at the EOT visit, and 90 days (±5 days) after last study treatment administration. The time estimated to complete the EORTC QLQ-C30 is approximately 10 to 15 minutes. The time estimated to complete the QLQ-MY20 and EQ-5D-5L is approximately 5 to 10 minutes.

x **Study treatments**: In both arms, carfilzomib will be given as a 30-minute infusion at a dose of 20 mg/m² Day 1 and Day 2 on Cycle 1 and then escalated to 56 mg/m² on Days 8, 9, 15, and 16 of Cycle 1 and Days 1, 2, 8, 9, 15, and 16 for subsequent cycles. The carfilzomib infusion should follow the isatuximab infusion and should begin just after the end of the isatuximab infusion. Dexamethasone will be given at 20 mg for patients on Days 1, 2, 8, 9, 15, 16, 22, and 23. Patients will be asked to maintain a diary to record the doses of dexamethasone PO to document all oral administration. In addition, in the IKd arm, isatuximab will be given at a dose of 10 mg/kg IV on Days 1, 8, 15, and 22 in the first cycle, then Days 1 and 15 in subsequent cycles (premedication will include acetaminophen or paracetamol, ranitidine or equivalent, and diphenhydramine or equivalent, in addition to dexamethasone).

y **Dexamethasone**: Oral dexamethasone will be recorded in patient diaries when not taken at the site level.

z **AE/SAE assessment**: All AEs, including AEs of new onset as well as worsening of baseline signs and symptoms are to be reported from the signing of the informed consent to 30 days following the last administration of study treatment. When diagnosis can be done, only main diagnosis (without its signs and symptoms) will be recorded as AE. After the 30-day follow-up, all ongoing related AEs, all ongoing SAEs whatever relationship with study treatment, all new related AEs whatever seriousness, and second primary malignancy are to be reported and followed up until resolution or stabilization. Severity will be graded according to NCI-CTCAE v4.03.

aa **Prior medications** (which are not prior anti-myeloma therapy) administered within 21 days prior to randomization will be collected. **Concomitant medications** to be collected from randomization to EOT.

bb **Further anti-myeloma treatments** will be collected: drug name, start and stop date, best overall response and date of PD.

cc **EOT**: EOT visit will be done 30 days after last study treatment administration or before further anti myeloma therapy initiation whichever comes first.

dd **Follow-up:**

Patients who discontinue study treatment due to PD: Follow-up visit will be done every 3 months from the date of last study treatment administration until death: AEs according to footnote [z], ePROs (at EOT and 90 days [±5 days] after last study treatment administration), further anti-myeloma therapies (up to OS cut-off date), and survival status will be collected. Every effort will be made to follow all patients. If survival follow-up is missed and is not obtained at the time of the scheduled interval, it should be retrieved immediately. For subsequent survival follow-up, the patient follow-up visit should be scheduled at the original scheduled survival follow-up interval. If the patient is unable to visit the clinical center, the follow-up may be done via phone from the Investigator or designee to the patient or the patient's caregiver or a family member, but this should be exception and any effort should be done to schedule follow-up visit at clinical center.

Patients who discontinue the study treatment without PD will be followed every month for laboratory disease assessment (central laboratory) and radiological assessment every 12 weeks (±1 week) in case of extramedullary disease (plasmacytoma) at baseline and once a year and as clinically indicated for bone lytic disease assessment (skeletal survey or whole body CT-scan) until confirmation of PD (even for patients who would initiate further anti-myeloma therapy without PD), BMA for plasma cell involvement and MRD assessment if appropriate, AEs according to footnote [z], further anti-myeloma therapy if any. In addition, ePROs will be assessed at EOT and 90 days [±5 days] after last study treatment administration. After PD, patients will be followed every 3 months as described above.

1.3 PHARMACOKINETIC/PHARMACODYNAMIC FLOW CHART

1.3.1 Cycle 1: IKd arm only (approximately 12 patients)

		Cycle 1														
Day within the cycle		**Day 1**			**Day 8**	**Day 15**									**Day 18**	**Day 22**
Time relative to isatuximab (decimal hours)		SOI	EOI	1h post EOI	SOI	SOI	EOI							4.5h post EOI	72h post EOI	SOI
Time window[a]		-10min	±10min	±10min	-10min										±5h	-10min
Time relative to carfilzomib (decimal hours)							SOI	EOI	5 mins post EOI	15 mins post EOI	30 mins post EOI	1h post EOI	2 h post EOI	4h post EOI		
Indicative clock time		8:00 AM	12:00 PM	1:00 PM	8:00 AM	8:00 AM	12:00 PM	12:30 PM	12:35 PM	12:45 PM	1:00 PM	1:30 PM	2:30 PM	4:30 PM	12:00 PM	8:00 AM
Treatment																
Isatuximab (IV infusion)		X			X	X										X
Carfilzomib (IV infusion)			X				X									
Pharmacokinetic[b]																
Isatuximab	RNT (hour)	0	4	5	0	0	4							8.5	76	0
	Sample ID	P00[c]	P01[d]	P02[e]	P03[c]	P04[c]	P05[d]							P06	P07	P08[c]
Carfilzomib	RNT (min/ hour)					0		30 min	35 min	45 min	60 min	1h 30 min	2h 30 min	4h 30 min		
	Sample ID					P00[c]		P01[d]	P02	P03	P04	P05	P06	P07		
Immunogenicity																
ADA (anti-drug antibody)[f]		AB00[c]														

a Time window permitted for PK/PDy and immunogenicity sampling. No time window are allowed on Cycle 1 Day 15 for the 12 patients with carfilzomib PK sampling.
b Refer to laboratory manual for sample collection, processing and shipping.
c Sample collected just (within 10 mins) and strictly before the start of isatuximab infusion (ie, after administration of the isatuximab premedications).
d Sample collected just before actual EOI.
e Sample collected 1 hour after the actual end of infusion.
f The sampling times for ADA detection can be modified based on the updated knowledge of isatuximab on immunogenicity.

1.3.2 Subsequent cycles: IKd arm only (approximately 12 patients) up to Cycle 10

		Cycle 2		Cycle 3	Cycle 4	Up to Cycle 10	3 months later
Day within the cycle		**Day 1**		**Day 1**	**Day 1**	**Day 1**	**±5 days after last ADA positive at cycle 10**
Time relative to isatuximab (decimal hours)		SOI	EOI	SOI	SOI	SOI	
Time window[a]		-10 mins	±10 mins	-10 mins	-10 mins	-10 mins	
Indicative clock time		8:00 AM	12:00 PM	8:00 AM	8:00 AM	8:00 AM	8:00 AM
Treatment							
Isatuximab (IV infusion)		X		X	X	X	
Carfilzomib (IV infusion)			X				
Pharmacokinetic[b]							
Isatuximab	RNT (hour)	0	4	0	0	0	
	sample ID	P00[c]	P01[d]	P00[c]	P00[c]	P00[c]	
Immunogenicity							
ADA (anti-drug antibody)[e]		AB00[c]		AB00[c]	AB00[c], [f]	AB00[c]	AB F00[f]

a Time window permitted for PK/PDy and immunogenicity sampling.

b Refer to laboratory manual for sample collection, processing and shipping.

c Sample collected just (within 10 mins) and strictly before the start of isatuximab infusion (ie, after administration of the isatuximab premedications).

d Sample collected just before actual EOI.

e The sampling times for ADA detection can be modified based on the updated knowledge of isatuximab on immunogenicity.

f At Cycle 10, if patient is positive or inconclusive for ADA, additional ADA will be collected 3 months later. No further ADA will be sampled, even if this 3-month sample is positive. If isatuximab is stopped prior to carfilzomib and dexamethasone, before Cycle 10 and last ADA is positive or inconclusive, ADA will be sampled 3 months later. No further ADA will be sampled, even if this 3-month sample is positive. For patients with less than 10 cycles at the cut-off date, both PK and ADA samples collection will be stopped from the cut-off date. If last ADA before cut-off date is positive, one additional sampling time for ADA evaluation should be collected 3 months later. No further ADA will be sampled, even if this 3-month sample is positive.

1.3.3 All cycles: IKd arm only (approximately 168 patients) up to Cycle 10

Study Phase		Treatment Phase											3 months later
		Cycle 1						Cycle 2		Cycle 3	Cycle 4	Subsequent Cycles up to 10 cycles	±5 days after last ADA positive at cycle 10
Day		Day 1			Day 8	Day 15	Day 22	Day 1		Day 1	Day 1	Day 1	
Time (decimal hours)		SOI	EOI	EOI + 1h	SOI	SOI	SOI	SOI	EOI	SOI	SOI	SOI	
Time window[a]		-10min	±10min	±10min	-10min	-10min	-10min	-10min	±10min	-10min	-10min	-10min	
Indicative clock time		8:00 AM	12:00 PM	1:00 PM	8:00 AM	8:00 AM	8:00 AM	8:00 AM	12:00 AM	8:00 AM	8:00 AM	8:00 AM	8:00 AM
Treatment													
isatuximab (IV infusion)		X			X	X	X	X		X	X	X	
Pharmacokinetics[b]													
isatuximab	RNT (hour)	0	4	5	0	0	0	0	4	0	0	0	
	Sample ID	P00[c]	P01[d]	P02[e]	P03[c]	P04[c]	P05[c]	P00[c]	P01[d]	P00[c]	P00[c]	P00[c]	
Immunogenicity													
ADA (anti-drug antibody)[f]		AB00[c]						AB00[c]		AB00[c]	AB00[c]	AB00[g]	ABF00[h]

a Time window permitted for PK/PDy and immunogenicity sampling.

b Refer to laboratory manual for sample collection, processing and shipping.

c Sample collected just (within 10 mins) and strictly before the start of isatuximab infusion (ie, after administration of the isatuximab premedications).

d Sample collected just before actual EOI.

e Sample collected 1 hour after the actual end of infusion.

f The sampling times for ADA detection can be modified based on the updated knowledge of isatuximab on immunogenicity.

g At Cycle 10, if patient is positive or inconclusive for ADA, additional ADA will be sampled 3 months later.

h At Cycle 10, if patient is positive or inconclusive for ADA, additional ADA will be sampled 3 months later. No further ADA will be sampled, even if this 3-month sample is positive. If isatuximab is stopped prior to carfilzomib and dexamethasone before Cycle 10 and last ADA was positive or inconclusive, additional ADA will be sampled 3 months later. No further ADA will be sampled, even if this 3-month sample is positive. For patients with less than 10 cycles at the cut-off date, both PK and ADA samples collection will be stopped from the cut-off date. If last ADA before cut-off date is positive, one additional sampling time for ADA evaluation should be collected 3 months later. No further ADA will be sampled, even if this 3-month sample is positive.

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2.2 LIST OF FIGURES

3 LIST OF ABBREVIATIONS

ADA:	anti-drug antibody
AEs:	adverse event
AESI:	adverse event of special interest
AIDS:	acquired immunodeficiency syndrome
ALT:	alanine aminotransferase
ANC:	absolute neutrophil count
anti-HBc:	Hepatitis B core antibody
anti-HBs:	Hepatitis B surface antibody
ASCT:	autologous stem cell transplantation
AST:	aspartate aminotransferase
BM:	bone marrow
BSA:	body surface area
BUN:	blood urea nitrogen
CHF:	congestive heart failure
CI:	confidence interval(s)
CID:	clinically important difference
CR:	complete response
CT:	computed tomography
CV:	coefficient of variation
DL:	dose level(s)
DMC:	data monitoring committee
DOR:	duration of response
DRF:	discrepancy resolution form
ECG:	electrocardiogram
ECOG:	eastern cooperative oncology group
eCRF:	electronic case report form
ELISA:	enzyme-linked immunosorbent assay
EOI:	end of infusion
EORTC:	European Organisation for Research and Treatment of Cancer
EOT:	end of treatment
ePROs:	electronic patient-reported outcome(s)
EQ-5D-5L:	european quality of life group questionnaire with 5 dimensions and 5 levels per dimension
FISH:	fluorescence in situ hybridization
FLC:	free light chain
FSH:	follicle stimulating hormone
GCP:	good clinical practice
G-CSF:	granulocyte colony stimulating factor
GHS:	Global Health Status
GMP:	Good Manufacturing Practice
HBsAg:	Hepatitis B surface antigen

HBV:	Hepatitis B Virus
HCV:	Hepatitis C
HLGT:	high-level group term
HLT:	high-level term
HR:	hazard ratio
HRQL:	health-related quality of life
HRT:	hormonal replacement therapy
IAR:	infusion associated reaction
ICH:	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC:	independent ethics committee
IF:	immunofixation
IKd:	isatuximab carfilzomib dexamethasone
IMWG:	International Myeloma Working Group
IRB:	institutional review board
IRC:	Independent Response Committee
IRT:	Interactive Response Technology
ITT:	intent-to-treat
IUD:	intrauterine device
IUS:	intrauterine hormone-releasing system
IV:	intravenous(ly)
Kd:	carfilzomib dexamethasone
KRd:	carfilzomib lenalidomide dexamethasone
LC-MS/MS:	liquid chromatography with tandem mass spectrometry
LDH:	lactate dehydrogenase
mAb:	monoclonal antibody
max:	maximum
MDRD:	modification of diet in renal disease
min:	minimum
MM:	multiple myeloma
MR:	minimal response
MRD:	minimal residual disease
MRI:	magnetic resonance imaging
MUGA:	multigated acquisition
NCI-CTCAE:	National Cancer Institute Common Terminology for Adverse Events
ORR:	overall response rate
OS:	overall survival
PCSA:	potentially clinically significant abnormalities
PD:	progressive disease
PDy:	pharmacodynamic(s)
PFS:	progression free survival
PFS2:	time from the date of randomization to the date of second PD or death from any cause, whichever happens first
PK:	pharmacokinetic(s)
PML:	progressive multifocal leukoencephalopathy
PO:	oral(ly)

PR:	partial response
PRES:	posterior reversible encephalopathy syndrome
PS:	performance status
PT:	preferred term
QLQ-C30:	quality of life questionnaire with 30 questions
QLQ-MY20:	EORTC myeloma module with 20 items
RBC:	red blood cell(s)
Rd:	lenalidomide dexamethasone
RDI:	relative dose intensity
R-ISS:	Revised International Staging System
RNA:	ribonucleic acid
RNT:	relative normal time
RRMM:	relapsed refractory multiple myeloma
SAE:	serious adverse event
SAP:	statistical analysis plan
sCR:	stringent complete response
SCT:	stem cell transplantation
SD:	stable disease
SEM:	standard error of the mean
SOC:	system organ class
SOI:	start of infusion
SPD:	sum of the products of the maximal perpendicular diameters of measured lesions
SPEP:	serum immunoelectrophoresis
TBD:	to be determined
TEAEs:	treatment-emergent adverse event
TLS:	tumor lysis syndrome
TTP:	time to progression
ULN:	upper limit of normal
UPEP:	urine immunoelectrophoresis
US:	United States
VAS:	visual analog scale
Vd:	bortezomib dexamethasone
VGPR:	very good partial response
WBC:	white blood cell(s)
WOCBP:	woman/women of childbearing potential

4 INTRODUCTION AND RATIONALE

Multiple myeloma (MM), with 114,251 new cases per year, is the third most frequent hematological malignancy worldwide, after leukemia and non-Hodgkin lymphoma (1).
The treatment of MM has improved remarkably over the last 2 decades with the development and introduction of numerous novel agents leading to more effective treatments, including 3 generations of immunomodulator agents (thalidomide, lenalidomide, pomalidomide), 2 generations proteasome inhibitor (bortezomib, then carfilzomib and ixazomib), and the most recent one, the first anti-CD38 antibody (daratumumab). These novel agents improved significantly overall survival (OS) of MM patients with a median OS improving from 3 to 6 years (2); however, MM remains a fatal disease in majority of cases and the development of new therapeutic strategies with this evolving armamentarium and new drugs are still needed.

Front line strategy is well defined with treatment sequence including induction plus or minus maintenance (with/without consolidation), depending on response induced by each regimen. For younger and fit patients, autologous stem cell transplantation (ASCT) is part of the front line strategy. For patients who are not eligible for high-dose therapy and ASCT, conventional treatments with immunomodulator agents, proteasome inhibitors, and other agents will be utilized. However, and whatever the front line treatment, the vast majority of the patients will progress or relapse and will need further lines of therapies. Drugs used in front line include more and more often thalidomide, bortezomib, and/or lenalidomide and new therapeutic options are to be developed for further lines.

4.1 ISATUXIMAB

4.1.1 Isatuximab description

CD38 (see Appendix L) is the most strongly and uniformly expressed antigen identified on the malignant clonal populations of myeloma cells compared with its pattern of expression on normal cells. Therefore, this antigen may be a useful target for the in vivo depletion of tumor cells while sparing normal cells (3).

Isatuximab (SAR650984) is a naked chimeric monoclonal antibody (mAb) that binds selectively to a unique epitope on the human surface antigen CD38. Isatuximab kills tumor cells via multiple biological mechanisms, antibody-dependent cellular-mediated cytotoxicity, complement-dependent cytotoxicity, direct induction of apoptosis (pro-apoptosis) without crosslinking, and inhibition of CD38 enzymatic activity.

4.1.2 Isatuximab non-clinical and clinical data

For preclinical and clinical data of isatuximab in single agent and in combination with proteasome inhibitors (bortezomib and carfilzomib), please refer to the Investigator's Brochure.

4.2 CARFILZOMIB

4.2.1 Carfilzomib description

Carfilzomib is a tetrapeptide epoxyketone proteasome inhibitor that irreversibly binds to the N-terminal threonine-containing active sites of the 20S proteasome, the proteolytic core particle within the 26S proteasome. Carfilzomib had antiproliferative and proapoptotic activities in vitro in solid and hematologic tumor cells. In animals, carfilzomib inhibited proteasome activity in blood and tissue and delayed tumor growth in models of MM, hematologic, and solid tumors.

Carfilzomib is structurally and mechanistically different from bortezomib. It has improved specificity for the proteasome and has less off-target activity when measured against a broad panel of proteases including metallo, aspartyl, and serine proteases compared to bortezomib. Thus, the selectivity of carfilzomib may be responsible for the reductions in myelosuppression and neuropathy observed in preclinical studies comparing carfilzomib with bortezomib (4). In animal models, carfilzomib has been administered intravenously (IV) for 5 consecutive days with excellent tolerability and prolonged proteasome inhibition (5). In contrast, uninterrupted daily dosing of boronated proteasome inhibitors in animal models demonstrated substantial morbidity and mortality (6). In addition, following brief exposure, carfilzomib was more cytotoxic than bortezomib, regardless of cell type, in multiple tumor cell lines (5). Carfilzomib was able to overcome acquired drug resistance in human MM cell lines.

4.2.2 Carfilzomib clinical data

Carfilzomib was first approved in the United States (US) in 2012 based on response rate in monotherapy reported in a single-arm multicenter study conducted in patients with at least 2 prior lines, having responded to at least 1 prior line and being refractory to the most recent therapy (7). Patients received carfilzomib 20 mg/m^2 at each dose in Cycle 1, and 27 mg/m^2 in subsequent cycles. Dexamethasone 4 mg orally (PO) or IV was administered prior to carfilzomib doses in the first and second cycles. A total of 266 patients were enrolled. The overall response rate (ORR) as determined by the Independent Response Committee (IRC) assessment using International Myeloma Working Group (IMWG) criteria was 23.7% (95% confidence interval [CI]: 18.7 to 29.4) (N = 257 evaluable patients). The median duration of response was 7.8 months (95% CI: 5.6 to 9.2). Common adverse events (AEs) were fatigue (49%), anemia (46%), nausea (45%), and thrombocytopenia (39%). Thirty-three patients (12.4%) experienced peripheral neuropathy, primarily Grades 1 or 2. Thirty-three patients (12.4%) withdrew because of an AE.

Carfilzomib has been further approved in combination with lenalidomide and dexamethasone in relapsed refractory multiple myeloma (RRMM; see Appendix H) patients with 1 to 3 prior lines (see Appendix G), based on the result of a study in which 792 patients were randomized 1:1 to receive carfilzomib biweekly 20 mg/m^2 on Days 1 and 2, and then 27 mg/m^2/day plus lenalidomide (Revlimid®) 25 mg per day over 21 days and dexamethasone 40 mg on Days 1, 8, 15, and 22 (KRd) or lenalidomide 25 mg per day over 21 days and dexamethasone 40 mg (Rd) (8). Patients were previously pretreated with 1 to 3 lines of therapy. Patients in the KRd arm demonstrated improved progression free survival (PFS) compared with those in the Rd arm (hazard ratio [HR] = 0.69, with 2-sided p-value = 0.0001) as determined using standard objective

IMWG/European Society for Blood and Marrow Transplantation response criteria by an IRC. The median PFS was 26.3 months (95% CI: 23.3 to 30.5 months) in the KRd arm versus 17.6 months (95% CI: 15.0 to 20.6 months) in the Rd arm. The results of OS were not significantly different at the interim analysis. The most frequent AEs were diarrhea (42.3%), fatigue (32.9%), cough, pyrexia and upper respiratory tract infection (28.8% each), hypokalemia (27.6%), and muscle spasm (26.5%).

Clinical data of isatuximab in combination with carfilzomib and dexamethasone (IKd) are detailed in next section.

4.3 ISATUXIMAB IN COMBINATION WITH CARFILZOMIB

One Investigator-sponsored Phase Ib study (TCD12795) is currently ongoing in US in patients with RRMM (NCT02332850) with the objective to determine the maximum tolerated dose of isatuximab when combined with carfilzomib. Three dose levels (DL)/schedules of isatuximab are being assessed: 10 mg/kg Q2W (DL1), 10 mg/kg QW/Q2W (DL2), and 20 mg/kg QW/Q2W (DL3). Isatuximab is combined to a fixed dose of carfilzomib 20 mg/m^2 on Day 1 and Day 2 and then 27 mg/m^2 on Days 8, 9, 15, and 16 on Cycle 1; twice weekly, 3 weeks out of 4 from Cycle 2 to 8 and twice every 2 weeks after Cycle 8. Dexamethasone 20 mg is given as premedication prior to first infusion of isatuximab, and then 10 to 20 mg prior to each infusion. In addition, dexamethasone 4 mg is given as premedication prior to each carfilzomib infusion at Cycle 1 and then is given at the Investigator discretion.

Recruitment is ongoing and preliminary data of this ongoing study were presented at American Society of Hematology meeting in 2016 (9), on the first 11 treated patients: 3, 3, and 5 patients treated at DL1, DL2, and DL3, respectively. The median number of prior lines was 4.5 (2 to 8), all patients were previously treated with lenalidomide, and 10 patients previously received bortezomib. Ten patients were refractory to their previous therapy. The median number of cycles administered was 6 (minimum [min]-maximum [max]: 1 to 20). No dose-limiting toxicity was reported. Infusion associated reaction was reported in 6 (54%) patients (4 patients with Grade 1 and 2 patients with Grade 2), and all infusions were completed. The other most frequent treatment-emergent adverse events (TEAEs) were dyspnea (45%), fatigue (45%), nausea (45%), pain (back, chest wall, and pelvis; 36%), peripheral neuropathy (36%), hypertension (27%), cough (27%), anorexia (27%), gastroesophageal reflux disease (18%), constipation (18%), diarrhea (18%), nasal congestion (18%), and hypokalemia (18%). Grade 3/4 non-hematological TEAEs were reported in fewer than 5% of patients. Hematological abnormalities were mild; 9% Grade 3/4 anemia, 9% Grade 3/4 neutropenia, and 64% Grade 3/4 lymphopenia. The most frequent serious adverse event (SAE) was Grade 3 pneumonia (18%).

Interesting preliminary efficacy results were reported in 10 patients evaluable for response: 2 patients had very good partial response (VGPR), 6 patients had partial response (PR), 1 patient had minimal response (MR), and 1 patient had stable disease (SD).

The pharmacokinetics (PK) of isatuximab analyzed in 10 patients are not modified by the co-administration of carfilzomib (unpublished data).

4.4 STUDY DESIGN RATIONALE

4.4.1 Choice of standard arm

Bortezomib in combination with dexamethasone (Vd) has been utilized as standard of treatment for RRMM for over 10 years globally. Recently, the results of a Phase 3 study (ENDEAVOR study) conducted in 929 patients with RRMM after 1 to 3 prior treatments showed superiority of carfilzomib in combination with dexamethasone (Kd) versus Vd leading to registration of the Kd combination in this patient population in 2016 (10). A pre-specified interim analysis was planned when 395 (75%) of the 526 required progression or death events occurred. At the time of the interim analysis (made with 414 events and all patient were already recruited), the experimental arm (carfilzomib 20/56 mg/m^2) demonstrated significant advantage in PFS with a median of 18.7 vs 9.4 months (HR: 0.53, 95% CI: 0.44 to 0.65, p <0.0001) crossing the pre-specified O'Brien-Fleming stopping boundary for efficacy of 0.023, adding this combination to the available therapeutic armamentarium for RRMM. The objective response rate was also significantly better in favor of Kd (77% vs. 63%, p <0.0001). The AEs of any grade occurring in more than 15% of patients were diarrhea (27%), fatigue (24%), dyspnea (23%), pyrexia (26%), anemia and cough (25%), insomnia (24%), peripheral edema (21%), upper respiratory syndrome, nausea and muscle spasm (18% each), asthenia (17%), and hypertension and headache (16% each). Grade 3/4 AEs occurring in ≥5% of patients were hypertension (9%, no Grade 4), and fatigue and dyspnea (5% each, no Grade 4). Grade 4 was reported for pyrexia in 2 patients and back pain in 1 patient.

At the time of the interim analysis for PFS, OS data were immature. Results of a planned OS interim analysis showed a significant increase in OS in favor of Kd vs. Vd, with a median OS of 47.6 months for Kd versus 40.0 for Vd, (HR = 0.79, 95% CI, 0.65 to 0.96) (11). Adverse events observed in this updated analysis were consistent with those previously reported for ENDEAVOR. The most common AEs (≥20%) in patients receiving Kd were anemia, diarrhea, pyrexia, dyspnea, fatigue, hypertension, cough, insomnia, upper respiratory tract infection, peripheral edema, nausea, bronchitis, asthenia, back pain, thrombocytopenia, and headache.

Consistent efficacy results on PFS and OS of the Kd combination clearly established this regimen as standard treatments for patients with RRMM and demonstrated Kd being a better treatment option than Vd. This support Kd as standard arm in this Phase 3 study.

Comparison of the IKd combination to the standard treatment option Kd will allow clear assessment of the effect of the addition of isatuximab to the standard treatment.

4.4.2 Isatuximab dose and regimen

Isatuximab single agent has shown an efficacy dose effect between 3 and 10 mg/kg and above.

The recommended dose of isatuximab when administered in combination has been determined based on the study TCD11863 (lenalidomide and dexamethasone combination), and was then used in expansion cohorts of Phase I combination studies TCD14079 (pomalidomide and dexamethasone combination) and TCD13983 (bortezomib, cyclophosphamide, and dexamethasone combination) as well as in new studies TCD14906 (REGN2801 combination)

and EFC14335 (pomalidomide and dexamethasone combination). In the dose escalation part of studies TCD14079, TCD13983, and TCD12795 (carfilzomib and dexamethasone combination), exposure of isatuximab when administered with these combinations was in the range of exposure reported in TCD11863 and in single agent, for all explored dose levels.

No evident difference was seen for safety and tolerability across the different dose levels. Analogously, the available data in combination with lenalidomide and pomalidomide do not demonstrate major differences in efficacy between 10 and 20 mg/kg with comparable response rate in heavily pretreated patients. Pharmacokinetic/PDy analyses performed with TCD11863 data, including trial simulations and simulations of serum M protein-profiles, showed higher predicted ORR and reduction in M protein at 8/12 weeks at doses ≥10 mg/kg. However, the benefit in terms of ORR increase or in terms of serum M protein reduction appeared limited when increasing the dose from 10 to 20 mg/kg QW x 4, Q2W. Therefore, based on clinical efficacy, safety, PK simulations, and PK/PDy analyses, the dose selected for further isatuximab combination studies is 10 mg/kg QW x 4 administrations followed by 10 mg/kg Q2W (refer to Investigator's Brochure).

Based on these data, the dose of isatuximab 10 mg/kg is the selected dose for combination therapies.

4.5 BENEFIT RISK ASSESSMENT

4.5.1 Efficacy

All patients randomized in the study will receive Kd combination, an established standard treatment option for patients with MM having received 1 to 3 prior lines of treatment, either alone or with addition of isatuximab, which means that all patients will receive effective treatment.

As of 05 January 2017, 323 patients have received isatuximab across 5 ongoing or completed Phase I/II clinical studies conducted in patients with MM or other hematological malignancies (319 patients with MM). Isatuximab has been investigated either as a monotherapy or in combination with conventional treatment regimens in MM. Anti-tumor activity of isatuximab has been shown in heavily pre-treated MM patients across these clinical studies and preliminary efficacy results reported in the ongoing study assessing isatuximab in combination with carfilzomib support further evaluation of this combination.

4.5.2 Safety

Isatuximab used as monotherapy or in combination treatments was well tolerated with a manageable safety profile consistent across multiple studies. Infusion associated reaction is the main AE related to isatuximab and is adequately managed with steroid and antihistamine premedication. All grades and Grade ≥3 infusion associated reactions (IARs) were reported in 49.5% and 2.2% of the patients treated with isatuximab single agent, respectively. With premedication, IAR were Grade 1 or 2 in more than 95% of the patients who experienced IARs. Infusion-associated reactions occurred once at the first infusion in more than 90% of the patients and led to treatment discontinuation in fewer than 5% of patients.

The safety profile of Kd combination is known and manageable.

Beside the IARs, other adverse drug reactions known to be associated with both isatuximab and carfilzomib (including symptoms of IAR reported as AEs in previous isatuximab studies) are anemia, neutropenia, thrombocytopenia, diarrhea, nausea, vomiting, chills, fatigue, fever, pneumonia, headache, cough, dyspnea, and hypertension. In the ongoing study assessing isatuximab with carfilzomib twice weekly at 27 mg/m^2, preliminary safety results showed a safety profile consistent with the known safety profile of each drug, supporting the feasibility of this combination for further assessment.

Close monitoring of the safety is planned and an independent data monitoring committee (DMC) will regularly monitor the safety of the patients. The first safety review will be done after the first 15 patients will have completed 2 cycles in the isatuximab in combination with carfilzomib and low-dose dexamethasone (IKd) arm.

Based on available data, the overall risk/benefit appears favorable and supports the evaluation of the combination of isatuximab with carfilzomib and dexamethasone in MM patients previously treated with 1 to 3 prior lines.

5 STUDY OBJECTIVES

5.1 PRIMARY

The primary objective of this study is to demonstrate the benefit of isatuximab in combination with carfilzomib and dexamethasone in the prolongation of PFS using IMWG criteria (see Appendix F) as compared to carfilzomib and dexamethasone in patients with relapsed and/or refractory MM previously treated with 1 to 3 lines of therapy.

5.2 SECONDARY

The key efficacy objectives are as follows:

- To evaluate ORR.
- To evaluate rate of VGPR or better.
- To evaluate rate of VGPR or better (IMWG criteria) with minimal residual disease (MRD) negativity in both arms.
- To evaluate complete response (CR) rate in both arms (IMWG criteria).
- To evaluate OS in both arms.

Other secondary objectives are as follows:

- To evaluate safety in both arms.
- To evaluate duration of response (DOR) in both arms.
- To evaluate time to progression (TTP) in both arms.
- To evaluate PFS2 (see definition in Section 9.2.2) in both arms.
- To evaluate time to first response in both arms
- To evaluate time to best response in both arms
- To determine the PK profile of isatuximab and carfilzomib when combined together.
- To evaluate immunogenicity of isatuximab in isatuximab arm.
- To evaluate generic and disease- and treatment-specific health-related quality of life (HRQL), and changes in HRQL, health state utility, and health status in both arms.

5.3 EXPLORATORY

Exploratory objectives are as follows:

- To explore PK and pharmacodynamics (PDy) relationship.
- To explore the relationship between immune genetic determinants and efficacy endpoints.
- To explore relationship between cytogenetics abnormalities not part of Revised International Staging System (R-ISS) including but not limited to del (1p) and gain (1q) and efficacy endpoints.
- To explore the impact of M-protein measurement without isatuximab interference on best overall response assessment.

6 STUDY DESIGN

6.1 DESCRIPTION OF THE STUDY

This is a prospective multicenter, multinational, randomized, open label, parallel group, 2-arm study assessing the clinical benefit of isatuximab at 10 mg/kg weekly in the first cycle (4 weeks) and then combined with carfilzomib at 56 mg/m^2 twice weekly 3 out of 4 weeks and dexamethasone twice weekly (IKd arm) versus carfilzomib at 56 mg/m^2 twice weekly 3 out of 4 weeks and dexamethasone twice weekly (Kd arm), in terms of PFS in patients with relapsed and/or refractory MM previously treated with 1 to 3 prior lines. After confirmation of eligibility criteria, patients will be randomly assigned to 1 of the 2 arms using an Interactive Response Technology (IRT) system in a 3:2 ratio:

- Isatuximab in combination with carfilzomib and low-dose dexamethasone (IKd [experimental] arm).
- Carfilzomib and low-dose dexamethasone (Kd [control] arm).

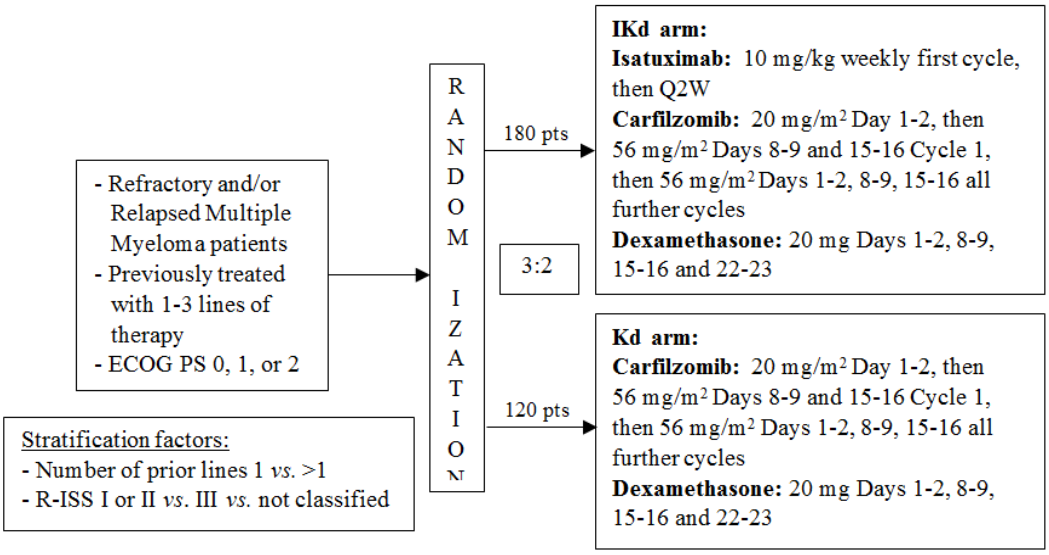
Isatuximab, carfilzomib, and dexamethasone are defined in this protocol as "study treatment".

Randomization will be stratified by number of prior lines 1 versus >1 and R-ISS (12) I or II versus III versus not classified (inconclusive fluoroscence in situ hybridization [FISH] unless stage can be determined on lactate dehydrogenase [LDH], albumin, and β2 microglobulin only) (See Appendix A).

Patients will be treated until disease progression, unacceptable AE, or patient decision to stop the study treatment.

Study design is summarized in Figure 1.

Figure 1 - Study design



6.2 DURATION OF STUDY PARTICIPATION

6.2.1 Duration of study participation for each patient

The patient will be considered in the study from informed consent signature until death, consent withdrawal, or the OS analysis cut-off date, whichever comes first.

The duration of the study for a patient will include a period for screening of up to 3 weeks. A cycle duration is 28 days. Patients will continue study treatment until disease progression, unacceptable AEs, patient wish to discontinue further study treatment, or any other reasons (see Section 10.3). All AEs occurring after informed consent signature will be reported up to 30 days after last study treatment administration.

After study treatment discontinuation, patients will return to the study site 30 days after the last dose of study treatment for end of treatment or before further anti myeloma therapy initiation, whichever comes first (EOT) assessments, and 90 days after the last dose of study treatment for HRQL questionnaires.

Related AEs and all SAEs regardless of relationship to the study treatment ongoing at the time of study treatment discontinuation will be followed during the follow-up period until resolution or stabilization. During the follow-up period, all (serious or non-serious) new AEs related to study treatment and any second primary malignancy will be collected and followed up until resolution or stabilization.

Patients who discontinue the study treatment due to progressive disease (PD) will be followed up every 3 months (12 weeks) for HRQL at first FU visit (90 days after the last study treatment) and for further anti-myeloma therapies, second primary malignancies, PFS2, and survival until death or the implementation of amended protocol #10, whichever comes first. Patients who discontinue the study treatment prior to documentation of PD will be followed-up every 4 weeks until disease progression (even for patients who would initiate further anti-myeloma therapy without PD), HRQL 90 days after last study treatment, and then after confirmation of disease progression, every 3 months (12 weeks) for further anti-myeloma therapies, second primary malignancies, PFS2, and survival, until death or the implementation of amended protocol #10, whichever comes first.

For all alive patients at the implementation of amended protocol #10, survival status will be collected approximately twice a year until death, or OS analysis cut-off date, whichever comes first.

Patients still on treatment at the time of the implementation of amended protocol #10 or OS analysis cut-off date, and benefitting from the study treatment, can continue the study treatment until disease progression, unacceptable AEs, patient wish to discontinue further study treatment, or any other reasons. For cycles administered after the cut-off dates, all ongoing SAEs (related or not) and all ongoing related non serious AEs at this cut-off date, all new related AEs (serious or not), IP administration, and reason of EOT will continue to be collected. If a patient received less than 10 cycles at the final PFS analysis cut-off date, anti-drug antibodies (ADA)/PK samples will be stopped. In case of the last ADA is positive or inconclusive an additional ADA will be sampled 3 months later. No further ADA will be sampled, even if this 3-month sample is positive.

6.2.2 Determination of end of clinical trial (all patients)

The PFS analysis (primary endpoint analysis) is event driven and the final PFS analysis cut-off date will be the date when 159 PFS events (progression or death, whichever comes first) assessed by the IRC have occurred (around 36 months from first patient being randomized).

It is assumed that OS will not be mature at the time of the PFS analysis. The OS analysis cut-off date will be approximately 3 years after the primary PFS analysis cut-off date. The primary analysis of PFS corresponds either to the positive interim analysis or the final PFS analysis.

The end of the study is defined as the date of the last visit of the last participant in the study.

6.3 INTERIM ANALYSIS

An interim analysis for efficacy assessment of PFS is planned when 65% of the 159 PFS events will be observed. The interim PFS cut-off date is expected approximately 24 months after the FPI. The procedure and criteria for undertaking an interim analysis are described in Section 11.5.

6.4 STUDY COMMITTEES

The **Steering Committee** will include a Chairman, investigators, and sponsor's representatives. The Steering Committee will be responsible for:

- Supervising the progress of the trial towards its overall objectives.
- Reviewing at regular intervals relevant information that may affect the study conduct.
- Discussing the implementation of the recommendations of the independent DMC.

An independent **DMC**, consisting of 3 external independent members (2 physicians with MM expertise and 1 statistician), not associated with the conduct of the study or other study committees will meet regularly to as specified in the DMC charter:

- Review the progress of the trial.
- Review the safety data.
- Advise the sponsor on potential modifications or communications that may be necessary to ensure the patient safety or protect the scientific integrity of the trial. The sponsor will make the final decision(s).
- Review the results of the planned PFS interim analysis by arm during the course of the study.

The first meeting will be set up to review early safety results (eg, after approximately 15 patients have completed at least 2 cycles in IKd arm), and then periodically. Ad-hoc DMC meetings may also be held if a significant safety issue or issue deemed important for discussion arise on this or any other studies of isatuximab. After each meeting, the DMC will advise the Steering Committee and the sponsor's representatives on recommendations regarding the continued safety of treating ongoing and future study patients, as well as the course of action regarding the conduct of the trial.

One PFS interim analysis is planned and, after review of the results by arm, the DMC will make recommendations on continuation of the study or not according to the stopping rules pre-specified in the protocol (see Section 11.5).

The DMC procedures will be detailed in the DMC charter and approved by the DMC members. The charter will be finalized before the first patient enrolled.

An **IRC** will determine disease response and progression according to efficacy MM laboratory data (central laboratory results), local bone marrow (BM) for plasma cell infiltration assessment as recorded in the eCRF, and imaging as per IMWG criteria and in line with the IRC charter up to additional analysis on PFS. IRC will review disease assessments until the last time point with M protein assessed by the central laboratory or overall survival cut-off date, whichever comes first.

7 SELECTION OF PATIENTS

7.1 INCLUSION CRITERIA

Patients will be considered for inclusion in this study if they meet all of the following criteria (all necessary baseline studies for determining eligibility must be obtained within 21 days prior to randomization):

I 01. Multiple myeloma.

I 02. Measurable disease: Serum M protein ≥0.5 g/dL measured using serum protein immunoelectrophoresis and/or urine M protein ≥200 mg/24 hours measured using urine protein immunoelectrophoresis.

I 03. Patient with relapsed and/or refractory MM with at least 1 prior line and no more than 3 prior lines.

I 04. Patient has given voluntary written informed consent before performance of any study related procedures not part of normal medical care.

7.2 EXCLUSION CRITERIA

Patients who have met all the inclusion criteria listed in Section 7.1 will be screened for the following exclusion criteria:

E 01. Less than 18 years (or country's legal age of majority if the legal age is >18 years).

E 02. Primary refractory MM defined as patients who have never achieved at least a MR with any treatment during the disease course.

E 03. Patient with serum free light chain (FLC) measurable disease only.

E 04. Patient with prior anti-CD38 mAb treatment with progression on or within 60 days after end of anti-CD38 mAb treatment or failure to achieve at least MR to treatment (ie, refractory to anti-CD38).

E 05. Any anti-myeloma drug treatment within 14 days before randomization, including dexamethasone.

E 06. Patient who has received any other investigational drugs or prohibited therapy for this study within 28 days prior to randomization (Section 8.8.2).

E 07. Prior treatment with carfilzomib.

E 08. Known history of allergy to captisol (a cyclodextrin derivative used to solubilize carfilzomib), prior hypersensitivity to sucrose, histidine (as base and hydrochloride salt), polysorbate 80, or any of the components (active substance or excipient) of study treatment that are not amenable to premedication with steroids, or H2 blockers, that would prohibit further treatment with these agents.

E 09. Patients with contraindication to dexamethasone.

E 10. Prior allogenic hematopoietic stem cell transplant with active graft versus host disease (any grade and/or being under immunosuppressive treatment within 2 months before randomization).

E 11. Known amyloidosis or concomitant plasma cell leukemia.

E 12. Pleural effusions requiring thoracentesis or ascites requiring paracentesis or any major procedures within 14 days before randomization: eg, plasmapheresis, curative radiotherapy, major surgery (kyphoplasty is not considered a major procedure).

E 13. Eastern Cooperative Oncology Group (ECOG) performance status (PS) >2 (see Appendix D).

E 14. Platelets <50,000 cells/µL if <50% of BM nucleated cells are plasma cells and <30,000 cells/µL if ≥50% of BM nucleated cells are plasma cells. Platelet transfusion is not allowed within 3 days before the screening hematological test.

E 15. Absolute neutrophil count (ANC) <1000 µ/L (1 x 10^9/L). The use of granulocyte colony stimulating factor (G-CSF) is not allowed to reach this level.

E 16. Creatinine clearance <15 mL/min/1.73 m^2 (Modification of Diet in Renal Disease [MDRD] Formula, see Appendix B).

E 17. Total bilirubin >1.5 x upper limit of normal (ULN), except for known Gilbert syndrome.

E 18. Corrected serum calcium >14 mg/dL (>3.5 mmol/L).

E 19. Aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) >3 x ULN.

E 20. Ongoing toxicity (excluding alopecia and those listed in eligibility criteria) from any prior anti-myeloma therapy of Grade >1 (National Cancer Institute Common Terminology for Adverse Events [NCI-CTCAE] v4.03; see Appendix E).

E 21. Prior malignancy. Adequately treated basal cell or squamous cell skin or superficial (pTis, pTa, and pT1) bladder cancer or low risk prostate cancer or any in situ malignancy after curative therapy are allowed, as well as any other cancer for which therapy has been completed ≥5 years prior to randomization and from which the patient has been disease-free for ≥5 years.

E 22. Any of the following within 6 months prior to randomization: myocardial infarction, severe/unstable angina pectoris, coronary/peripheral artery bypass graft, New York Heart Association class III or IV congestive heart failure (CHF), Grade ≥3 arrhythmias, stroke, or transient ischemic attack.

E 23. Left ventricular ejection fraction <40%.

E 24. Known acquired AIDS related illness or HIV disease requiring antiretroviral treatment, or to have active hepatitis A, B (defined as a known positive hepatitis B surface antigen

(HBsAg) result), or C (defined as known quantitative HCV RNA results greater than the lower limits of detection of the assay or positive HCV antigen) infection.

E 25. Any of the following within 3 months prior to randomization: treatment resistant peptic ulcer disease, erosive esophagitis or gastritis, infectious or inflammatory bowel disease, diverticulitis, pulmonary embolism, or other uncontrolled thromboembolic event.

E 26. Any severe acute or chronic medical condition which could impair the ability of the patient to participate in the study or interfere with interpretation of the study results (eg, systemic infection unless anti-infective therapy is employed), or patient unable to comply with the study procedures.

E 27. Female patients who are pregnant or lactating.

E 28. Women of childbearing potential (WOCBP) not protected by highly-effective method of birth control and/or who are unwilling or unable to be tested for pregnancy (see contraceptive guidance in Appendix C).

E 29. Male participant with a female partner of childbearing potential not protected by highly-effective method of birth control.

8 STUDY TREATMENTS

8.1 INVESTIGATIONAL MEDICINAL PRODUCTS

In case of a regional or national emergency declared by a governmental agency that results in travel restrictions, confinement, or restricted site access, the oral IMP may be supplied at the site or from the PI/site/Sponsor to the participant via a Sponsor-approved courier company where allowed by local regulations and agreed upon by the participant during the time the measures are applied.

8.1.1 Isatuximab

8.1.1.1 Pharmaceutical form

The C1P2F2 drug product is presented as a concentrate for solution for infusion in vials containing 20 mg/mL (500 mg/25 mL) isatuximab in 20 mM histidine, 10% (w/v) sucrose, 0.02% (w/v) polysorbate 80, and pH 6.0 buffer.

It is supplied for parenteral administration as a sterile, nonpyrogenic, injectable, 20 mg/mL concentrate for solution for infusion essentially free of visible particulates and is packaged in 30 mL glass vials fitted with elastomeric closure. Each vial contains a nominal content of 500 mg of isatuximab. The fill volume has been established to ensure removal of 25 mL.

For administration to patients, the appropriate volume of isatuximab will be diluted in a 250-mL infusion bag of 0.9% sodium chloride or 5% dextrose solution.

Please refer to the Pharmacy Manual for more information.

8.1.1.2 Dilution method

Isatuximab concentrate for solution for infusion will be diluted in an infusion bag with 0.9% sodium chloride or 5% dextrose solution to achieve the appropriate drug concentration for infusion.

Infusion via a central line is preferred, if available. In case of patients with local intolerance after peripheral IV infusion, the decision to use a central line is left to the Investigator’s decision. The final infusion volume corresponding to the dose of isatuximab will be administered by IV infusion for the period of time that will depend on total dose administered.

Prior to dosing, each patient's dose will be individually prepared by the study pharmacist and labeled with protocol number, patient number, and treatment description. The total dose will be calculated based on the most recent weight available the day of the infusion preparation: the weight on the day of the infusion or the most recent weight assuming it was assessed in a reasonable time frame according to investigator assessment. If the infusion is prepared with the most recent weight assessed in a reasonable time frame, this will not prevent to assess the weight on D1 of each cycle, which has to be recorded in the eCRF.

Detail instructions for dilution of the isatuximab concentrate for solution for infusion is provided in a Pharmacy Manual.

8.1.2 Carfilzomib

Carfilzomib (Kyprolis®) from available commercial supplies will be used for this study where applicable; otherwise, it will be re-labeled by the sponsor according to Good Manufacturing Practice (GMP) guidelines before supplies are provided to the study sites.

Please refer to package insert for further details as regards to formulation, storage, and handling procedures.

8.1.2.1 Dilution method

The lyophilized product is reconstituted with water for injection to a final carfilzomib concentration of 2 mg/mL prior to administration.

8.1.3 Dexamethasone IV/PO

Dexamethasone IV/PO from available commercial supplies will be used for this study where applicable; otherwise, it will be re-labeled by the sponsor according to GMP guidelines before supplies are provided to the study sites.

Please refer to package insert for further details as regards to formulation and handling procedures.

8.2 DOSAGE AND SCHEDULE

There is no limitation in the number of cycles to be administered in the absence of major toxicity, disease progression or any other discontinuation criteria as defined in Section 10.3. In case of PD diagnosis made on laboratory criteria, this needs to be confirmed by 2 consecutive measures before to treatment discontinuation, the treatment should continue until confirmation of the PD.

Dose adjustment (dose delay, dose omission, and for carfilzomib and dexamethasone dose reduction) will be permitted for subsequent treatment cycles based on individual patient tolerance. No dose reductions are allowed for isatuximab infusion (see Section 8.2.4).

8.2.1 Study treatments (IMP)

Study treatment is defined as isatuximab/carfilzomib/dexamethasone in IKd experimental arm and carfilzomib/dexamethasone in Kd control arm.

Both isatuximab and carfilzomib can induce IARs and premedication is required prior to their administration.

Patients allocated to IKd arm should routinely receive premedications, which also includes dexamethasone, prior to isatuximab infusion to reduce the risk and severity of IARs commonly observed with mAbs and with carfilzomib. Dexamethasone should be administered prior to carfilzomib for patients allocated to the Kd arm, and for patients allocated to IKd arm,

dexamethasone should be administered prior to carfilzomib administration when there is no isatuximab infusion (on Days 2, 9, and 16 at Cycle 1 and on Days 2, 8, 9, and 16 at further cycles).

Hydration is required prior to the 2 first carfilzomib administrations (on Day 1 and Day 2 Cycle 1). Hydration should be started orally at least 48 h prior Day 1 Cycle 1. Hydration for further infusions within cycle 1 and further cycles is left to Investigator judgment. Details for hydration are given in Section 8.2.3.

Patients with a BSA >2.2 m^2 will use 2.2 m^2 for the determination of carfilzomib dose.

Detailed guidelines for the premedication are provided in Section 8.2.2 and details for management of IARs are provided in Section 10.6.1.

IKd arm (experimental arm)

Drug administration (after pre-medication as described Section 8.2.2) for patients treated with isatuximab, carfilzomib, and dexamethasone combination is as follows:

- Dexamethasone 20 mg on Days 1, 2, 8, 9, 15, 16, 22, and 23 in a 28-day cycle, between 15 to 30 minutes (but no longer than 60 minutes) prior to isatuximab or at least 30 minutes prior to carfilzomib on the days when there is no isatuximab administration. Dexamethasone will be administered IV on the days of isatuximab and/or carfilzomib administration and PO on the other days (see Section 8.2.2).
- Isatuximab is to be administered IV at a dose of 10 mg/kg weekly for the first month, then Q2W thereafter. The rate of infusion for isatuximab should be initiated at 175 mg/hour.

  Patients still receiving isatuximab will switch to the registered infusion rate as described below. For those patients, premedication for the prevention of infusion reaction (IR) has to be given for the first isatuximab infusions. Patients who do not experience an IR upon 4 consecutive administrations of isatuximab may have their need for subsequent premedication reconsidered, at the Investigator's discretion.

  - First isatuximab infusions: initiate infusion at 25 mL/hour. In the absence of IRs after 1 hour of infusion, increase infusion rate by 25 mL/hour increments every 30 minutes, to a maximum of 150 mL/hour. In case of grade 2 IR during first infusion, infusion could be restarted at one-half of the initial infusion rate (12.5 mL/hour) when the IR improves to Grade ≤1. If symptoms do not recur after 30 minutes, the infusion rate may be increased by 25 mL/hour increments every 30 minutes, until the total volume is infused to maximum rate of 150 mL/hr.
  - Second infusion: Initiate infusion at 50 mL/hour. In the absence of Grade 2 IR after 30 minutes of infusion, increase rate to 100 mL/hour for 30 minutes, then, to 200 mL/hour until the total volume is infused.
  - In case of Grade 2 IR during second infusion, infusion could be restarted at one-half of the initial infusion rate (25 mL/hour) when the IR improves to Grade ≤1. If symptoms do not recur after 30 minutes, the infusion rate may be increased by 50 mL/hour increments every 30 minutes, until the total volume is infused to maximum rate of 200 mL/hr.

- Third and subsequent infusions: Initiate infusion at a fixed infusion rate of 200 mL/hour, until the total volume is infused. In case of Grade 2 IR during third infusion, infusion could be restarted at one-half (100 mL/hour) of the infusion rate (100 mL/hour) when the IR improves to Grade ≤1. If symptoms do not recur after 30 minutes, the infusion rate may be increased by 50 mL/hour increments every 30 minutes, until the total volume is infused to maximum rate 200 mL/hr.
- Guidelines for patients who develop IARs are provided in Section 10.6.1.

- Carfilzomib (after appropriate hydration, see Section 8.2.3) is to be administered IV over 30 minutes at a dose of 20 mg/m^2 on Days 1 and 2, 56 mg/m^2 on Days 8, 9, 15, and 16 of Cycle 1, and then 56 mg/m^2 on Days 1, 2, 8, 9, 15, and 16 of all further cycles. The carfilzomib infusion should follow the isatuximab infusion and should begin just after the end of the isatuximab infusion. The dose will be escalated to 56 mg/m^2 on Day 8 and for further administrations if the patient did not experience any toxicity Grade >2 (except non-complicated hematological toxicity (toxicity meaning related to study treatment) or recovered tumor lysis syndrome (TLS)).

Kd arm (control arm)

Drug administration for patients treated with carfilzomib and dexamethasone combination is as follow:

- Dexamethasone 20 mg on Days 1, 2, 8, 9, 15, 16, 22, and 23, at least 30 mins prior to carfilzomib on the days of carfilzomib administration. Dexamethasone will be administered IV on the days of carfilzomib administration and PO on the other days.
- Carfilzomib (after appropriate hydration, see Section 8.2.3) is to be administered IV over 30 mins at a dose of 20 mg/m^2 on Days 1 and 2, 56 mg/m^2 on Days 8, 9, 15, and 16 of Cycle 1, then 56 mg/m^2 on Days 1, 2, 8, 9, 15, and 16 of all further cycles. The dose will be escalated to 56 mg/m^2 on Day 8 and for further administrations if the patient did not experience any toxicity higher than Grade 2 (except non-complicated hematological toxicity (toxicity meaning related to study treatment) or recovered TLS).

As per amended protocol 09, for patients still on treatment in IKd arm and patients in Kd arm, the omission of carfilzomib dosing on Days 8 and 9 while keeping or not dexamethasone dosing on Day 8, 9, 22, 23 is authorized if patient requests a more convenient schedule and if investigator judges that the maximum benefit has been reached with the weekly schedule. Same dose modification recommendations will be followed. If carfilzomib dose was decreased due to adverse event at the time the decision is taken, dose of carfilzomib cannot be re-increased while it could be possible for dexamethasone based on Investigator judgement.

8.2.2 Premedication (NIMP): prevention of infusion associated reactions

Patients allocated to the IKd arm should routinely receive premedication prior to isatuximab infusion to reduce the risk and severity of IARs commonly observed with mAbs. The recommended premedication agents are diphenhydramine 25 to 50 mg IV (or equivalent), dexamethasone IV/PO (dose defined below), ranitidine 50 mg IV (or equivalent), and acetaminophen 650 to 1000 mg PO 15 to 30 minutes (but no longer than 60 minutes) prior to

isatuximab infusion. Once the premedication regimen is completed, the isatuximab infusion must start immediately.

The day of isatuximab administration, the following order is recommended:

- Acetaminophen (paracetamol) 650 mg to 1000 mg PO.
- Ranitidine 50 mg IV (or equivalent). The use of ranitidine or equivalent as IR premedication will be based on Investigators' judgement.
- Diphenhydramine 25 mg to 50 mg IV (or equivalent).
- Dexamethasone 20 mg IV (which is also part of study treatment).

In countries where there is no IV formulation of diphenhydramine or equivalent, per os formulation is allowed from the first isatuximab infusion. In this case, it should be taken one to two hours prior to isatuximab infusion start.

When carfilzomib is administered without isatuximab (patients allocated to the Kd arm and on Days 2, 8, and 16 for patients allocated to the IKd arm), dexamethasone is to be administered at least 30 minutes prior to carfilzomib infusion.

In case of dexamethasone being prematurely stopped and other study treatment being continued, steroid premedication can be considered with methylprednisolone 100 mg IV if IAR premedication is still needed for isatuximab and/or carfilzomib according to investigator judgment.

For the patients who do not experience an IAR upon 4 consecutive administrations of isatuximab, the Investigator may reconsider the need of specific isatuximab premedication for IAR.

General guidelines for the management of the IAR are provided in Section 10.6.1.

8.2.2.1 Ranitidine or equivalent

Ranitidine is presented as a solution for IV infusion. Commercial supplies of ranitidine or equivalent (other approved H2 antagonists, oral proton pump inhibitors) will be used for this study. Please refer to package insert for further details as regards to formulation, storage, and handling purposes.

The use of ranitidine or equivalent as IR premedication will be based on Investigators' judgement.

8.2.2.2 Diphenhydramine or equivalent

Diphenhydramine is presented as a solution for IV infusion. Commercial supplies of diphenhydramine or equivalent (cetirizine, promethazine) will be used for this study. Please refer to package insert for further details as regards to formulation, storage, and handling purposes.

8.2.2.3 Acetaminophen or equivalent

Commercial supplies of acetaminophen or equivalent will be used for this study. Please refer to package insert for further details as regards to formulation, storage, and handling purposes.

8.2.3 Carfilzomib hydration

At least 48 hours before Cycle 1 Day 1, oral hydration should be given as follows: 30 mL/kg/day (approximately 6 to 8 cups of liquid per day) continuing up to the time of treatment. Patient compliance must be assessed before initiating treatment, which is to be delayed if oral hydration is not adequate. Oral hydration may be continued for infusions within Cycle 1 and in Cycle 2 and beyond at the Investigator's discretion. In case of TLS occurred after prior study treatment administration, hydration for subsequent infusions will be done as needed as per investigator judgement.

Patients with a history of cardiac disease (such as CHF and cardiomyopathy) or pulmonary edema should be monitored closely for signs of fluid overload. Patients with hypertension in medical history must have controlled blood pressure before treatment initiation.

Intravenous hydration will be given immediately prior to carfilzomib on D1 and D2 during Cycle 1, and at the Investigator's discretion after Cycle 1. This will consist of 500 mL normal saline or other appropriate IV fluid prior to carfilzomib infusion over 30 to 60 minutes. The goal of the hydration program is to maintain robust urine output (eg, ≥2 L/day). Patients should be monitored periodically during this period for evidence of fluid overload.

The days where both isatuximab and carfilzomib are administered, the volume of isatuximab infusion should be considered in hydration required prior to carfilzomib infusion. If the volume of isatuximab infusion does not reach at least 500 mL, additional hydration should be administered to reach at least 500 mL. In this case, additional volume should be administered prior start of isatuximab infusion. Total volume of hydration can be less than 500 mL (no less than 250 mL) or kept at 500 mL but administered on a longer time for patients with borderline LVEF (above, but close to the eligibility criteria threshold of 40%) and/or for whom there is a risk of cardiac decompensation according to investigator's judgement. The carfilzomib infusion should be started after isatuximab infusion is completed.

8.2.4 Dose modifications

8.2.4.1 General rules

Dose modifications are permitted according to the guidelines described in this section.

Dose reduction and/or cycle delay are permitted in case of toxicity. Patients may have a dose omitted (isatuximab and/or carfilzomib and/or dexamethasone) within a cycle if toxicity occurs and the patient does not recover within 3 days after the planned day of infusion/administration. If a patient experiences several toxicities and there are conflicting recommendations, the most conservative dose adjustment recommended (dose reduction/omission/delay appropriate to the most severe toxicity) should be followed. Once a dose of carfilzomib or dexamethasone has been decreased, intra-patient re-escalation back to the previous dose level is not permitted, except for dexamethasone in case of dexamethasone if maintained on Day 8, and 9 and decision was taken after patient request for convenience to omit carfilzomib dosing on Days 8 and 9 (see Section 8.2.1). If a dose reduction is required, it is to be applied compared to the last dose level received by the patient.

Administration of the study treatment (isatuximab and/or carfilzomib and/or dexamethasone) will be discontinued in the event of an AE that persists despite appropriate dose modifications or any other AE that, in the opinion of the Investigator, warrants discontinuation.

All changes to study treatment administration must be recorded in the electronic case report form (eCRF).

Patients will receive the next cycle of study treatment after recovery of the toxicity as described below.

A new cycle of study treatment may begin on the scheduled Day 1 of a subsequent cycle if the following criteria are met.

- ANC >1000/ mm^3.
- Platelet count ≥50,000/ mm^3. For patients with plasma cells >50% of BM nucleated cells at baseline, to initiate Cycle 2, platelet counts should be ≥30,000/mm^3 regardless response status at end of Cycle 1. During Cycles 2 to 4, platelet counts should be ≥30,000/mm^3, if last response is not better than SD, but if last response is PR or better during Cycles 2 to 4, Day 1 next cycle can be administered only if platelet counts ≥50,000/mm^3. For Day 1 administration beyond Cycle 4, platelet counts should be ≥50,000/mm^3.
- Any other carfilzomib, dexamethasone, or isatuximab related AE that may have occurred in the previous cycle has recovered to Grade ≤1 or baseline severity (or according to the dose modifications shown in Section 8.2.4.3 and Section 8.2.4.4.

If these criteria are not met on the scheduled Day 1, Day 1 should be delayed until patients recover as defined above and if D1 delay is more than 3 days, the reason should be documented. If these criteria are not met within 14 days of the scheduled Day 1 (planned Day 1 Cycle n +1 corresponds to Day 29 cycle n), the patient should be discontinued from study treatment, unless there is strong evidence of clinical benefit to justify continuation of dosing with study treatment. The Investigator must discuss the rationale with the sponsor before a decision is taken. A delay for patient's convenience should be avoided during the first cycles and a delay more than 14 days has to be discussed with the Sponsor before a decision is taken.

If there are dose modifications within the previous cycle, these guidelines should be followed for the initiation of a new cycle:

- If carfilzomib dosing was omitted during the previous cycle and was restarted with a 1-level dose reduction without requiring an interruption for the remainder of the cycle, then that reduced dose level will be initiated on Day 1 of the new cycle. Once a dose of carfilzomib or dexamethasone has been reduced, intra-patient re-escalation back to the previous dose level is not permitted.
- If there are no other AEs that require a dose reduction and thrombocytopenia and/or neutropenia can be managed with supportive measures, no dose reductions are required.
- Patients may have study treatment dose delay within a cycle if toxicity occurs and recovers within the 3 days after the planned day. If toxicity does not recover within these 3 days, the dose should be omitted. The reason for a dose delay of more than 1 day and dose omission should be documented. Patients will receive the next treatment administration after recovery of the toxicity as described in Section 8.2.4.2.

If one of the study treatments is prematurely permanently discontinued, then other drug(s) can be continued until disease progression, unacceptable toxicity, or the patient wishes to discontinue further study treatment. The end of study treatment in this case will be 30 day after the date of the last study treatment administration.

8.2.4.2 Modification of isatuximab/carfilzomib/dexamethasone dose levels in case of dose reduction

No dose reduction of isatuximab is permitted. Dose omissions are allowed in case of toxicity.

If the dose of carfilzomib or dexamethasone requires reduction due to AEs, the dose will be reduced by 1 dose level relative to the current dose the patient is receiving. Several dose reductions are permitted and weekly doses can be omitted in case of ongoing AEs. Dose reduction steps for carfilzomib are shown in Table 1 and dose reduction steps for dexamethasone are shown in Table 2.

Table 1 - Dose levels for carfilzomib dose reduction

Starting dose (IV)	Dose level -1	Dose level -2	Dose level -3
20 mg/m²	15	11	-
56 mg/m²	45	36	27

Table 2 - Dose levels for dexamethasone dose reduction

Starting dose (PO/IV)	Dose level -1	Dose level -2	Dose level -3
20 mg	12	8	4

8.2.4.3 Dose adjustments in IKd arm

Details of the guidelines for dose adjustments in the case of hematologic toxicities are presented in Table 3.

Table 3 - Guidelines for dose adjustments for hematological toxicities - isatuximab/carfilzomib/dexamethasone combination

Adverse event		Recommended action on isatuximab, carfilzomib, and dexamethasone
Platelets		
Platelet count <30 x 10^9/L	Platelet count between 10 x 10^9/L and 30 x 10^9/L without bleeding	Day 1 of cycle: Delay Day 1 administration until recovery[a] as defined in Section 8.2.4.1 and maintain same dose. Within cycle: Maintain same dose isatuximab, carfilzomib, and dexamethasone.
	Platelet count <10 x 10^9/L or evidence of bleeding	Day 1 of cycle: Delay Day 1 administration until recovery[a] as defined in Section 8.2.4.1 and maintain same dose. Within cycle: Hold isatuximab, carfilzomib, and dexamethasone until platelets counts improve to ≥10 x 10^9/L and/or bleeding is controlled, and then re-start all study treatment at the same dose level. If delay is >3 days, omit the dose.
For each subsequent drop in platelet count to <30 x 10^9/L	Platelet count between 10 x 10^9/L and 30 x 10^9/L without bleeding	Day 1 of cycle: Delay Day 1 administration until recovery[a] as defined in Section 8.2.4.1 and maintain same dose. Within cycle: Maintain same dose of isatuximab, carfilzomib, and dexamethasone.
	Platelet count <10 x 10^9/L or evidence of bleeding	Day 1 of cycle: Delay Day 1 administration until recovery[a] as defined in Section 8.2.4.1 and then administer with reduction of carfilzomib by 1 dose level and same dose of isatuximab and dexamethasone. Within cycle: Hold isatuximab, carfilzomib, and dexamethasone until platelets counts improve to ≥10 x 10^9/L and/or bleeding is controlled, and then re-start with reduction of carfilzomib by 1 dose level and same dose of isatuximab and dexamethasone. If delay is >3 days, omit the dose.
Neutropenia		
Neutrophil count <1.0 x 10^9/L	Neutrophil count between 0.5-1.0 x 10^9/L	Day 1 of cycle: Delay Day 1 administration until recovery[a] as defined in Section 8.2.4.1 and maintain same dose. Within cycle: Maintain same dose of isatuximab, carfilzomib, and dexamethasone.
	Neutrophil count between <0.5 x 10^9/L	Day 1 of cycle: Delay Day 1 administration until recovery[a] as defined in Section 8.2.4.1 and maintain same dose. Within cycle: Full dose isatuximab and dexamethasone and omit dose carfilzomib until neutrophil counts improve to ≥0.5 x 10^9/L and then re-start all study treatments at the same dose level.

Adverse event	Recommended action on isatuximab, carfilzomib, and dexamethasone	
For each subsequent drop in neutrophil count to <1.0 x 10^9/L	Neutrophil count between 0.5 to 1.0 x 10^9/L	Day 1 of cycle: Delay Day 1 administration until recovery[a] as defined in Section 8.2.4.1 and maintain same dose. Within cycle: Maintain same dose of isatuximab, carfilzomib, and dexamethasone.
	Neutrophil count between <0.5 x 10^9/L	Day 1 of cycle: Delay Day 1 administration until recovery[a] as defined in Section 8.2.4.1 and maintain same dose. Within cycle: Full dose isatuximab and dexamethasone and omit dose carfilzomib until neutrophil counts improve to ≥0.5 x 10^9/L and then re-start with reduction of carfilzomib by 1 dose level and same dose of isatuximab and dexamethasone.
Febrile neutropenia and/or neutropenic infection	Day 1 of cycle: Delay Day 1 administration until recovery[a] and add G-CSF until ANC >1 x 10^9/L. Within cycle: Omit isatuximab, carfilzomib, and dexamethasone (use of G-CSF can be considered) until ANC >1 x 10^9/L and fever/infection resolved. If no other AEs, then resume study treatment at the same dose. If delay is >3 days, omit the dose. If further episodes, same instructions, but then reduce by 1 dose level of carfilzomib.	

a A dose delay of up to 14 days between cycles is permitted in order for a patient to recover to their baseline status. Beyond 14 days, the patient must be permanently discontinued from the study (see Section 8.2.4.1).

Dose adjustments for patients treated with isatuximab, carfilzomib, and dexamethasone combination in the case of non-hematological toxicity are shown in Table 4.

Table 4 - Guidelines for dose adjustments for non-hematologic adverse events – isatuximab/carfilzomib/dexamethasone combination

Adverse event	Recommended action		
	Isatuximab[a]	Carfilzomib[a]	Dexamethasone[a]
Renal dysfunction			
CrCl ≥15 mL/mins CrCl <15 mL/mins	Full dose isatuximab and same dose level of carfilzomib and dexamethasone. Day 1 of cycle: Delay Day 1 administration until CrCl returns to ≥15 mL/mins[b]. Within cycle: Omit isatuximab, carfilzomib, and dexamethasone. When CrCl returns to ≥15 mL/mins, resume full dose isatuximab, and same dose level of carfilzomib and dexamethasone. If delay is >3 days, omit the dose.		
Liver function			
AST, ALT, or total bilirubin Grade ≥3	Day 1 of cycle: Delay Day 1 administration until improvement to Grade 2 and then resume isatuximab and dexamethasone at the same dose level and reduce carfilzomib by 1 dose level[b]. Within cycle: Full dose isatuximab, dexamethasone at the same dose level, and hold carfilzomib until improvement to Grade 2 and resume carfilzomib with dose reduction by 1 dose level. If delay is >3 days, omit the dose. Discontinue carfilzomib if recurrence despite 3 dose reductions.		

Adverse event	Recommended action		
	Isatuximab[a]	Carfilzomib[a]	Dexamethasone[a]
Grade 3-4 infection without concomitant neutropenia	Day 1 of cycle: Delay Day 1 administration until systemic treatment of infection complete[b]. Within cycle: Hold study treatment until systemic treatment of infection complete. If delay is >3 days, omit the dose. Resume isatuximab, carfilzomib, and dexamethasone at the same dose level.		
Peripheral neuropathy			
Grade 2 with pain or Grade 3	Day 1 of cycle: Delay Day 1 administration until improvement to Grade 2 without pain and administer isatuximab and dexamethasone at the same dose level, and reduce carfilzomib by 1 dose level[b]. Within cycle: Full dose isatuximab, dexamethasone at the same dose level, and hold carfilzomib until improvement to Grade 2 without pain and reduce by 1 dose level. Discontinue carfilzomib if recurrence despite 3 dose reductions.		
Grade 4	Discontinue carfilzomib and hold isatuximab and dexamethasone. When improvement at least Grade 2 with pain or Grade 3, resume isatuximab and dexamethasone at the same dose level.		
Cardiac toxicity			
Congestive heart failure or Decreased LVEF <40% or reduction LVEF to <55% with drop greater than 20% from baseline	Day 1 of cycle: Delay Day 1 administration until returns to >40%, or if held due to a drop to >55% until returns to within 15% of baseline and resume full dose isatuximab, dexamethasone at the same dose level, and based on benefit risk assessment to re-start carfilzomib with dose reduced by 1 dose level or to stop carfilzomib[b]. Within cycle: Hold study treatment until returns to >40%, or until returns to within 15% of baseline and resume full dose isatuximab, dexamethasone at the same dose level and based on benefit risk assessment to re-start carfilzomib with dose reduced by 1 dose level or to stop carfilzomib. If delay is >3 days, omit the dose. Discontinue carfilzomib if recurrence despite 1 dose reduction.		
Myocardial infarction	Discontinue carfilzomib. Day 1 of cycle: Delay Day 1 administration until recovery, resume full isatuximab dose and dexamethasone at the same dose level if and when clinically appropriate[b]. Within cycle: After recovery, resume full isatuximab dose and dexamethasone at the same dose level if and when clinically appropriate. If delay is >3 days, omit the dose.		
Pulmonary hypertension	Day 1 of cycle: Delay Day 1 administration until recovery or return to baseline value and then resume full isatuximab dose and dexamethasone at the same dose level, and based on benefit risk assessment to re-start carfilzomib with dose reduced by 1 dose level or to stop carfilzomib[b]. Within cycle: Hold study treatment until resolution or return to baseline value and resume dexamethasone at the same dose level and based on benefit risk assessment to re-start carfilzomib with dose reduced by 1 dose level or to stop carfilzomib. If delay is >3 days, omit the dose. Discontinue carfilzomib if recurrence despite 1 dose reduction.		
Pneumonitis/interstitial disease (as ADRS were associated with these symptoms)			
Including acute distress respiratory syndrome, acute respiratory failure	Day 1 of cycle: Delay Day 1 administration until Grade ≤1, and resume full isatuximab dose and dexamethasone at the same dose level, and based on benefit risk assessment to re-start carfilzomib with dose reduced by 1 dose level or to stop carfilzomib. Within cycle: Hold study treatment until Grade ≤1 and resume full isatuximab dose and dexamethasone at the same dose level, and based on benefit risk assessment to re-start carfilzomib with dose reduced by 1 dose level or to stop carfilzomib. If delay is >3 days, omit the dose. Discontinue carfilzomib if recurrence despite 1 dose reduction.		

Adverse event	Recommended action		
	Isatuximab[a]	Carfilzomib[a]	Dexamethasone[a]
Thrombotic microangiopathy			
Including thrombotic thrombocytopenic purpura and hemolytic uremic syndrome	Day 1 of cycle: Delay Day 1 administration until Grade ≤1, and resume full isatuximab dose and dexamethasone at the same dose level, and based on benefit risk assessment to re-start carfilzomib with dose reduced by 1 dose level or to stop carfilzomib. Within cycle: Hold study treatment until Grade ≤1 and resume isatuximab dose and dexamethasone at the same dose level, and based on benefit risk assessment to re-start carfilzomib with dose reduced by 1 dose level or to stop carfilzomib. If delay is >3 days, omit the dose. Discontinue carfilzomib if recurrence despite 1 dose reduction.		
Posterior reversible encephalopathy syndrome (PRES)			
Symptom can include headaches, altered mental status, seizures, visual loss, and hypertension	Discontinue carfilzomib. Day 1 of cycle: Delay Day 1 administration until recovery, resume full isatuximab dose and dexamethasone at the same dose level if and when clinically appropriate[b]. Within cycle: After recovery, resume full isatuximab dose and dexamethasone at the same dose level if and when clinically appropriate. If delay is >3 days, omit the dose.		
Edema excluding infusion associated reaction and excluding edema from cardiac origin			
Grade ≥3 (limiting function and unresponsive to therapy or anasarca)	Day 1 of cycle or within cycle: Maintain full dose isatuximab as planned.	Day 1 of cycle or within cycle: Maintain full dose carfilzomib as planned.	Diuretics as needed, and decrease dexamethasone dose by 1 dose level; if edema persists despite above measures, decrease dose another dose level. If symptoms persist despite second reduction, dexamethasone permanently discontinued.
Confusion or mood alteration not related to PRES			
Grade ≥2 (interfering with function ±daily activities)	Day 1 of cycle or within cycle: Maintain full dose isatuximab as planned.	Day 1 of cycle or within cycle: Maintain same dose level of carfilzomib as planned.	Hold dexamethasone until symptoms resolve. Restart with 1 dose level reduction. If symptoms persist despite above measures, dexamethasone permanently discontinued.
Herpes zoster	Hold study treatment until lesions are dry, then resume all at the same dose level with appropriate prophylaxis.		
Gastrointestinal Dyspepsia, gastric or duodenal ulcer, gastritis			
Grade 1-2 (requiring medical management)	Day 1 of cycle or within cycle: Maintain full dose isatuximab as planned.	Day 1 of cycle or within cycle: Maintain same dose level of carfilzomib as planned.	Maintain same dose level of dexamethasone. Treat with H2 blockers, sucralfate, or omeprazole. If symptoms persist despite above measures, decrease dexamethasone dose by 1 dose level.

Adverse event	Recommended action		
	Isatuximab[a]	**Carfilzomib**[a]	**Dexamethasone**[a]
Grade ≥3 (requiring hospitalization or surgery)	Day 1 of cycle: Delay Day 1 administration until recovery[b].Then, restart full dose isatuximab and same dose level of carfilzomib, and decrease dexamethasone by 1 dose level of current dose along with concurrent therapy with H2 blockers, sucralfate, or omeprazole. Within cycle: Hold study treatment until symptoms adequately controlled. Then, restart full dose isatuximab and same dose level of carfilzomib, and decrease dexamethasone by 1 dose level of current dose along with concurrent therapy with H2 blockers, sucralfate, or omeprazole. If delay >3 days, omit the dose. If symptoms persist despite above measures, dexamethasone permanently discontinued.		
Acute pancreatitis	Dexamethasone permanently discontinued. Day 1 of cycle: Delay Day 1 administration until recovery[c] and re-start full dose isatuximab and same dose level of carfilzomib[b]. Within cycle: Hold all study treatment until recovery and re-start full dose isatuximab and same dose level of carfilzomib. If delay is >3 days, omit the dose.		
Hyperglycemia Grade ≥3	Day 1 of cycle or within cycle: Maintain full dose isatuximab as planned.	Day 1 of cycle or within cycle: Maintain same dose level of carfilzomib as planned.	Treatment with insulin or oral hypoglycemic agents as needed. If uncontrolled despite above measures, decrease dose by 1 dose level until levels are satisfactory.
Muscle weakness Grade ≥2 (symptomatic and interfering with function ±daily activities)	Day 1 of cycle or within cycle: Maintain full dose isatuximab as planned.	Day 1 of cycle or within cycle: Maintain same dose level of carfilzomib as planned.	Decrease dexamethasone by 1 dose level. If weakness persists despite above measures decrease dose by 1 level. If symptoms persist, dexamethasone permanently discontinued.
Any other drug related non-hematologic Grade 3-4 AE (please also refer to Section 8.2.9 for handling of TLS)	Day 1 of cycle: Delay Day 1 administration until recovery and apply rules of dose modification described below[b]. Within cycle: For isatuximab attribution, omit dose if the event has not recovered within 3 days. Resume at full dose when toxicity has improved to Grade 2 or less or to baseline grade. Second episode, isatuximab discontinuation. For dexamethasone attribution omit dose if the event has not recovered within 3 days. Resume with 1 dose level decrease when toxicity has resolved to Grade 2 or less or to baseline grade. Second episode, apply new dose reduction. Third episode, dexamethasone discontinuation. For carfilzomib attribution, hold dose. Resume with 1 dose level decrease when toxicity has improved to Grade 2 or less or recovered to baseline grade. Second episode, apply new dose reduction. Third episode, carfilzomib discontinuation.		

a Patients may have isatuximab, carfilzomib, and/or dexamethasone dose omission within a cycle if certain toxicities do not recover within 3 days following the day of planned infusion (see Section 8.2.4.1).

b A dose delay of up to 14 days between cycles is permitted in order to recover to the patient´s baseline status. Beyond 14 days, the patient must be permanently discontinued from the study (see Section 8.2.4.1).

c See Section 10.6.1 for IAR management.

8.2.4.4 Dose adjustments in Kd arm

Dose adjustments for patients treated with carfilzomib and dexamethasone combination in the case of hematological toxicity are shown in Table 5.

Table 5 - Guidelines for dose adjustments for hematologic toxicities – carfilzomib/dexamethasone combination

Adverse event	Recommended action	
Platelets	**Carfilzomib**	**Dexamethasone**
Platelet count <30 x 10^9/L	Platelet count between 10 x 10^9/L and 30 x 10^9/L without bleeding	Day 1 of cycle: Delay Day 1 administration until recovery[a] as defined in Section 8.2.4.1 and maintain same dose. Within cycle: Maintain same dose of carfilzomib and dexamethasone
	Platelet count <10 x 10^9/L or evidence of bleeding	Day 1 of cycle: Delay Day 1 administration until recovery[a] as defined in Section 8.2.4.1 and maintain same dose. Within cycle: Hold carfilzomib and dexamethasone until platelets counts improve to ≥10 x 10^9/L and/or bleeding is controlled, and then re-start all study treatment at the same dose level. If delay is >3 days, omit the dose.
For each subsequent drop in platelet count to <30 x 10^9/L	Platelet count between 10 x 10^9/L and 30 x 10^9/L without bleeding	Day 1 of cycle: Delay Day 1 administration until recovery[a] as defined in Section 8.2.4.1 and maintain same dose. Within cycle: Maintain same dose of carfilzomib and dexamethasone.
	Platelet count <10 x 10^9/L or evidence of bleeding	Day 1 of cycle: Delay Day 1 administration until recovery[a] as defined in Section 8.2.4.1 and then administer with reduction of carfilzomib by 1 dose level and same dose of dexamethasone. Within cycle: Hold carfilzomib and dexamethasone until platelets counts improve to ≥10 x 10^9/L and/or bleeding is controlled, and then re-start with reduction of carfilzomib by 1 dose level and same dose of dexamethasone. If delay is >3 days, omit the dose.
Neutropenia		
Neutrophil count <1.0 x 10^9/L	Neutrophil count between 0.5-1.0 x 10^9/L	Day 1 of cycle: Delay Day 1 administration until recovery[a] as defined in Section 8.2.4.1 and maintain same dose. Within cycle: Maintain same dose of carfilzomib and dexamethasone.
	Neutrophil count between <0.5 x 10^9/L	Day 1 of cycle: Delay Day 1 administration until recovery[a] as defined in Section 8.2.4.1 and maintain same dose. Within cycle: Hold carfilzomib and dexamethasone until neutrophil counts improve to ≥0.5 x 10^9/L and then re-start all study treatment at the same dose level. If delay is >3 days, omit the dose.

Adverse event		Recommended action
For each subsequent drop in neutrophil count to <1.0 x 10^9/L	Neutrophil count between 0.5-1.0 x 10^9/L	Day 1 of cycle: Delay Day 1 administration until recovery[a] as defined in Section 8.2.4.1 and maintain same dose. Within cycle: Maintain same dose of carfilzomib and dexamethasone.
	Neutrophil count between <0.5 x 10^9/L	Day 1 of cycle: Delay Day 1 administration until recovery[a] as defined in Section 8.2.4.1 and maintain same dose. Within cycle: Hold carfilzomib and dexamethasone until neutrophil counts improve to ≥0.5 x 10^9/L and then re-start with reduction of carfilzomib by 1 dose level and same dose of dexamethasone. If delay is >3 days, omit the dose.
Febrile neutropenia and/or neutropenic infection	Day 1 of cycle: Delay Day 1 administration until recovery[a]. and add G-CSF until ANC >1 x 10^9/L. Within cycle: Omit carfilzomib and dexamethasone (use of G-CSF can be considered) until ANC >1 x 10^9/L and fever/infection resolved. If no other AEs, then resume study treatment at the same dose. If delay is >3 days, omit the dose. If further episodes, same instructions, but then reduce by 1 dose level of carfilzomib.	

a A dose delay of up to 14 days between cycles is permitted in order for a patient to recover to their baseline status. Beyond 14 days, the patient must be permanently discontinued from the study (see Section 8.2.4.1).

Dose adjustments for patients treated with carfilzomib and dexamethasone combination in the case of non-hematological AEs are shown in Table 6.

Table 6 - Guidelines for dose adjustments for non-hematologic adverse events – carfilzomib/dexamethasone combination

Adverse event	Recommended action	
	Carfilzomib[a]	**Dexamethasone[a]**
Renal dysfunction		
CrCl ≥15 mL/mins	Same dose level of carfilzomib and dexamethasone.	
CrCl <15 mL/mins	Day 1 of cycle: Delay Day 1 administration until CrCl returns to ≥15 mL/mins.b Within cycle: Hold carfilzomib and dexamethasone. When CrCl returns to ≥15 mL/mins, resume same dose level of carfilzomib and dexamethasone. If delay is >3 days, omit the dose.	
Liver function		
AST, ALT, or total bilirubin Grade ≥3	Day 1 of cycle: Delay Day 1 administration until improvement to Grade 2 and then resume dexamethasone at the same dose level and reduce carfilzomib by one dose level[b]. Within cycle: Dexamethasone at the same dose level, and omit carfilzomib until improvement to Grade 2 and then resume carfilzomib with dose reduction by 1 dose level. Discontinue carfilzomib if recurrence despite 3 dose reductions.	
Grade 3-4 infection without concomitant neutropenia	Day 1 of cycle: Delay Day 1 administration until systemic treatment of infection complete[b]. Within cycle: Hold study treatment until systemic treatment of infection complete. If delay is >3 days, omit the dose. Resume carfilzomib and dexamethasone at the same dose level.	

Adverse event	Recommended action	
	Carfilzomib[a]	Dexamethasone[a]
Peripheral neuropathy		
Grade 2 with pain or Grade 3	Day 1 of cycle: Delay Day 1 administration until improvement to Grade 2 without pain and administer dexamethasone at the same dose level and reduce carfilzomib by 1 dose level. Within cycle: Dexamethasone at the same dose level and hold carfilzomib until improvement to Grade 2 without pain and reduce by 1 dose level. Discontinue carfilzomib if recurrence despite 3 dose reductions.	
Grade 4	Discontinue carfilzomib and hold dexamethasone. When improvement at least Grade 2 with pain or Grade 3 resume dexamethasone at the same dose level.	
Cardiac toxicity		
Congestive heart failure or Decreased LVEF <40% or reduction LVEF to <55% with drop greater than 20% from baseline	Day 1 of cycle: Delay Day 1 administration until returns to >40% or, if held due to a drop, to >55%, until returns to within 15% of baseline and resume dexamethasone at the same dose level, and carfilzomib with dose reduced by 1 dose level based on benefit risk assessment[b]. Within cycle: Hold study treatment until returns to >40%, or until returns to within 15% of baseline and resume dexamethasone at the same dose level and carfilzomib with dose reduced by 1 dose level based on benefit risk assessment. If delay is >3 days, omit the dose. Discontinue carfilzomib if recurrence despite 1 dose reduction.	
Myocardial infarction	Discontinue all study treatment.	
Pulmonary hypertension	Day 1 of cycle: Delay Day 1 administration until recovery or return to baseline value and then resume dexamethasone at the same level, and based on benefit risk assessment to re-start carfilzomib with dose reduced by 1 dose level or to stop carfilzomib[b]. Within cycle: Hold study treatment until resolution or return to baseline value and resume dexamethasone at the same dose level and carfilzomib with dose reduced by 1 dose level based on benefit risk assessment. If delay is >3 days, omit the dose. Discontinue study treatment if recurrence despite 1 dose reduction.	
Pneumonitis/interstitial disease (as ADRS were associated with these diagnoses)		
Including acute distress respiratory syndrome, acute respiratory failure	Day 1 of cycle: Delay Day 1 administration until Grade ≤1, and based on benefit risk assessment to re-start carfilzomib with dose reduced by 1 dose level and same dose dexamethasone or to stop study treatment. Within cycle: Hold study treatment until Grade ≤1 and based on benefit risk assessment to re-start carfilzomib with dose reduced by 1 dose level and same dose of dexamethasone or to stop study treatment. If delay is >3 days, omit the dose. Discontinue study treatment if recurrence despite 1 dose reduction.	
Thrombotic microangiopathy		
Including thrombotic thrombocytopenic purpura and hemolytic uremic syndrome	Day 1 of cycle: Delay Day 1 administration until Grade ≤1, and based on benefit risk assessment to re-start carfilzomib with dose reduced by 1 dose level and same dose dexamethasone or to stop study treatment. Within cycle: Hold study treatment until Grade ≤1 and based on benefit risk assessment to re-start carfilzomib with dose reduced by 1 dose level and same dose of dexamethasone or to stop study treatment. If delay is >3 days, omit the dose. Discontinue study treatment if recurrence despite 1 dose reduction.	

Adverse event	Recommended action	
	Carfilzomib[a]	Dexamethasone[a]
Posterior reversible encephalopathy syndrome (PRES)		
Symptom can include headaches, altered mental status, seizures, visual loss and hypertension	Discontinue all study treatment.	
Edema excluding infusion associated reaction and excluding edema from cardiac origin		
Grade ≥3 (limiting function and unresponsive to therapy or anasarca)	Day 1 of cycle or within cycle: Maintain full dose carfilzomib as planned.	Diuretics as needed and decrease dexamethasone dose by 1 dose level; if edema persists despite above measures, decrease dose another dose level. If symptoms persist despite second reduction, dexamethasone permanently discontinued.
Confusion or mood alteration not related to PRES		
Grade ≥2 (interfering with function ±daily activities)	Day 1 of cycle or within cycle: Maintain same dose level of carfilzomib as planned.	Hold dexamethasone until symptoms resolve. Restart with 1 dose level reduction. If symptoms persist despite above measures, dexamethasone permanently discontinued.
Herpes zoster	Hold study treatment until lesions are dry, then resume all at the same dose level with appropriate prophylaxis.	
Gastrointestinal Dyspepsia, gastric or duodenal ulcer, gastritis		
Grade 1-2 (requiring medical management)	Day 1 of cycle or within cycle: Maintain same dose level of carfilzomib as planned.	Treat with H2 blockers, sucralfate, or omeprazole. If symptoms persist despite above measures, decrease dexamethasone dose by 1 dose level.
Grade ≥3 (requiring hospitalization or surgery)	Day 1 of cycle: Delay Day 1 administration until recovery.[c] Then, restart same dose level of carfilzomib, and decrease dexamethasone by one dose level of current dose along with concurrent therapy with H2 blockers, sucralfate, or omeprazole. Within cycle: Hold study treatment until symptoms adequately controlled. Then, restart same dose level of carfilzomib, and decrease dexamethasone by 1 dose level of current dose along with concurrent therapy with H2 blockers, sucralfate, or omeprazole. If delay >3 days, omit the dose. If symptoms persist despite above measures, dexamethasone permanently discontinued.	
Acute pancreatitis	Dexamethasone permanently discontinued. Day 1 of cycle: Delay Day 1 administration until recovery[c] and re-start same dose level of carfilzomib. Within cycle: Hold all study treatment until recovery and re-start same dose level of carfilzomib.	
Hyperglycemia Grade ≥3	Day 1 of cycle or within cycle: Maintain same dose level of carfilzomib as planned.	Treatment with insulin or oral hypoglycemic agents as needed. If uncontrolled despite above measures, decrease dose by 1 dose level until levels are satisfactory.
Muscle weakness Grade ≥2 (symptomatic and interfering with function ±daily activities)	Day 1 of cycle or within cycle: Maintain same dose level of carfilzomib as planned.	Decrease dexamethasone by 1 dose level. If weakness persists despite above measures decrease dose by 1 level. If symptoms persist dexamethasone permanently discontinued.

Adverse event	Recommended action	
	Carfilzomib[a]	Dexamethasone[a]
Any other drug related non-hematologic Grade 3-4 AE (please also refer to Section 8.2.9 for handling of TLS)	Day 1 of cycle: Delay Day 1 administration until recovery[c] and apply rules of dose modification described below. Within cycle: For dexamethasone attribution omit dose if the event has not recovered within 3 days. Resume with 1 dose level decrease when toxicity has resolved to Grade 2 or less or to baseline grade. Second episode, apply new dose reduction. Third episode, dexamethasone discontinuation. For carfilzomib attribution, hold dose. Resume with 1 dose level decrease when toxicity has improved to Grade 2 or less or recovered to baseline grade. Second episode, apply new dose reduction. Third episode, carfilzomib discontinuation.	

a Patients may have carfilzomib and/or dexamethasone dose omission within a cycle if certain toxicities do not recover within 3 days following the day of planned infusion (see Section 8.2.4.1).
b A dose delay of up to 14 days between cycles is permitted in order to recover to the patient´s baseline status. Beyond 14 days, the patient must be permanently discontinued from the study (see Section 8.2.4.1).
c See Section 10.6.1 for IAR management.

8.2.5 Infusion reactions

Patients should receive premedications prior to isatuximab and carfilzomib infusion as detailed in Section 8.2.2 to reduce the risk and severity of IARs commonly observed with mAbs and with carfilzomib. Infusion associated reactions (including, for example, NCI-CTCAE v4.03 terms 'infusion related reaction', 'anaphylactic reaction', or 'cytokine release syndrome') are defined as AEs related to product administration with onset typically within 24 hours from the start of the infusion. Possible increase in creatinine has been reported on the subsequent day of carfilzomib administration which may be the clinical sequelae of rapid tumor lysis and/or cytokine release.

Please refer to the current edition of the Investigator's brochure for IARs manifestations reported in patients treated with isatuximab and refer to carfilzomib product information for IARs manifestation reported with carfilzomib.

In case of IAR while receiving or after isatuximab/carfilzomib administration, additional medication can be provided for symptom treatment as per Investigator judgment including diphenhydramine 25 mg IV (or equivalent) and methylprednisolone 100 mg IV, IV fluids, vasopressors, oxygen, bronchodilators, and acetaminophen or paracetamol. These patients must be informed of the potential risk of recurrent IARs.

Further treatment with isatuximab (subsequent infusions) with the fixed rate:

- In case of Grade 2 IR during second infusion, infusion could be restarted at one-half of the initial infusion rate (25 mL/hour) when the IR improves to Grade ≤1. If symptoms do not recur after 30 minutes, the infusion rate may be increased by 50 mL/hour increments every 30 minutes, until the total volume is infused to maximum rate of 200 mL/hr.
- In case of Grade 2 IR during third infusion and subsequent, infusion could be restarted at one-half (100 mL/hour) of the infusion rate (100 mL/hour) when the IR improves to Grade ≤1. If symptoms do not recur after 30 minutes, the infusion rate may be increased by 50 mL/hour increments every 30 minutes, until the total volume is infused to maximum rate 200 mL/hr.

Patients with a Grade 3 or 4 IAR must have the causative study treatment permanently discontinued and appropriate supportive therapy should be administered. If there is no possibility to distinguish which drug induced the IAR, study treatment should be permanently discontinued.

In case of Grade 3 or 4 IAR occurring during isatuximab infusion, carfilzomib infusions will be postponed by one day (eg, planned D1 will be done on D2 and planned D2 will be done on D3) assuming that the IAR improved to Grade ≤1.

Grade ≥3 IARs must be reported as AESIs (see Section 10.4.1.3).

Table 7 - Management of infusion associated reactions

NCI-CTCAE v4.03 criteria definition	Intervention recommendation
Mild (Grade 1) Infusion interruption or intervention not indicated	Continuation of isatuximab/carfilzomib infusion per the judgment of the Investigator following close direct monitoring of the patient's clinical status. Isatuximab/carfilzomib infusion may be stopped at any time if deemed necessary. If stopped, IAR will be classified as Grade 2 as per NCI-CTCAE.
Moderate (Grade 2) Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hours	Stop isatuximab/carfilzomib infusion. Give additional medication with IV diphenhydramine 25 mg IV (or equivalent, see Section 8.2.3) and/ or IV methylprednisolone 100 mg (or equivalent) as needed. Isatuximab/carfilzomib may be resumed only after patient recovery, with slower infusion rate for isatuximab and with close monitoring.
Severe or life-threatening (Grade 3 or 4) Grade 3: Prolonged (eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae Grade 4: Life-threatening consequences; urgent intervention indicated	Stop isatuximab/carfilzomib infusion. Give additional medication with diphenhydramine 25 mg IV (or equivalent, see Section 8.2.3) and/ or IV methylprednisolone 100 mg (or equivalent) and/or epinephrine as needed. If responsible drug has been clearly identified, permanent discontinuation of this drug. If responsible drug cannot be clearly identified, definitive study treatment discontinuation.

Note: The infusion should be completed within 16 hours from the end of infusion preparation or a new infusion should be prepared with the remaining dose to be administered the same day.

8.2.6 Posterior reversible encephalopathy syndrome and progressive multifocal leukoencephalopathy

Patients should be monitored for any new or worsening neurologic, cognitive or behavioral signs and symptoms.

If posterior reversible encephalopathy syndrome (PRES) or progressive multifocal leukoencephalopathy (PML) is suspected, study treatment should be interrupted and the Investigator should refer patient to a specialist and appropriate diagnosis testing should be initiated.

If PRES or PML is confirmed, carfilzomib should be discontinued. The full dose of isatuximab and dexamethasone at the same dose level should be resumed if and when clinically appropriate. If the delay is more than 14 days, the study treatment should be discontinued unless there is strong evidence of clinical benefit to justify continuation of dosing with isatuximab and dexamethasone. The Investigator must discuss the rationale with the sponsor before a decision is taken.

8.2.7 Hepatitis B virus infection

An active hepatitis B (defined as a known positive HBsAg) is an exclusion criterion. Patients with resolved HBV infection (HBsAg negative and anti-HBc and/or anti-HBs positive) are allowed to be enrolled. HBV reactivation was noted in MM patients with resolved HBV infection who are treated with immunosuppressive chemotherapy and either novel agents. Following identification of risk of hepatitis B virus (HBV) infection reactivation among patients treated with carfilzomib reported in September 2019, HBV serology (HBsAg, hepatitis B core antibody [anti-HBc] and hepatitis B surface antibody [anti-HBs]) should be done once for patients still receiving carfilzomib with unknown HBV status. Serology will be repeated if clinically indicated. Patients with HBsAg positive and/or anti-HBc antibody positive should also have HBV DNA testing by polymerase chain reaction.

To consider consulting a specialist for patients who test positive for HBV during study treatment with carfilzomib.

For patients who are carriers of HBV (HBsAg negative and anti-HBc positive [13]), prophylaxis with antivirals should be considered. These patients should be closely monitored for signs and symptoms of active HBV infection throughout and following the end of treatment with carfilzomib (up to 3 months or initiation of further anticancer therapy).

Carfilzomib should be withheld for patients with active HBV infection until infection is adequately controlled. The safety of resuming carfilzomib after HBV reactivation is adequately controlled is not known.

Patients with HBV positive serology should be monitored throughout the study treatment and in follow-up up to 3 months or initiation of further anticancer therapy.

8.2.8 Cardiac failure

Death due to cardiac arrest has occurred within a day of carfilzomib administration. New onset or worsening of pre-existing CHF with decreased left ventricular function or myocardial ischemia has occurred following administration of carfilzomib. Cardiac failure events (eg, cardiac failure congestive, pulmonary edema, and ejection fraction decreased) were reported in 7% of patients. Close monitoring should therefore be done for cardiac complications, which should be managed promptly.

Any patients with symptoms of CHF or any other suspected acute cardiac event, whether or not drug related, must have study treatment held until resolution. After the event has resolved or returned to baseline, treatment may continue at a reduced carfilzomib dose. In case of recurrence occurs despite 1 dose level reduction of carfilzomib, after the event has resolved or returned to baseline, carfilzomib will be discontinued and the full dose of isatuximab and dexamethasone at the same level dose can be continued. Treatment may continue at a reduced carfilzomib dose.

In the case of any sign of persistent CHF or LV dysfunction as described in Table 4 and Table 5, or if there is no resolution of CHF after 2 weeks, study treatment is to be discontinued unless there is strong evidence of clinical benefit to justify continuation of dosing with isatuximab and dexamethasone. The Investigator must discuss the rationale with the sponsor before a decision is taken.

8.2.9 Tumor Lysis syndrome

Tumor lysis syndrome may occur and is a life threatening event. Hydration prior carfilzomib is required for all patients prior D1 and D2 infusions of Cycle 1 and is left to Investigator judgment for further cycles.

The patients at greatest risk of TLS are those with high tumor burden prior to treatment. These patients should be monitored closely and appropriate precautions should be taken (such as use of prophylactic uric acid lowering agents [eg, allopurinol or rasburicase], regular measurement of electrolytes).

Tumor lysis syndrome has to be managed according to site usual practice. Table 8 provides some parameters to be checked in case of TLS suspicion and high level recommendations for TLS management. Abnormalities listed in Table 8 do not support exclusively TLS diagnosis and any differential diagnosis also needs to be assessed if appropriate.

After recovery, study treatment can be re-administered as planned at the same dose.

Table 8 - Management of tumor lysis syndrome

TLS main possible diagnosis criteria	Recommended action
Laboratory TLS: ≥2 simultaneous abnormalities within 3 days prior to and up to 7 days after treatment start: • Uric acid >8 mg/dL (>475.8 µmol/L) • Potassium >6.0 mmol/L • Phosphorus >4.5 mg/dL (>1.5 mmol/L) • Corrected calcium <7.0 mg/dL (<1.75 mmol/L), ionized calcium <1.12 mg/dL (<0.3mmol/L)[a]	Omit study treatment until all serum chemistries have resolved. Ensure adequate hydration, correct laboratory abnormalities, fluid overload, uric acid lowering agents (such as rasburicase), electrolyte, or acid-base deviation. Monitor TLS complications including renal functions. Reinstitute study treatment at full dose after resolution.
Clinical TLS: Laboratory TLS in addition to 1 of the following complications: • Acute kidney injury: Increase in the serum creatinine level of 0.3 mg/dL (26.5 µmol/L) or the presence of oliguria, defined as an average urine output of <0.5 mL/kg/hour for 6 hours. • Seizures, cardiac dysrhythmia, neuromuscular irritability (tetany, paresthesias, muscle twitching, carpopedal spasm, Trousseau's sign, Chvostek's sign, laryngospasm, bronchospasm), hypotension, or heart failure probably or definitely caused by hypocalcemia. • Dysrhythmias probably or definitely caused by hyperkalemia.	

a The corrected calcium level in milligrams per deciliter = measured calcium level in milligrams per deciliter + 0.8 x (4-albumin in grams per deciliter).
Adapted from Howard et al (14).

8.2.10 Other adverse drug reactions

For Grade ≥3 ADRs except fatigue, local reaction, fluid retention, anemia, and other ADRs that are uncomfortable but do not cause serious morbidity, study treatment should be held for a maximum of 2 weeks from the planned date of next cycle until resolution to Grade ≤1, then reinstituted, if medically appropriate. A reduction of subsequent doses will be left to the Investigator's judgment.

8.3 BLINDING PROCEDURES

During the trial, administration of isatuximab is to be open-label, and no attempt will be made to blind administration.

Despite the open-label administration of isatuximab, assessment of outcomes will be based on the review of the data objectively collected for disease evaluation (radiological assessment and central laboratory disease assessments) by IRC blinded to study treatment arms.

Blinding rules for the sponsor study team will be detailed in a separate document.

8.4 METHOD OF ASSIGNING PATIENTS TO TREATMENT GROUP

All eligible patients will be randomly assigned to a treatment group (either IKd arm or Kd arm) in a 3:2 ratio using an IRT. Patient assignment to a treatment group will be performed according to a stratified randomization list according to number of prior lines 1 vs. >1 and R-ISS I or II versus III versus not classified (inconclusive FISH unless stage can be determined on LDH, albumin, and β2 microglobulin only).

After each patient has completed the necessary screening visit procedures, the corresponding baseline eCRFs have been completed and the patient is deemed eligible for study entry by the Investigator or designee based on the laboratory evaluations as defined in the study flow chart, the study site will contact the IRT.

Screen failure patients can be re-screened and all screen procedures will have to be re-started for these patients.

The randomization strata will be used by the IRT to assign the patient to the IKd or Kd arm according to the predefined randomization schedule. Details of the IRT procedure will be provided in the IRT Site Manual.

WARNING: Randomization will be blocked if study treatment is not available at site level. A minimum of time will be required between screening registration call and study treatment delivery at site level. Please consider this time between screening call and randomization call, which indicated in the IRT manual.

Study treatment should be initiated within 3 working days after randomization.

8.5 INVESTIGATIONAL MEDICINAL PRODUCT PACKAGING AND LABELING

8.5.1 Isatuximab

Isatuximab is packaged in 30 mL glass vials fitted with elastomeric closure.

Packaging is in accordance with the administration schedule. The content of the labeling is in accordance with the local regulatory specifications and requirements.

8.5.2 Carfilzomib

Please refer to package insert for further details for formulation and handling purposes.

For carfilzomib supplied by the Sponsor, the content of the labeling is in accordance with the local regulatory specifications and requirements.

8.5.3 Dexamethasone IV/PO

Please refer to package insert for further details for formulation and handling purposes.

For dexamethasone supplied by the Sponsor, the content of the labeling is in accordance with the local regulatory specifications and requirements.

8.6 STORAGE CONDITIONS AND SHELF LIFE

8.6.1 Isatuximab

Investigators or other authorized persons (eg, Pharmacists) are responsible for storing isatuximab in a secure and safe place with restricted access in accordance with local regulations, labeling specifications, policies, and procedures.

Control of isatuximab storage conditions, especially control of temperature (eg, refrigerated storage), and information on in-use stability and instructions for handling the Sanofi compound should be managed according to the rules provided by the Sponsor.

Isatuximab is to be stored at +2°C to +8°C (36°F to 46°F). All vials must be kept in their box until use.

No protection from light is required for storage in the infusion bags.

Details of the storage conditions for the diluted solution are provided in the Pharmacy Manual.

8.6.2 Carfilzomib

Please refer to package insert for storage conditions.

8.6.3 Dexamethasone IV/PO

Please refer to package insert for storage conditions.

8.7 RESPONSIBILITIES

The Investigator, the hospital pharmacist, or other personnel allowed to store and dispense the study treatment will be responsible for ensuring that the study treatment used in the clinical trial is securely maintained as specified by the Sponsor and in accordance with applicable regulatory requirements.

All study treatment will be dispensed in accordance with the Investigator's prescription and it is the Investigator's responsibility to ensure that an accurate record of study treatment issued and returned is maintained.

Any quality issue noticed with the receipt or use of a study treatment (deficiency in condition, appearance, pertaining documentation, labeling, expiration date, etc.) must be promptly notified to the Sponsor. Some deficiencies may be recorded through a complaint procedure (see Section 10.4.5).

A potential defect in the quality of study treatment may be subject to initiation of a recall procedure by the Sponsor. In this case, the Investigator will be responsible for promptly addressing any request made by the Sponsor, in order to recall the study treatment and eliminate potential hazards.

Under no circumstances will the Investigator supply study treatment to a third party (except for DTP shipment, for which a courier company has been approved by the Sponsor), allow the study treatment to be used other than as directed by this clinical trial protocol, or dispose of study treatment in any other manner.

8.7.1 Treatment accountability and compliance

Administration of the study treatment will be supervised by the Investigator or Subinvestigator.

The person responsible for dispensing study treatment is required to maintain adequate records of the study treatment. These records (eg, drug movement form) include the date the study treatment is received from the Sponsor, dispensed for patient and destroyed or returned to the Sponsor. The packaging batch number (PR Nr) on the vial must be recorded on the drug accountability form.

The person responsible for study treatment administration to the patient will record precisely the date and the time of the study treatment administration to the patient.

For dexamethasone PO, a patient diary will be used to document all oral dexamethasone (if not administered at the site level).

8.7.2 Return and/or destruction of treatments

Partially-used and used study treatment will be destroyed at the study site according to the standard practices of the site after an accurate accountability has been performed and signed by the Investigator (or the Pharmacist). A detailed treatment log form of the destroyed study treatment will be established with the Investigator (or the Pharmacist) and countersigned by the Investigator and the Monitoring Team.

The Investigator must not destroy the unused study treatment unless Sanofi provides written authorization.

8.8 CONCOMITANT MEDICATION

A concomitant medication is any treatment received by the patient concomitantly to any study treatment(s).

All treatments being taken by the patient 21 days prior to randomization, at any time during the treatment period and up to 30 days after the last dose are regarded as prior and concomitant treatments respectively, and will be reported on the appropriate pages of the eCRF.

Concomitant medications are allowed if not listed in prohibited medications and if these are considered necessary for the patient's welfare and are unlikely to interfere with the investigational product. They may be given at the discretion of the Investigator and recorded in the eCRF.

Antiviral prophylaxis, antibacterial prophylaxis and thromboprophylaxis will be done according to site/Investigator practice and local labelling of carfilzomib. For patients who are HBV carriers, prophylaxis with antivirals should be considered.

Co-treatment of dexamethasone with CYP3A inhibitors should be avoided unless the benefit outweighs the increased risk of systemic corticosteroid side-effects, in which case patients should be monitored for systemic corticosteroid side-effects (please refer to dexamethasone package insert).

8.8.1 G-CSF prophylaxis

Prophylactic administration of G-CSF in a patient who is experiencing recurrent difficulties with neutropenia, or therapeutic use in patients with serious neutropenic complications (such as tissue infection, sepsis syndrome, or fungal infection) may be considered at the Investigator’s discretion, consistent with American Society of Clinical Oncology guidelines (2006) in order to decrease the risk of neutropenia specially in patients with baseline extensive BM involvement and/or low neutrophil count.

8.8.2 Prohibited concomitant therapy

- Concurrent treatment with any other anti-myeloma therapy not specified in the protocol, including immunotherapy, hormonal therapy, targeted therapy, biological therapies, other investigational drug, or curative radiotherapy. However, palliative radiotherapy may be given to control pain. The irradiated area should be as small as possible and should never involve more than 20% of the BM in any given 3-week period. In all such cases, the possibility of tumor progression should be ruled out by physical, biochemical, and radiological assessments of the tumor. The irradiated area cannot be used as a parameter for response assessment.
- Concomitant systemic corticosteroids, other than as part of the protocol-specified therapeutic regimen or for treatment of hypersensitivity reaction, are prohibited. Additional glucocorticoids, antihistamines, and analgesics for the management of IAR are permitted. Inhaled glucocorticosteroids may be used whenever indicated.
- Live vaccines should be avoided; however, given the increased risk of infection, routine vaccinations are recommended for the patients and their contacts. Prophylactic vaccination is recommended for influenza A and B virus, pneumococci, and hemophilus influenza.

9 ASSESSMENT OF INVESTIGATIONAL MEDICINAL PRODUCT

9.1 PRIMARY ENDPOINT

The primary endpoint is PFS.

Progression free survival is defined as the time from the date of randomization to the date of first documentation of PD (as determined by the IRC) or the date of death from any cause, whichever comes first. Response will be determined according to IMWG criteria. Progression based on paraprotein will be confirmed based on 2 consecutive assessments.

The following disease assessment procedures will be performed at screening (for eligibility), at Cycle 1 Day 1 prior to study treatment administration (baseline for response assessment), Day 1 of every cycle during treatment up to progression, EOT, and for patients who discontinue study treatment without PD, every month during follow-up until PD (even patients who would initiate further anti-myeloma therapy without PD):

- M protein quantification (serum and 24-hour urine, protein immunoelectrophoresis, and IF) (central laboratory). After Cycle 1 Day 1, IF will be done in case of undetectable M protein (serum and urine).
- Serum free light chains quantification (central laboratory).
- Quantitative immunoglobulins (central laboratory).
- Bone marrow aspiration (or biopsy as clinically indicated) at baseline (bone marrow disease involvement, FISH, and MRD), and then in case of VGPR or better (local laboratory for bone marrow disease involvement and central laboratory will be done to assess MRD).
- Bone disease assessment:
  - Skeletal survey or low-dose whole body computed tomography (CT) scan at baseline, then once a year, and anytime during the study if clinically indicated.
- Extramedullary disease (plasmacytoma) assessment (including bone plasmacytoma):
  - If known extramedullary disease at baseline, CT scan or magnetic resonance imaging (MRI) is to be done at baseline, repeated every 12 weeks (±1 week) until PD (even for patients who would initiate further anti-myeloma therapy without PD), and if clinically indicated.
  - If suspected extramedullary disease (plasmacytoma) at baseline, CT scan or MRI is to be done at baseline and in case plasmacytoma is confirmed, CT scan or MRI is to be repeated every 12 weeks (±1 week) until PD (even for patients who would initiate further anti-myeloma therapy without PD), and if clinically indicated.
  - At any time during study treatment in case of suspicion of progression of existing plasmacytoma or if clinically indicated in a patient with no previous positive image for extramedullary disease.

  Note: For bone lesion assessment and extramedullary disease, the same modality (skeletal survey or low-dose whole-body CT scan; CT scan or MRI) should be used throughout the study for each individual patient. All imaging must be sent for central review.

Central labs will be used for investigator's assessment of response and continuation of treatment decisions. Response/progression will be determined according to IMWG criteria (Appendix F). Response/progression based on paraprotein will be confirmed based on 2 consecutive assessments. A blinded IRC will evaluate disease response at each cycle including progression and response status of each patient per IMWG criteria (Appendix F) and as described in the IRC Charter. The IRC assessment of response will be performed using results from central laboratory, central assessment of radiological images and, if any, local bone marrow assessment (plasma cell infiltration). Further details on the handling of missing disease assessments and the IRC process for determining the date of disease progression and overall objective response are described in the IRC Charter and/or the statistical analysis plan (SAP).

Progressive disease (IMWG criteria) is defined for patients with measurable serum and/or urine M protein as any one of the following (biological criteria in 2 consecutive assessments)::

- Increase of ≥25% in Serum M-component from nadir (the absolute increase must be ≥0.5 g/dL); serum M component increases ≥1 g/dL in 2 consecutive assessments are sufficient to define relapse if starting M component is ≥5 g/dL; and/or
- Increase of ≥25% in Urine M-component from nadir (the absolute increase must be ≥200 mg/24 hour); and/or
- Definite development of new bone lesions or soft tissue extramedullary disease or increase ≥50% from nadir in the sum of perpendicular diameters of existing soft tissue extramedullary disease lesions if >1 lesion or ≥50% increase in the longest diameter of a previous soft tissue extramedullary disease lesion >1 cm in short axis.

Clinical deterioration could be considered progression in the primary analysis of PFS if IRC considers clinical data reported in the CRF supports clinical progression. In case of hypercalcemia, a full disease assessment will be performed in order to identify any measurable parameter of myeloma progression (eg, serum and urine M protein, lytic lesions assessment and plasmacytoma assessment) and potential alternative causes of hypercalcemia should be ruled out.

Progression cannot be diagnosed on FLC progression only.

Patients with only FLC measurable disease are not allowed in the protocol.

In case of both serum and urine M protein becomes below level of eligibility on efficacy laboratory performed on Cycle 1 Day 1, please refer to Appendix F for assessment of progression and overall response.

9.2 SECONDARY ENDPOINTS

9.2.1 Key secondary efficacy endpoints

The key secondary efficacy endpoints are:

- **ORR**: Best overall response per patient will be assessed in order to determine ORR, defined as the proportion of patients with stringent complete response (sCR), CR, VGPR, and PR as best overall response as assessed by the IRC using the IMWG response criteria. Bone marrow biopsy can be done for sCR assessment as per investigator decision.
- **Rate of VGPR or better:** Defined as the proportion of patients with sCR, CR, and VGPR.

- **Rate of VGPR or better with MRD negativity (15):** Defined as the proportion of patients for whom MRD assessed by sequencing is negative at any time after first dose of study treatment. Minimal residual disease will be assessed centrally by next-generation sequencing in BM samples from patients who achieve VGPR or better, to determine the depth of response at the molecular level. Threshold for negativity will be at least 10^{-5}. Bone marrow aspirates will be collected at screening and at the time of VGPR or better confirmation. If the patient presents with VGPR or better but is determined MRD positive, another BM sample will be collected 3 months (3 cycles) later, in order to identify late negativity. A third sample may be collected after another 3 months, if the patient remains MRD positive and is still being treated. No more than 3 on-treatment BM samples are to be obtained unless a patient achieves CR after a third BM sample MRD positive performed during VGPR. In this case no more than 3 additional BM samples will be collected. Therefore, a maximum of 6 BMA could be performed by patient (no more than 3 per category of response). However, because BMA is invasive procedure, the following guidance is given in the purpose to limit as much as possible the number of BMA.
  For patients with CR without previous documentation of VGPR, first bone marrow for MRD assessment will be collected at time of confirmation of CR (ie, at the second time point showing CR) If patient is determined MRD positive, another BM sample will be collected 3 months (3 cycles) later, in order to identify late negativity. A third sample may be collected after another 3 months if the patient remains MRD positive and is still being treated.
  For patients with VGPR:
  - First bone marrow will be collected when VGPR is confirmed at the second time point or at a later time point as per investigator judgement based on kinetic of M protein decrease and/or if a plateau phase is reached (plateau is defined as variation less than 20% over 12 weeks [16]).
  - If MRD is positive on first BMA, a second BMA will be collected 3 months later (3 cycles) to identify late negativity.
  - In case of MRD is still positive on second BMA made while patient is in VGPR, the timing to perform the third BMA can be postponed until CR achievement.
  - In case of the patient becomes CR and patient was MRD positive on the last BMA performed during VGPR, a BMA will be done for MRD assessment at time of confirmation of CR.
  - After the first BMA during CR is done and in case patient was MRD positive on this BMA, the additional BMA planned by the protocol can be discussed with the patient.
- **CR rate:** Defined as the proportion of patients with sCR and CR. Patients with demonstrated isatuximab interference will be considered in the BOR category corresponding to the M protein assessment obtained without interference, when the antibody-capture interference assay will be available.
- **OS:** Defined as the time from the date of randomization to death from any cause.

9.2.2 Other secondary efficacy endpoints

Other secondary efficacy endpoints will be evaluated as follows:

- **DOR:** Defined as the time from the date of the first IRC determined response for patients achieving PR or better to the date of first documented PD determined by IRC or death, whichever happens first.
- **TTP:** Defined as time from randomization to the date of first documentation of PD (as determined by the IRC).
- **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.
- **Time to first response:** 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:** 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.

9.2.3 Safety endpoints

Safety in terms of TEAEs/AEs/SAEs, IARs, ECOG PS, laboratory parameters, vital signs, and findings from physical examination will be assessed through the study and will be reported in the eCRF.

Adverse event data will be collected throughout the study. Treatment-emergent AEs are defined as 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. Adverse events and laboratory parameters will be graded using NCI-CTCAE v4.03 (Appendix E).

Full details of safety reporting and AE monitoring procedures are provided in Section 10.4 and Section 10.7.

9.2.4 Patient-reported outcomes (HRQL/health economic variables/other endpoints)

Patient-reported outcome measures to be included are the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life questionnaire with 30 questions (QLQ-C30), the EORTC myeloma module with 20 items (QLQ-MY20), and the European Quality of Life Group measure with 5 dimensions and 5 levels per dimension (EQ-5D-5L). Each questionnaire is described in this section and presented in Appendix I (QLQ-C30), Appendix J (QLQ-MY20), and Appendix K (EQ-5D-5L).

All 3 questionnaires have been designed for self-completion. All PROs are in electronic form (ePROs) and are to be completed at the site by the patient using the study tablet provided. To minimize any bias, patients will fill out the ePROs before clinician assessments and discussion of their clinical condition, treatment plan, AEs, and any other related topics that could influence patient's perception and feelings prior to responding to the questions.

Timing of Assessments

Cycle 1 Day 1 will serve as the baseline assessment for all patients. While on treatment, ePROs are to be completed prior to treatment on Day 1 of every cycle, at the EOT visit and at 90 ±5 days after last study treatment administration. The time estimated to complete the EORTC QLQ-C30 and the EORTC QLQ-MY20 together is approximately 10 to 15 minutes. The time estimated to complete the EQ-5D-5L is approximately 5 to 10 minutes.

Since the patients are to complete ePRO questionnaires on their own, there will be 20 minutes time allocated for training patients on ePRO technology at Cycle 1 Day 1 visit. Meanwhile, assistance will be provided if a patient needs longer time to learn or have training questions (eg, a refresher) during consequent cycles. For the ePRO data it is mandatory that a key person (eg, research nurse) at each center be responsible for ePRO data collection, in order to optimize compliance of the patient and to ensure completeness of the data.

The planned statistical analysis of the 3 ePROs will be detailed in the SAP.

9.2.4.1 EORTC QLQ-C30

The EORTC QLQ-C30 is a cancer-specific instrument that contains 30 items and provides a multidimensional assessment of HRQL (17, 18, 19). The validity and reliability of the EORTC QLQ-C30 has been established in various types of cancers (20).

The EORTC QLQ-C30 provides a comprehensive assessment of the principal HRQL dimensions identified as relevant by cancer patients (physical functioning, emotional functioning, cognitive functioning, role functioning, social functioning, global HRQL, and impact of symptoms and of toxicities). The EORTC QLQ-C30 is one of the standard instruments used in oncology for the evaluation of new cancer therapies.

The QLQ-C30 is composed of 3 domains with multi-item scales. These include:

- Global health status (GHS)/quality of life (2 items).
- Functional scales:
  - Physical functioning (5 items).
  - Role functioning (2 items).
  - Emotional functioning (4 items).
  - Cognitive functioning (2 items).
  - Social functioning (2 items).
- Symptom scales/items:
  - Fatigue (3 items).
  - Nausea and vomiting (2 items).
  - Pain (2 items).
  - Dyspnea; Insomnia; Appetite loss; Constipation; Diarrhea; Financial impact (item each).

Scoring is based on 4-point Likert scales and 7-point numerical rating scales. All of the scales and single-item measures range in score from 0 to 100. A higher score for a functional scale/GHS represents a higher/healthy level of HRQL, whereas a higher score for symptoms/ items represents a higher level of symptomatology/problems. The recall period for this instrument is 1 week.

9.2.4.2 EORTC QLQ-MY20

The EORTC QLQ-MY20 is to be used in conjunction with the EORTC QLQ-C30 to assess symptoms and side effects due to the treatment or the disease which impact HRQL in patients with MM (21, 22). It contains 20 items, 4 independent subscales covering 2 functional domains:

- Symptom scales:
  - Disease symptoms (6 items).
  - Side-effects of treatment (10 items).
- Function scale:
  - Future perspective (3 items).
  - Body image (1 item).

Scores are based on the 4-point Likert scale ranging from "Not at all" to "Very much", ranging by items from 0 to 100. Higher scores for Disease Symptoms and Side Effects of Treatment indicate more symptoms and side effects and lower HRQL, whereas a high score for Future Perspective and Body Image represents better outcomes.

These are reliable and valid measures of HRQL in cancer patients and the 2 EORTC instruments (QLQ-C30 and QLQ-MY20) together (50 items) take approximately 15 minutes on average to administer. The instruments have been validated and used in many countries.

9.2.4.3 EQ-5D-5L

The EQ-5D-5L is a standardized measure of health status that provides a simple, generic measure of health utility, and consists of 2 sections: descriptive and visual analog scale (VAS).
The descriptive system consists of 5 dimensions:

- Mobility.
- Self-care.
- Usual activities.
- Pain/discomfort.
- Anxiety/Depression.

Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. Once the data have been collected and a database created, a scoring function can be used to assign a value (ie, EQ-5D™ index score) to self-reported health states from a set of population-based preference weights. For the US general population, the possible EQ-5D™ index scores range from -0.11 (ie, 33333) to 1.0 (ie, 11111) on a scale where 0.0 = death and 1.0 = perfect health.

The VAS records the respondent's self-rated health on a 20 cm vertical VAS with endpoints labelled 'the best health you can imagine' and 'the worst health you can imagine', anchored from 0 to 100 respectively. This information can be used as a quantitative measure of health as judged by the individual respondents.

The instrument is designed for self-completion by patients. Response options are measured with a 5-point Likert scale with higher scores indicate better HRQL. The EQ-5D™ produces 3 types of data for each respondent:

- A profile indicating the extent of problems on each of the 5 dimensions represented by a 5-digit descriptor
- A population preference weighted-health index score based on the descriptive system
- A self-reported assessment of health status based on the EQ-VAS

9.2.5 Pharmacokinetics

Pharmacokinetic evaluation for isatuximab will be performed in all patients in the IKd arm. Blood samples will be collected from all patients treated with isatuximab up to Cycle 10 using a sparse sampling strategy in order to assess the PK profile of isatuximab using population PK approach.

In a subset of approximately 12 patients from the IKd arm, blood samples will be collected at selected time points at Cycle 1 Day 15 for carfilzomib PK evaluation. Non evaluable patients will be replaced (see Section 11.3.3 for definition of evaluable patient).

9.2.5.1 Sampling time

The sampling times for blood collection can be found in the PK Flow Chart (Section 1.3).

- It is of utmost importance to collect all blood samples at the specified times and according to the specifications.
- Samples not collected, missed or lost, for any reason should be recorded.
- Actual days and times of blood collection should be recorded in the eCRF.
- The days and the times of drug administration should also be precisely recorded.

9.2.5.2 Pharmacokinetics handling procedure

Special procedures for collection, storage, and shipment will be provided in a separate laboratory manual.

9.2.5.3 Bioanalytical method

The bioanalytical method is summarized in Table 9. The sites of bioanalyses will be specified in the PK manual.

Table 9 - Bioanalytical methods for isatuximab and carfilzomib pharmacokinetic analysis

Analyte	Isatuximab	Carfilzomib
Matrix	Plasma	Plasma
Analytical technique	ELISA	LC-MS/MS
Assay volume	100 µL	250 µL
Lower limit of quantification	0.500 ng/mL	0.250 ng/mL
Site of bioanalysis	Refer to PK manual	Refer to PK manual

Elisa: enzyme linked immunosorbant assay, LC-MS/MS: liquid chromatography mass spectrometry and tandem mass spectometry

9.2.5.4 Pharmacokinetics parameters

9.2.5.4.1 Non-compartmental analysis for carfilzomib

The following PK parameters will be calculated with PKDMS software (Pharsight) using non-compartmental methods from plasma of carfilzomib concentrations. The parameters will include, but may not be limited to, the following:

Table 10 - List of pharmacokinetic parameters and definitions

Parameters	Definition
C_{eoi}	Concentration observed at the end of IV infusion
C_{max}	Maximum concentration observed after the first infusion
t_{max}	Time to reach C_{max}
C_{last}	Last concentration observed above the lower limit of quantification
t_{last}	Time of C_{last}
C_{trough}	Plasma concentration observed just before treatment administration during repeated dosing
AUC_{last}	Area under the plasma concentration versus time curve calculated using the trapezoidal method from time 0 to t_{last}
AUC	Area under the plasma concentration versus time curve extrapolated to infinity according to the following equation : $AUC = AUC_{last} + C_{last}/\lambda z$

9.2.5.4.2 Population approach for isatuximab

Blood concentrations of isatuximab will be used for population PK analysis by non-linear mixed effects modeling. Additional details of the analysis plan and the results will be provided in a separate document. This analysis will involve an estimation of inter-patient PK variability, the population PK parameters estimates, and the assessments of carfilzomib and pathophysiologic covariate effects on CL and possibly on volume if warranted. Empirical Bayesian estimation of individual parameters and of individual exposure (AUCs, C_{max} and trough) will also be performed. The PK estimates will then be investigated as prognostic factors for clinical outcome, including safety and efficacy endpoints, if possible.

9.2.6 Immunogenicity

Human ADA to isatuximab will be assessed for the IKd patients only on Day 1 prior to isatuximab administration from Cycle 1 to Cycle 10. Blood samples will be collected for ADA detection according to the Flow Charts (see Section 1.2 and Section 1.3).

It is of utmost importance to collect all blood samples at the specified times and according to the specifications.

Samples missed or lost, for any reason should be recorded. Actual times of blood collection should be recorded in the eCRF. The days of sampling and times of drug administration should also be precisely recorded.

Special procedures for collection, storage, and shipment will be provided in a separate laboratory manual.

Bioanalytical method used for immunogenicity assessment is summarized in Table 11.

Table 11 - Bioanalytical method for isatuximab immune response assessment

Analyte	Isatuximab
Matrix	Plasma
Analytical technique	Polyethylene glycol precipitation and acid dissociation method (PandA)
Assay volume	100 µL
Lower limit of detection	Not applicable
Site of bioanalysis	Refer to PK manual

A sample will be considered as ADA positive if ADA is detected ie, sample generates an assay signal equal to or greater than the cut-point in the screening assay and is tested positive in the confirmatory assay.

A sample will be considered as ADA inconclusive if ADAs are not detected but drug is present in the same sample at a level that can interfere in the ADA detection method then the negative ADA result cannot be incontrovertibly confirmed.

In case of positivity or inconclusive sample at Cycle 10, additional assessment of ADA will be performed 3 months later. No further ADA will be sampled, even if this 3-month sample is positive.

If isatuximab is stopped prior to carfilzomib and dexamethasone and prior to Cycle 10 and last ADA is positive or inconclusive, one additional sampling time for ADA evaluation will be collected 3 months later. No further ADA will be sampled, even if this 3-month sample is positive. For patients with less than 10 cycles at the cut-off date, the ADA sample collection will be stopped from the cut-off date. If last ADA before the final PFS analysis cut-off date is positive, one additional sampling time for ADA evaluation should be collected 3 months later. No further ADA will be sampled, even if this 3-month sample is positive.

The sampling times for ADA detection of isatuximab can be modified based on the updated knowledge of isatuximab immunogenicity.

Definitions:

- Pre-existing ADA: Defined as ADA that are present in samples drawn during the pre-treatment period (ie, before the first isatuximab administration).
- Treatment-induced ADA: Defined as ADA that developed at any time during the ADA on-study observation period in patients without pre-existing ADA (including patients without pre-treatment samples).
- Treatment boosted ADA: Defined as pre-existing ADA with an increase in titer during the ADA on-study observation period.

- Transient ADA response:
  - Treatment-induced ADA detected only at 1 sampling time point during the treatment or follow-up observation period (excluding the last sampling time point, which ought to be considered persistent unless shown to be undetectable at a later time) or
  - Treatment-induced ADA detected at 2 or more sampling time points 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:
  - Treatment-induced ADA detected at 2 or more sampling time points 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.
- Intermediate ADA response
  - Only the last sampling time point is positive or
  - The last two samples separated by a period less than 16 weeks are positive.
- ADA positive patients: Defined as patients with at least 1 treatment-induced or treatment-boosted ADA positive sample at any time following the first isatuximab administration.
- ADA prevalence: Defined as the sum of the number of patients with pre-existing ADA and the number of patients with treatment induced ADAs, divided by the number of evaluable patients.
- ADA incidence: Defined as the number of ADA positive patients divided by the number of evaluable patients.

9.3 EXPLORATORY ENDPOINTS

9.3.1 Exploratory biomarker analysis

A blood sample will be collected on Day 1 of Cycle 1. Leukocyte DNA will be extracted and analyzed for immune genetic determinants (such as Fcγ receptor polymorphisms) and correlated with parameters of clinical response.

In IKd arm only, an additional blood sample will be collected at all time-points to evaluate the potential interference of isatuximab in the M protein assessment (central laboratory) up to Cycle 30. This sample will be collected after Cycle 30 and until disease progression only for patients who reach at least VGPR at this cycle. In case of isatuximab is stopped before progression, sample interference assay will be collected up to 3 months or PD, whichever comes first. After Cycle 1 Day 1, IF sample is analyzed in case of M protein is 0 g/dL in all patients. In addition, in order to identify patients with potential isatuximab interference, IF samples will be analyzed also in patients with serum M protein ≤0.2 g/dL.

In addition to the 3 cytogenetic abnormalities (del(17p), t(4:14) and t(14:16)) assessed by FISH at baseline to determine R-ISS stage which is stratification factor, other cytogenetic abnormalities such as but not limited to del (1p) and gain (1q) deletion will be assessed and correlated with parameters of clinical response.

9.4 FUTURE USE OF SAMPLES

For patients who have consented to it, the samples that are unused or left over after testing may be used for other research purposes (excluding genetic analysis providing information on the likelihood of developing a disease) related to isatuximab efficacy, safety, and metabolism, or related to MM.

These other research analyses will help to understand either disease subtypes or drug response, to develop and/or validate a bioassay method, and/or to identify new drug targets or biomarkers.

These samples will remain labelled with the same identifiers used during the study (ie, patient ID). They will be transferred to a Sanofi site (or a subcontractor site) which can be located outside of the country where the study is conducted. The Sponsor has included safeguards for protecting patient confidentiality and personal data (see Section 14.3 and Section 14.5). These samples may be stored for a period of up to 5 years after completion of the final study report. After that period, any samples remaining will be destroyed.

9.5 APPROPRIATENESS OF MEASUREMENTS

Each of the efficacy and safety assessments chosen for use in this study is considered well established and relevant in a hemato-oncology setting. In addition, suitable steps have been built into each of these assessments to ensure their reliability and accuracy and to minimize any risks to patient safety.

10 STUDY PROCEDURES

10.1 VISIT SCHEDULE

All patients entering the study must be evaluated according to the schedule outlined in the Flow Charts (see Section 1.2 and Section 1.3) and described below. The results of the evaluation will be recorded in the eCRF pages until the patients are no longer followed.

10.1.1 Screening/baseline

The screening assessments are to be performed within 21 days prior to randomization, unless indicated otherwise. All of the inclusion criteria (and none of the exclusion criteria) must be met, and informed consent must be signed by the patient before any study-specific procedure is performed. Inform consent can be signed more than 21 days prior to randomization. Screening time indicates in which time frame exams used to support eligibility have to be done prior to randomization.

The following procedures are to be performed/assessed:

- Signed informed consent.
- Demography (age, gender, and race) and medical/surgical history (including smoking status).
- Myeloma history and prior anti-myeloma treatment: Includes date of initial diagnosis of symptomatic MM, stage and type of disease at diagnosis and study entry (heavy and light chain component) and previous anti-myeloma therapy (including transplant if any, drug name, start and stop dates, intent, date of progression, best response, and reason for discontinuation).
- Physical examination (≤7 days prior to randomization): Includes examination of main body systems including neurological, digestive, respiratory (signs and symptoms, respiratory rate), hepatic and spleen span, and lymph node examinations. Patient's weight and height will be recorded.
- Vital signs including blood pressure, heart rate, body temperature, and respiratory rate.
- Cardiac ultrasonography (MUGA scan or MRI are accepted if it is the site practice).
- 12-lead electrocardiogram (ECG).
- ECOG PS.
- Prior medications use in the 21 days prior to randomization.
- All AEs/SAEs occurring after signed informed consent for all patients.

Local laboratory assessments

- Serum or urine pregnancy test to be performed prior to randomization (should be within 7 days prior to first study treatment administration) for females of childbearing potential.
- Hematology: Hemoglobin, hematocrit, red blood cells (RBC), white blood cells (WBC) with differential and platelet count.

- Blood chemistry: AST, ALT, bilirubin (total and direct), alkaline phosphatase, LDH, sodium, potassium, chloride, bicarbonate or carbon dioxide (venous) (if bicarbonate or carbon dioxide are assessed only on arterial blood at site level, to be done only if clinically indicated), calcium, corrected serum calcium, magnesium, phosphate, uric acid, serum creatinine and estimated creatinine clearance (MDRD Formula), urea or blood urea nitrogen (BUN), fasting glucose (according to site guidelines), albumin, and total protein.
- Coagulation: Prothrombin time or international normalized ratio and activated partial thromboplastin time.
- Quantitative or semi quantitative (according to site practice and if semi quantitative method can provide with an absolute numeric value of the parameters) urinalysis: RBCs, protein, glucose, pH, ketones, bilirubin, and leucocytes.
- Serum β2-microglobulin.
- Complete blood phenotyping (IKd arm only) if not already available (C,c; E,e; Kell. Kidd; Duffy; S,s is recommended, if not available follow site's standard) and antibody screening (Indirect Coombs Test or Indirect Antiglobulin Test [IAT]), after randomization and prior to study treatment initiation. The blood type card will be kept by the patient with the study card. Blood transfusions are to be recorded in the eCRF. The blood bank needs to be informed that the patient is receiving a treatment with an anti-CD38 and a potential interference with the Coombs test is possible.

Disease assessment:

- Laboratory disease assessment (central laboratory):
  - Serum M protein: Immunoelectrophoresis and IF.
  - Urine M protein (24-hour urine): Immunoelectrophoresis and IF.
  - Serum FLCs: Quantification and ratio involved/non-involved.
  - Immunoglobulins: IgG, IgA, IgM, IgD, and IgE (IgD or E only if the heavy chain component of the disease is known to be E or D).
- Bone marrow aspirate will be collected (local and central laboratory):
  - FISH (including, but may not be limited to, del(17p), t(4:14), t(14:16) and MRD analyses in central laboratory. Central laboratory samples for FISH will be collected and analyzed for all patients; R-ISS used as stratification factor will be assessed with FISH central laboratory results. Additional cytogenetic abnormalities will be tested including, but may not be limited to, del (1p) and gain (1q). Central laboratory samples for MRD will be collected for all patients but will be analyzed only for patients who will reach VGPR or better.
  - Bone marrow disease assessment (plasma cells involvement) in local laboratory. For this assessment, biopsy can be done if clinically indicated.

Note: In case of randomization would be delayed due to unplanned event after BMA was done, BMA will not need to be done again if BMA remains within 8 weeks prior to randomization.

- Radiological disease assessment:
  - Skeletal survey (including skull, spine, all long bones, pelvis, and chest) or low dose whole body CT scan at baseline ([see Appendix M], within 21 days prior to randomization).
  - Extramedullary disease (plasmacytoma) assessment (including bone plasmacytoma):
    - If known extramedullary disease at baseline, CT scan or MRI is to be done at baseline until PD (even for patients who would initiate further anti-myeloma therapy without PD).
    - If suspected extramedullary disease (plasmacytoma) at baseline, CT scan or MRI is to be done at baseline.

Note: For bone lesion assessment and extramedullary disease, the same modality (skeletal survey or low-dose whole body CT scan; CT scan or MRI) should be used throughout the study for each individual patient. All imaging should be sent for central review. Intravenous contrast is recommended if not medically contra-indicated. Patients who have contra-indication to CT scan with IV contrast may have MRI exams performed instead.

10.1.2 Randomization

Randomization will take place once the consented patient has completed all the necessary screening procedures and is deemed eligible for study entry by the Investigator or designee (based on myeloma specific results from central laboratory [see below] and hematology/biochemistry local laboratory results).

Results for central paraprotein must be available before the patient is randomized.

All eligible patients must be randomized by contacting the IRT (see Section 8.3).

The results of the screening examinations will be recorded in each randomized patient's eCRF. Source documentation to support the screening results must be maintained in the patient's medical record. Every effort should be done to start treatment within 3 working days of randomization.

10.1.3 Treatment period

Procedures to be performed on Day 1, Day 8 and on Day 15 can be performed within one day prior to study treatment administration unless specified otherwise. This is not applicable for samples to be drawn on D2, D9 and D16.

10.1.3.1 Cycle 1 (Days 1-2, Days 8-9, Days 15-16, and Days 22-23)

The following procedures are to be performed/assessed prior to first study treatment administration in both arms unless specified otherwise:

- Physical examination on Days 1, 8, 15, and 22: Only main diagnoses will be reported in the eCRF as AEs or medical history. Signs and symptoms related to MM ongoing on Day 1 Cycle 1 will be recorded in AE page.

- Vital signs including blood pressure, heart rate, body temperature, and respiratory rate on Days 1, 2, 8, 9, 15, and 16 in both arms, plus on Day 22 in the IKd arm. In the IKd arm, vital signs are to be measured prior to start of each isatuximab infusion, 1 hour after start of each infusion, and at the end of each infusion.
- 12-lead ECG on Day 1 if Screening test >7 days prior Day 1.
- ECOG PS on Day 1.
- Study treatment administration:
  - Isatuximab (IKd only) on Days 1, 8, 15, and 22.
  - Carfilzomib: Days 1, 2, 8, 9, 15, and 16.
  - Dexamethasone: Days 1, 2, 8, 9, 15, 16, 22, and 23. Oral dexamethasone will be recorded in patient diaries when not taken at site level.
- ePROs on Day 1: EORTC QLQ-C30, QLQ-MY20, and EQ-5D-5L.
- All AEs/SAEs throughout the cycle.
- Concomitant medications from 21 days prior to randomization and then throughout the cycle.

Local laboratory assessments:

- Blood Chemistry
  - Full blood biochemistry prior to Day 1 if Screening test >7 days prior Day 1, and on Days 8, 15, and 22 administration: AST, ALT, bilirubin (total and direct), alkaline phosphatase, LDH, sodium, potassium, chloride, bicarbonate or carbon dioxide (venous) (if bicarbonate or carbon dioxide are assessed only on arterial blood at site level, to be done only if clinically indicated), calcium, corrected serum calcium, magnesium, phosphate, uric acid, serum creatinine and estimated creatinine clearance (MDRD Formula), urea or BUN, fasting glucose (according to site guidelines), albumin, and total protein.
  - Restricted biochemistry on Days 2, 9, and 16: Sodium, potassium, chloride, bicarbonate or carbon dioxide (venous), urea or BUN, serum creatinine, and estimated creatinine clearance (MDRD formula).
- Hematology on Day 1 if Screening test >7 days prior Day 1, and on Days 1, 8, 15, and 22: Hemoglobin, hematocrit, RBC, WBC with differential and platelet count.
- Serum or urine pregnancy test for females of childbearing potential.

Central laboratory disease assessments:

Values of the tests performed on Day 1 of Cycle 1 (prior to study treatment administration) will be the reference value to assess response during study treatment. Assessments on Day 1 include:

- Serum M protein: Immunoelectrophoresis and IF.
- Urine M protein (24-hour urine): Immunoelectrophoresis and IF.
- Serum FLCs: Quantification and ratio involved/non-involved.
- Immunoglobulins: IgG, IgA, IgM, IgD, and IgE (IgD or E only if the heavy chain component of the disease is known to be E or D).

Any unplanned laboratory disease assessment should be sent to central laboratory.

Central laboratory assessments:

- Immune genetic determinants (such as Fcγ receptor polymorphism).
- IKd arm only:
  - Blood sample collection for PK (see Section 1.3).
  - Blood sample collection on Day 1 for ADA evaluation.
  - An additional blood sample will be collected to evaluate the potential interference of isatuximab in the M protein assessment (central laboratory).

If clinically indicated only:

- Coagulation at any time during the cycle.
- Urinalysis at any time during the cycle: quantitative (RBC, protein, glucose, pH, ketones, bilirubin, and leucocytes) or qualitative (dipstick: blood, protein, glucose, pH, ketones, bilirubin, and leucocytes).
- Bone marrow aspirate (BMA) for:
  - MRD analyses in central laboratory. Central laboratory samples for MRD will be collected only for patients who will reach VGPR or better (when it is confirmed).
  - Bone marrow disease assessment (% plasma cells) in case of VGPR or better (when it is confirmed) (local laboratory). Bone marrow biopsy can be done for sCR assessment as per Investigator decision.
- Radiological disease assessment (the same method of assessment as at Screening is to be used throughout the study):
  - Skeletal survey (including skull, spine, all long bones, pelvis, and chest).
  - Extramedullary disease (plasmacytoma) assessment.

10.1.3.2 Subsequent cycles (Days 1-2, Days 8-9, Days 15-16, and Days 22-23)

The following procedures are to be performed/assessed prior to Day 1 administration in both arms unless specified otherwise:

- Physical examination: Only the main diagnoses will be reported in the eCRF as AEs.
- Vital signs including blood pressure, heart rate, body temperature, and respiratory rate on Days 1, 2, 8, 9, 15, and 16 in both arms. In the IKd arm, vital signs are to be measured prior to start of each isatuximab infusion, 1 hour after start of each infusion and at the end of each infusion (on Days 1 and 15 up to Cycle 4 and as clinically indicated).
- 12-lead ECG.
- ECOG PS.
- Study treatment administration:
  - Isatuximab (IKd only) on Days 1 and 15.
  - Carfilzomib: Days 1, 2, 8, 9, 15, and 16.
  - Dexamethasone: Days 1, 2, 8, 9, 15, 16, 22, and 23. Oral dexamethasone will be recorded in patient diaries when not taken at site level.

- ePROs: EORTC QLQ-C30, QLQ-MY20, and EQ-5D-5L.
- All AEs/SAEs throughout the cycle.
- Concomitant medications at any time during the treatment period and up to 30 days after the last dose.

Local laboratory assessments:

- Blood chemistry:
  - Full blood biochemistry prior to Day 1 administration: AST, ALT, bilirubin (total and direct), alkaline phosphatase, LDH, sodium, potassium, chloride, bicarbonate or carbon dioxide (venous) (if bicarbonate or carbon dioxide are assessed only on arterial blood at site level, to be done only if clinically indicated), calcium, corrected serum calcium, magnesium, phosphate, uric acid, serum creatinine and estimated creatinine clearance (MDRD Formula), urea or BUN, fasting glucose (according to site guidelines), albumin, and total protein.
  - Restricted biochemistry prior to Days 8 and 15 administrations at Cycle 2, and then prior to Day 15 administration of each cycle thereafter: Sodium, potassium, chloride, bicarbonate or carbon dioxide (venous), urea or BUN, serum creatinine, and estimated creatinine clearance (MDRD formula).
- Hematology prior to Days 1 and 15 administrations: Hemoglobin, hematocrit, RBC, WBC with differential and platelet count.
- Serum or urine pregnancy test is to be done within one day before each cycle initiation for females of childbearing potential.
- Indirect Coombs test will be repeated once after study treatment initiation on Day 1 at Cycle 2 or on Day 1 of a later cycle if not done at Cycle 2, only for patients in IKd arm.
- One HBV serology test (HBsAg, anti-HBc and anti-HBs) in patients with HBV status unknown in September 2019. Patients with HBsAg positive and/or anti-HBc antibody positive should have also HBV DNA testing by polymerase chain reaction. To be repeated if clinically indicated.

Central laboratory disease assessment:

Assessments on Day 1 include:

- Serum M protein: Immunoelectrophoresis and IF.
- Urine M protein (24-hour urine): Immunoelectrophoresis and IF.
  After Cycle 1 Day 1, IF to be done if UPEP is negative in patients whose disease is evaluable in urine. The 24-hour urine collection should be completed prior new cycle initiation. If urine M protein is negative at baseline and Cycle 1 Day 1, this assessment is to be repeated every 3 cycles only (Cycle 4, Cycle 7, Cycle 10, etc) to confirm CR on blood labs.
- Serum FLCs: Quantification and ratio involved/non-involved.
- Immunoglobulins: IgG, IgA, IgM, IgD, and IgE (IgD or E only if the heavy chain component of the disease is known to be E or D).

Any unplanned laboratory disease assessment should be sent to central laboratory.

Central laboratory assessments IKd arm only:

- Blood sample collection for PK (see Section 1.3) up to Cycle 10. Pharmacokinetic samples are stopped after Cycle 10.
- Blood sample collection on Day 1 up to Cycle 10 for ADA evaluation. In case of ADA positive or inconclusive at Cycle 10, one additional ADA will be sampled 3 months later. No further ADA will be sampled, even if this 3-month sample is positive.
- An additional blood sample will be collected at all time-points to evaluate the potential interference of isatuximab in the M protein assessment (central laboratory) up to Cycle 30. This sample will be collected after Cycle 30 for patients who reach at least VGPR at this cycle until disease progression. In case of isatuximab is prematurely stopped definitive treatment discontinuation, sample interference assay will be collected up to 3 months after isatuximab discontinuation or PD, whichever comes first.

If clinically indicated only:

- Coagulation at any time during the cycle.
- Urinalysis at any time during the cycle: Quantitative (RBC, protein, glucose, pH, ketones, bilirubin, and leucocytes) or qualitative (dipstick: blood, protein, glucose, pH, ketones, bilirubin, and leucocytes).
- Bone marrow aspirate will be collected for:
  - MRD analyses in central laboratory. Central laboratory samples for MRD will be collected only for patients who will reach VGPR or better (when it is confirmed). If a patient presents ≥ VGPR but is determined MRD positive, another BM sample will be collected 3 months (3 cycles) later, in order to identify late negativity. A third sample may be collected after another 3 months if the patient remains MRD positive and is still being treated. No more than 3 post-baseline samples are to be obtained unless a patient achieves CR after a third BM sample MRD positive performed during VGPR. In this case, no more than 3 additional BM samples will be collected. Therefore, a maximum of 6 BMA could be performed by patient (no more than 3 per category of response). However, because BMA is invasive procedure, the following guidance is given in the purpose to limit as much as possible the number of BMA.
    For patients with CR without previous documentation of VGPR, first bone marrow for MRD assessment will be collected at time of confirmation of CR (ie, at the second time point showing CR) If patient is determined MRD positive, another BM sample will be collected 3 months (3 cycles) later, in order to identify late negativity. A third sample may be collected after another 3 months if the patient remains MRD positive and is still being treated.
    For patients with VGPR:
    - First bone marrow will be collected when VGPR is confirmed at the second time point or at a later time point as per investigator judgement based on kinetic of M protein decrease and/or if a plateau phase is reached (plateau is defined as variation less than 20% over 12 weeks [16]).
    - If MRD is positive on first BMA, a second BMA will be collected 3 months later (3 cycles) to identify late negativity.

- In case of MRD is still positive on second BMA made while patient is in VGPR, the timing to perform the third BMA can be postponed until CR achievement.
- In case of the patient becomes CR and patient was MRD positive on the last BMA performed during VGPR, a BMA will be done for MRD assessment at time of confirmation of CR.
- After the first BMA during CR is done and in case patient was MRD positive on this BMA, the additional BMA planned by the protocol can be discussed with the patient.

- Bone marrow disease assessment (plasma cells involvement) in local laboratory in case of VGPR or better (when it is confirmed).
  In case of VGPR, plasma cell infiltration assessment is mandatory for patients in IKd arm with residual serum M protein of Ig G ≤ 0.5 g/dL and/or residual kappa IF positivity in urine, due to potential interference between isatuximab and M protein.
  In case of CR on M protein, plasma cell infiltration assessment is mandatory in IKd arm and in Kd arm, unless a previous assessment was made within 3 months and showed plasma cells ≤5%.
  Bone marrow biopsy can be done for sCR assessment as per investigator decision.

- Radiological disease assessment (the same method of assessment as at Screening is to be used throughout the study):
  - Skeletal survey (including skull, spine, all long bones, pelvis, and chest X-rays) or whole body CT scan once a year and additional exam as clinically indicated.
  - Extramedullary disease (plasmacytoma) assessment every 12 weeks in case of existing plasmacytoma at baseline or as clinically indicated if no plasmacytoma at baseline.

10.1.4 End of treatment

The EOT visit will occur 30 days after last study treatment administration or before further anti-myeloma therapy initiation whichever comes first. The following procedures are to be performed at the EOT visit:

- Physical examination.
- Vital signs.
- 12-lead ECG.
- ECOG PS.
- Serum or urine pregnancy for females of childbearing potential.
- ePROs (EORTC QLQ-C30, QLQ-MY20, and EQ-5D-5L).
- All AEs/SAEs occurring up to 30 days after last study treatment administration (will be collected in last treatment cycle).
- Concomitant medications up to 30 days from last study treatment administration.

Local laboratory tests:

- Blood chemistry: AST, ALT, bilirubin (total and direct), alkaline phosphatase, LDH, sodium, potassium, chloride, bicarbonate or carbon dioxide (venous) (if bicarbonate or carbon dioxide are assessed only on arterial blood at site level, to be done only if clinically indicated), calcium, corrected serum calcium, magnesium, phosphate, uric acid, serum creatinine and estimated creatinine clearance (MDRD Formula), urea or BUN, fasting glucose (according to site guidelines), albumin, and total protein.
- Hematology: hemoglobin, hematocrit, RBC, WBC with differential and platelet count.

Central laboratory disease assessment:

- Serum M protein: Immunoelectrophoresis and IF.
- Urine M protein (24-hour urine): Immunoelectrophoresis and IF.
- Serum FLCs: Quantification and ratio involved/non-involved.
- Immunoglobulins: IgG, IgA, IgM, IgD, and IgE (IgD or E only if the heavy chain component of the disease is known to be E or D).

Any unplanned laboratory disease assessment should be sent to central laboratory.

Central laboratory assessment IKd arm only:

- Additional blood sample collected until disease progression for patients who experienced at least a VGPR up to 3 months after end of isatuximab (central laboratory).
- ADA if the "3-month later" sample time is needed and occurs at EOT visit. No further ADA will be sampled, even if this 3-month sample is positive.

If clinically indicated only:

- Coagulation.
- Urinalysis: quantitative (RBC, protein, glucose, pH, ketones, bilirubin, and leucocytes) or qualitative (dipstick: blood, protein, glucose, pH, ketones, bilirubin, and leucocytes).
- Bone marrow aspirate will be collected for:
  - MRD analyses in central laboratory. Central laboratory samples for MRD will be collected only for patients who will reach VGPR or better (when it is confirmed). If a patient presents ≥ VGPR but is determined MRD positive, another BM sample will be collected 3 months (3 cycles) later, in order to identify late negativity. A third sample may be collected after another 3 months if the patient remains MRD positive and is still being treated. No more than 3 post-baseline samples are to be obtained unless a patient achieves CR after a third BM sample MRD positive performed during VGPR. In this case, no more than 3 additional BM samples will be collected. Therefore, a maximum of 6 BMA could be performed by patient (no more than 3 per category of response). However, because BMA is invasive procedure, the following guidance is given in the purpose to limit as much as possible the number of BMA.
    For patients with CR without previous documentation of VGPR, first bone marrow for MRD assessment will be collected at time of confirmation of CR (ie, at the second time point showing CR) If patient is determined MRD positive, another BM sample

will be collected 3 months (3 cycles) later, in order to identify late negativity. A third sample may be collected after another 3 months if the patient remains MRD positive and is still being treated.
For patients with VGPR:

- First bone marrow will be collected when VGPR is confirmed at the second time point or at a later time point as per investigator judgement based on kinetic of M protein decrease and/or if a plateau phase is reached (plateau is defined as variation less than 20% over 12 weeks [16]).
- If MRD is positive on first BMA, a second BMA will be collected 3 months later (3 cycles) to identify late negativity.
- In case of MRD is still positive on second BMA made while patient is in VGPR, the timing to perform the third BMA can be postponed until CR achievement.
- In case of the patient becomes CR and patient was MRD positive on the last BMA performed during VGPR, a BMA will be done for MRD assessment at time of confirmation of CR.
- After the first BMA during CR is done and in case patient was MRD positive on this BMA, the additional BMA planned by the protocol can be discussed with the patient.

- Bone marrow disease assessment (plasma cells involvement) in local laboratory in case of VGPR or better (when it is confirmed).
  In case of VGPR, plasma cell infiltration assessment is mandatory for patients in IKd arm with residual serum M protein of Ig G ≤0.5 g/dL and/or residual kappa IF positivity in urine, due to potential interference between isatuximab and M protein.
  In case of CR on M protein, plasma cell infiltration assessment is mandatory in IKd arm and in Kd arm, unless a previous assessment was made within 3 months and showed plasma cells ≤5%.
  Bone marrow biopsy can be done for sCR assessment as per investigator decision.

- Radiological disease assessment (the same method of assessment as at Screening is to be used throughout the study):
  - Skeletal survey (including skull, spine, all long bones, pelvis, and chest X-rays) or whole body CT scan once a year and additional exam as clinically indicated.
  - Extramedullary disease (plasmacytoma) assessment every 12 weeks in case of existing plasmacytoma at baseline or as clinically indicated if no plasmacytoma at baseline.

10.1.5 Post study treatment follow-up

Periodicity of follow-up visits to be performed after last study treatment administration will depend on reason of study treatment discontinuation:

- Every 3 months for patients with previous confirmed disease progression.
- Monthly for patients without previous confirmed disease progression up to confirmed disease progression (even if further anti-myeloma has been initiated before PD), and then every 3 months.

The following procedures are to be performed at each follow-up visit, whatever periodicity of FU visit:

- All ongoing related AEs/all SAEs to be reported and followed up until resolution or stabilization, all new AEs (serious or not) related to study treatment up until resolution or stabilization and any second primary malignancy.
- Further anti-myeloma therapies: Drug name, start and stop date, best overall response and date of PD according to Investigator assessment will be collected.
- Survival status.

For all patients, ePRO questionnaires 90 days after last study treatment administration will be completed (which corresponds to first FU visit in case of study treatment discontinuation due to PD or second FU visit in case of study treatment discontinuation without PD).

Serum or urine pregnancy test for females of childbearing potential will be performed monthly during follow-up up to 3 months in the Kd and 5 months in IKd, and can be performed at home for the patients with follow-up every 3 months or if date of test does not match with a FU visit.

The following procedures are to be performed every month in addition to the procedures above for patients **without previous confirmed disease progression (even patients who would initiate further anti-myeloma therapy without PD, unless otherwise specified):**

- **Central laboratory disease assessment:**
  - Serum M protein: Immunoelectrophoresis and IF.
  - Urine M protein (24-hour urine): Immunoelectrophoresis and IF.
  - Serum FLCs: Quantification and ratio involved/non-involved.
  - Immunoglobulins: IgG, IgA, IgM, IgD, and IgE (IgD or E only if the heavy chain component of the disease is known to be E or D).

  Any unplanned laboratory disease assessment should be sent to central laboratory.
- **Central laboratory assessment IKd arm only:**
  - In IKd arm only, additional blood sample collected until disease progression for patients who experienced at least a VGPR up to 3 months after end of isatuximab (central laboratory).
- **Radiological disease assessment** (the same method of assessment as at Screening is to be used throughout the study) if indicated**:**
  - Skeletal survey (including skull, spine, all long bones, pelvis, and chest X-rays) or whole body CT scan once a year and additional exam as clinically indicated.
  - Extramedullary disease (plasmacytoma) assessment every 12 weeks in case of existing plasmacytoma at baseline or as clinically indicated if no plasmacytoma at baseline.
- **Bone marrow aspirate** will be collected (except if further anti myeloma therapy is started):
  - For MRD analyses in central laboratory. Central laboratory samples for MRD will be collected only for patients who will reach VGPR or better (when it is confirmed). If a patient presents ≥ VGPR but is determined MRD positive, another BM sample will be

collected 3 months (3 cycles) later, in order to identify late negativity. A third sample may be collected after another 3 months if the patient remains MRD positive and is still being treated. No more than 3 post-baseline samples are to be obtained unless a patient achieves CR after a third BM sample MRD positive performed during VGPR. In this case, no more than 3 additional BM samples will be collected. Therefore, a maximum of 6 BMA could be performed by patient (no more than 3 per category of response). However, because BMA is invasive procedure, the following guidance is given in the purpose to limit as much as possible the number of BMA.
For patients with CR without previous documentation of VGPR, first bone marrow for MRD assessment will be collected at time of confirmation of CR (ie, at the second time point showing CR) If patient is determined MRD positive, another BM sample will be collected 3 months (3 cycles) later, in order to identify late negativity. A third sample may be collected after another 3 months if the patient remains MRD positive and is still being treated.
For patients with VGPR:

- First bone marrow will be collected when VGPR is confirmed at the second time point or at a later time point as per investigator judgement based on kinetic of M protein decrease and/or if a plateau phase is reached (plateau is defined as variation less than 20% over 12 weeks [16]).
- If MRD is positive on first BMA, a second BMA will be collected 3 months later (3 cycles) to identify late negativity.
- In case of MRD is still positive on second BMA made while patient is in VGPR, the timing to perform the third BMA can be postponed until CR achievement.
- In case of the patient becomes CR and patient was MRD positive on the last BMA performed during VGPR, a BMA will be done for MRD assessment at time of confirmation of CR.
- After the first BMA during CR is done and in case patient was MRD positive on this BMA, the additional BMA planned by the protocol can be discussed with the patient.

- For bone marrow disease assessment (plasma cells involvement) in local laboratory in case of VGPR or better (when it is confirmed).
  In case of VGPR, plasma cell infiltration assessment is mandatory for patients in IKd arm with residual serum M protein of Ig G ≤0.5 g/dL and/or residual kappa IF positivity in urine, due to potential interference between isatuximab and M protein.
  In case of CR on M protein, plasma cell infiltration assessment is mandatory in IKd arm and in Kd arm, unless a previous assessment was made within 3 months and showed plasma cells ≤5%.
  Bone marrow biopsy can be done for sCR assessment as per investigator decision.

10.1.6 After Implementation of Amended Protocol #10

Death date will be collected when site is informed of death. In addition, survival status will be collected twice a year after the implementation of amended protocol #10 until death, or OS analysis cut-off date, whichever comes first.

Patients still on study treatment at the implementation of amended protocol #10 can continue study treatment until at least 1 treatment discontinuation criterion as defined in Section 10.3.2 is met. Patients will be managed according to the site practice. The following information will be collected during the study treatment administration:

- IP administration.
- All SAEs regardless of relationship to study treatment, AEs considered related to study treatment and any second primary malignancy.
- Hematology and biochemistry, or any other laboratory results supporting the reported AEs.
- Other procedures supporting the reported AEs.
- Serum or urine pregnancy test for females of childbearing potential
- End of treatment reason.
- If patients received 10 or less cycles at the cut-off date and last ADA prior the final PFS analysis cut-off date is positive or inconclusive, additional ADA 3 months later sample to be done. No further ADA will be sampled, even if this 3-month sample is positive (central laboratory).

No follow-up information will be collected after these patients discontinue study treatment except:

- All SAEs still ongoing at the end of study treatment and all AEs considered as related to study treatment still ongoing or occurring after the end of study treatment, which will be followed until resolution/stabilization.
- Survival status and further anti-myeloma therapies twice a year if study treatment is stopped before the OS cut-off date.
- Serum or urine pregnancy test for females of childbearing potential will be performed monthly during follow-up up to 3 months in the Kd and 5 months in IKd, and can be performed at home.

10.1.7 Post OS analysis cut-off date

Patients still on study treatment at the OS analysis cut-off date can continue study treatment until at least 1 treatment discontinuation criterion as defined in Section 10.3.2 is met. Patients will be managed according to the site practice. The following information will be collected during the study treatment administration:

- IP administration.
- All SAEs regardless of relationship to study treatment and AEs considered related to study treatment.
- Hematology and biochemistry, or any other laboratory results supporting the reported AEs.

- Other procedures supporting the reported AEs.
- Serum or urine pregnancy test for females of childbearing potential
- End of treatment reason.
- Death date and reason if occurred during study treatment.

No follow-up information will be collected after these patients discontinue study treatment except:

- All SAEs still ongoing at the end of study treatment and all AEs considered as related to study treatment still ongoing or occurring after the end of study treatment, which will be followed until resolution/stabilization.
- Death date and reason if occurred in follow-up period due to related AE.
- Serum or urine pregnancy test will be performed monthly during follow-up up to 3 months in the Kd and 5 months in IKd, and can be performed at home.

10.2 DEFINITION OF SOURCE DATA

Source data includes all information in original records and certified copies of original records of clinical findings, observations, or other activities necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents.

Source documents are original documents, data, and records (eg, hospital records, clinical and office charts, laboratory notes, memoranda, patient diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcripts certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at the pharmacy, at the laboratories, and at medical-technical departments) involved in the clinical study. Source documentation must be maintained to support information provided within a CRF.

10.3 HANDLING OF PATIENT PERMANENT TREATMENT DISCONTINUATION AND OF PATIENT STUDY DISCONTINUATION

The study treatment should be continued whenever possible. Any study treatment discontinuation must be fully documented in the eCRF. In any case, the patient should remain in the study as long as possible.

Pregnancy will lead to definitive treatment discontinuation in all cases.

10.3.1 Permanent treatment discontinuation with investigational medicinal product(s)

Permanent treatment discontinuation is any treatment discontinuation associated with the definitive decision from the Investigator not to re-expose the patient to the study treatment at any time during the study, or from the patient not to be re-exposed to the study treatment whatever the reason.

10.3.2 List of criteria for permanent treatment discontinuation

The patients may withdraw from treatment with the study treatment if they decide to do so, at any time and irrespective of the reason, or this may be the Investigator's decision. All efforts should be made to document the reason(s) for treatment discontinuation and this should be documented in the eCRF.

Isatuximab, carfilzomib, and/or dexamethasone can be discontinued prematurely. The patient will remain on study treatment until the last study treatment is discontinued. The reason for premature discontinuation will be captured in the appropriate eCRF page.

All efforts should be made to document the reason for discontinuation of treatment with the study treatment:

- At the patient's request, at any time and irrespective of the reason (consents withdrawal), or at the request of their legally authorized representative. "Legally authorized representative" is considered to be an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective patient to the patient's participation in the procedure(s) involved in the research. Withdrawal of consent for treatment should be distinguished from withdrawal of consent for follow-up visits and from withdrawal of consent for non-patient contact follow-up, eg, medical records check. Patients requesting withdrawal should be informed that withdrawal of consent for follow-up may jeopardize the public health value of the study. The Investigator should make every effort to re-contact the patient, to identify the reason why he/she decided to withdraw, and to determine his/her health status, including at least his/her vital status.
- If, in the Investigator's opinion, continuation of the study treatment would be detrimental to the patient's wellbeing, such as:
  - Disease progression.
  - Unacceptable AE.
  - Poor compliance to the study protocol.
  - Any other reason such as intercurrent illness that prevents further administration of study treatment (will be specified).
- Patient is lost to follow-up.

If patients are clinically stable, and possibly deriving clinical benefit from therapy with minimal toxicity, the patient will be maintained on treatment for the maximum period of time defined in Section 6.2.

Patients who have been withdrawn from the study treatment cannot be re-included in the study. Their inclusion and treatment number must not be re-used.

10.3.3 Handling of patients after permanent treatment discontinuation

Patients will be followed-up according to the study procedures specified in this protocol up to the scheduled date of study completion, or up to recovery or stabilization of any AE to be followed-up as specified in this protocol, whichever comes last.

If possible, and after the permanent discontinuation of treatment, the patients will be assessed using the procedure normally planned for the EOT and follow-up visits.

All cases of permanent treatment discontinuation must be recorded by the Investigator in the appropriate pages of the eCRF when considered as confirmed.

10.3.4 Procedure and consequence for patient withdrawal from study

The patients may withdraw from the study before study completion if they decide to do so, at any time and irrespective of the reason without any effect on their care. However, if patients no longer wish to take the study treatment, they will be encouraged to remain in the study.

The Investigators should discuss with them key visits to attend. The value of all their study data collected during their continued involvement will be emphasized as important to the public health value of the study.

Patients who withdraw from the study treatment should be explicitly asked about the contribution of possible AEs to their decision, and any AE information elicited must be documented.

All study withdrawals must be recorded by the Investigator in the appropriate screens of the eCRF and in the patient's medical records. In the medical record, at least the date of the withdrawal and the reason should be documented.

In addition, a patient may withdraw his/her consent to stop participating in the study. Withdrawal of consent for treatment should be distinguished from withdrawal of consent for follow-up visits and from withdrawal of consent for non-patient contact follow-up, eg, medical record checks. The site should document any case of withdrawal of consent.

For patients who fail to return to the site, unless the patient withdraws consent for follow-up, the Investigator must make the best effort to recontact the patient (eg, contact patient's family or private physician, review available registries or health care databases), and to determine his/her health status, including at least his/her vital status. Attempts to contact such patients must be documented in the patient's records (eg, times and dates of attempted telephone contact, receipt for sending a registered letter).

The SAP will specify how these patients lost to follow-up for their primary endpoint will be considered.

Patients who have withdrawn from the study cannot be re-randomized (treated) in the study. Their inclusion and treatment numbers must not be reused.

10.4 OBLIGATION OF THE INVESTIGATOR REGARDING SAFETY REPORTING

10.4.1 Definitions of adverse events

10.4.1.1 Adverse event

An AE is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

10.4.1.2 Serious adverse event

An SAE is any untoward medical occurrence that at any dose:

- Results in death, or
- Is life-threatening, or
  Note: The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization, or
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect, or
- Is a medically important event.
  Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require medical or surgical intervention (ie, specific measures or corrective treatment) to prevent one of the other outcomes listed in the definition above.

  Note: The following list of medically important events is intended to serve as a guideline for determining which condition has to be considered a medically important event. The list is not intended to be exhaustive:
  - Intensive treatment in an emergency room or at home for:
    - Allergic bronchospasm.
    - Convulsions (seizures, epilepsy, epileptic fit, absence, etc.).
  - Development of drug dependence or drug abuse.
  - Suicide attempt or any event suggestive of suicidality.
  - Syncope, loss of consciousness (except if documented as a consequence of blood sampling).
  - Bullous cutaneous eruptions.

10.4.1.3 Adverse event of special interest

An adverse event of special interest (AESI) is an AE (serious or nonserious) of scientific and medical concern specific to isatuximab, for which ongoing monitoring and immediate notification by the Investigator to the Sponsor is required. Such events may require further investigation in order to characterize and understand them. Adverse events of special interest may be added, modified or removed during a study by protocol amendment.

The following AEs are considered AESIs:

- IARs Grade ≥ 3 (please refer to the current edition of the Investigator's brochure for IARs manifestations reported in patients treated with isatuximab). An IAR is a related AE typically with onset within 24 hours from the start of drug infusion.
- Pregnancy of a female patient entered in a study as well as pregnancy occurring in a female partner of a male patient entered in this study (see Section 10.4.1.4).
- Symptomatic overdose (serious or nonserious) with study treatment (isatuximab or carfilzomib or dexamethasone) / NIMP (see Section 10.4.1.5):
  - An overdose (accidental or intentional) with the study treatment is an event suspected by the Investigator or spontaneously notified by the patient (not based on systematic pills count).
  - Of note, asymptomatic overdose has to be reported as a standard AE.

10.4.1.4 Pregnancy

Pregnancy of a female patient entered in a study (as well as pregnancy occurring in a female partner of a male patient entered in this study) will be recorded as an AE in all cases. It will be qualified as a SAE only if it fulfills SAE criteria (See Section 10.4.1.2).

In the event of pregnancy in a female patient, study treatment should be discontinued and the Monitoring Team should be informed immediately (within 24 hours), even if the event does not fulfill a seriousness criterion, using the AE form together with the SAE complementary form to be sent to the representative of the Monitoring Team whose name, address and fax number appear on page 2 of the clinical trial protocol.

Follow-up of the pregnancy is mandatory until the outcome has been determined and for up to 1 year after the delivery of a newborn.

10.4.1.5 Overdose

In case of accidental or intentional overdose (at least 30% above the intended administered dose of isatuximab and carfilzomib at each administration, at least 30% above the intended administered dose of dexamethasone at each cycle) with the study treatment, even not fulfilling a seriousness criterion, is to be reported to the Sponsor immediately (within 24 hours) using the AE form together with the SAE complementary form to be entered in the eCRF.

Non-investigational medicinal product overdose is defined as at least twice the intended dose within the intended therapeutic interval.

10.4.2 General guidelines for reporting adverse events

- All AEs, regardless of seriousness or relationship to study treatment, spanning from the signature of the informed consent form until the end of the study as defined by the protocol for that patient, are to be recorded on the corresponding page(s) or screen(s) of the eCRF.
- Whenever possible, diagnosis or single syndrome should be reported instead of symptoms. The Investigator should specify the date of onset, intensity, action taken with respect to study treatment, corrective treatment/therapy given, additional investigations performed, outcome, and his/her opinion as to whether there is a reasonable possibility that the AE was caused by the study treatment or by the study procedure(s).
- The Investigator should take appropriate measures to follow all AEs until clinical recovery is complete and laboratory results have returned to normal, or until progression has been stabilized, or until death, in order to ensure the safety of the patients. This may imply that observations will continue beyond the last planned visit per protocol, and that additional investigations may be requested by the monitoring team up to as noticed by the Sponsor. Patients who experience an ongoing SAE or an AESI, at the prespecified study end-date, should be followed until resolution, stabilization, or death and related data will be collected. The duration of post-study follow-up and reporting of AEs will be specified (eg, until recovery).
- When treatment is prematurely discontinued, the patient's observations will continue until the end of the study as defined by the protocol for that patient.
- Laboratory abnormalities are to be recorded as AEs only if the lead to an action taken on study treatment (dose reduction, dose delay, dose interruption, study treatment discontinuation) or if they are serious.
- Vital signs or ECG abnormalities are to be recorded as AEs only if:
  - Symptomatic and/or
  - Requiring either corrective treatment or consultation, and/or
  - Leading to study treatment discontinuation or modification of dosing, and/or
  - Fulfilling a seriousness criterion, and/or
  - Defined as an AESI.

Instructions for AE reporting are summarized in Table 12.

10.4.3 Instructions for reporting serious adverse events

In the case of occurrence of an SAE, the Investigator or any designees must immediately:

- ENTER (within 24 hours) the information related to the SAE in the appropriate screens of the eCRF; the system will automatically send a notification to the monitoring team after approval of the Investigator within the eCRF or after a standard delay.
- There may be instances when copies of medical records for certain cases are requested by Sanofi. In such case, care should be taken to ensure that the patient's identity is protected and the patient's identifiers in the study are properly mentioned on any copy of a source document provided to the Company. For laboratory results, include the laboratory normal ranges.

- All further data updates should be recorded in the eCRF, as appropriate, within 24 hours of knowledge of the SAE. In addition, every effort should be made to further document any SAE that is fatal or life-threatening within a week (7 days) of the initial notification.
- A back-up plan (using a paper CRF process) is available and should be used when the eCRF system does not work.

Any SAE brought to the attention of the Investigator at any time after the end of the study for the patient and considered by him/her to be caused by the study treatment with a reasonable possibility, should be reported to the monitoring team.

10.4.4 Guidelines for reporting adverse events of special interest

For AESIs, the Sponsor must be informed immediately (ie, within 24 hours), as per SAE notification guidelines described in Section 10.4.3, even if not fulfilling a seriousness criterion, using the corresponding screens in the eCRF. Instructions for AE reporting are summarized in Table 12.

10.4.5 Guidelines for reporting product complaints

Any defect in the study treatment must be reported as soon as possible by the Investigator to the monitoring team that will complete a product complaint form within required timelines.

Appropriate information (eg, samples, labels or documents like pictures or photocopies) related to product identification and to the potential deficiencies may need to be gathered. The Investigator will assess whether or not the quality issue has to be reported together with an AE or SAE.

Table 12 - Summary of adverse event reporting instructions

Event category	Reporting timeframe	Specific events in this category	Case Report Form completion		
			AE form	Safety Complementary Form	Other specific forms
Adverse Event (non-SAE, non-AESI)	Routine	Any AE that is not SAE or AESI	Yes	No	No
Serious Adverse Event (non-AESI or AESI)	Expedited (within 24 hours)	Any AE meeting seriousness criterion per Section 10.4.1.2	Yes	Yes	No
Adverse Event of Special Interest	Expedited (within 24 hours)	IARs of Grade ≥3	Yes	Yes	No
		Pregnancy	Yes	Yes	Yes
		Symptomatic overdose	Yes	Yes	No

10.5 OBLIGATIONS OF THE SPONSOR

During the course of the study, the Sponsor will report in an expedited manner:

- All SAEs that are both unexpected and at least reasonably related to the study treatment, to the regulatory authorities, independent ethics committee (IECs)/institutional review boards (IRBs) as appropriate and to the Investigators.
- All SAEs that are expected and at least reasonably related to study treatment to the regulatory authorities, according to local regulations.
- The AESIs listed in Section 10.4.1.3 to the regulatory authorities requiring such reporting.

Adverse events that are considered expected will be specified by the reference safety information (see the current version of the Investigator's Brochure).

The Sponsor will report all safety observations made during the conduct of the trial in the clinical study report.

10.6 SAFETY INSTRUCTIONS

10.6.1 Guidelines for the management of potential infusion associated reactions

Patients should routinely receive premedications prior to study treatment infusion as detailed in Section 8.2.2 to reduce the risk and severity of IARs commonly observed with mAbs.

Details for management of IARs are provided in Section 8.2.5.

10.6.2 Guidelines for the management of tumor lysis syndrome

Details for the management of TLS are provided in Section 8.2.9.

10.7 ADVERSE EVENTS MONITORING

All adverse events will be managed and reported in compliance with all applicable regulations, and included in the final clinical study report.

11 STATISTICAL CONSIDERATIONS

The statistical considerations presented in this section forms the basis for the SAP, which will provide accurate definitions and detailed specifications for the analyses to be performed on the data collected from this study. A final SAP will be issued prior to first patient treated.

11.1 DETERMINATION OF SAMPLE SIZE

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

- Kd arm has a median PFS of 19 months.
- IKd arm will have 41% risk reduction in hazard rate in comparison to Kd arm. The targeted hazard ratio is 0.59. Assuming proportional hazards, this is expected to correspond to an improvement in the true median PFS time from 19 months to 32 months.
- Log-rank test at a 1-sided 2.5% significance level.
- 3:2 randomization ratio (IKd:Kd).
- An interim analysis for efficacy assessment of PFS is planned when 65% of the 159 PFS events will be observed. An O'Brien and Fleming α-spending function will be used to obtain the nominal significance levels for the interim and final analyses of PFS (see Section 11.5 for details).

Based on the above assumptions, a total of 159 PFS events are needed to achieve a 90% power for the study.

In addition, with a total of 300 patients (180 patients in IKd arm and 120 patients in Kd arm) and assuming a uniform accrual rate of 19 patients per month, the final PFS analysis cut-off date is expected to be approximately 36 months after first patient in.

Calculations were made using East 6.4 software.

11.2 DISPOSITION OF PATIENTS

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

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

Patients treated without being randomized will not be considered as randomized and will not be included in any analysis population. The safety experience of such patients will be reported separately.

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

The number of screened patients as well as the number and percentage of patients included in the analysis populations defined in Section 11.3 will be provided.

A summary of the reasons for definitive and premature treatment discontinuation by treatment group will be provided.

11.3 ANALYSIS POPULATIONS

11.3.1 Efficacy populations

11.3.1.1 Intent-to-treat population

The intent-to-treat (ITT) population is the randomized population. All patients 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. Patients will be analyzed according to the treatment group allocated by IRT, regardless of whether the patients received any study treatment or receive a different study treatment from that to which they were randomized.

This population is the primary population for all efficacy analyses.

11.3.2 Safety population

The safety population will include ITT patients who received at least 1 dose or a part of a dose of study treatment.

This population is the primary population for the analysis of all safety parameters. All analyses using this population will be based on the actual treatment received. For instance, patients who receive at least 1 isatuximab dose (even incomplete) during the trial, will be allocated to the IKd arm.

11.3.3 Pharmacokinetic population

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

11.3.4 ADA population

The ADA population will include safety population patients from the IKd arm with a least 1 ADA assessment during the ADA on-study observation period with a reportable result.

11.4 STATISTICAL METHODS

A list of study endpoints and their definitions are provided in Section 9.

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

11.4.1 Extent of study treatment exposure and compliance

The extent of study treatment exposure will be assessed and summarized by actual treatment received within the safety population.

The following variables will be described to summarize the overall study treatment exposure (all study treatments together):

- Overall number of cycles started, defined by the total number of cycles in which at least one dose of any study treatments is administered.
- Overall duration of exposure in weeks defined as [(last day of last cycle – first day of first cycle)/7].

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

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

- Date of last dose of isatuximab + 7 days if last cycle is Cycle 1 or date of last dose of isatuximab + 14 days if last cycle is Cycle 2 or later,
- Date of last dose of carfilzomib + 7 days if the last dose is administered on Day 1 or 8; or date of last dose of carfilzomib + 6 days if the last dose is administered on Day 2 or 9; or date of last dose of carfilzomib + 14 days if the last dose is administered on Day 15; or date of last dose of carfilzomib + 13 days is the last dose is administered on Day 16,
- Date of last dose of dexamethasone + 7 days if the last dose is administered on Days 1, 8, 15, or 22; or date of last dose of dexamethasone + 6 days if the last dose is administered on Days 2, 9, 16, or 23.

Cycle delay will be computed to describe overall dose modification. A cycle is deemed to have been delayed if the start date of the current cycle is >28 + 3 days beyond the start date of the previous cycle (planned cycle duration is 28 days).

In addition, the following variables will be summarized with descriptive statistics for isatuximab, carfilzomib, and dexamethasone separately:

- Number of cycles started with each drug.
- Duration of exposure in weeks, defined as:
  - For isatuximab:
    [date of last dose of isatuximab + 7 days - first dose of isatuximab] / 7 if last cycle is Cycle 1 or [date of last dose of isatuximab + 14 days - first dose of isatuximab] / 7 if last cycle is Cycle 2 or later,
  - For carfilzomib:
    [date of last dose of carfilzomib + 7 days - first dose of carfilzomib] / 7 if the last dose is administered on Day 1 or 8; or [date of last dose of carfilzomib + 6 days - first dose of carfilzomib] / 7 if the last dose is administered on Day 2 or 9; or
    [date of last dose of carfilzomib + 14 days - first dose of carfilzomib] / 7 if the last dose is administered on Day 15; or
    [date of last dose of carfilzomib + 13 days - first dose of carfilzomib] / 7 if the last dose is administered on Day 16,

  - For dexamethasone: [date of last dose of dexamethasone + 7 days - first dose of dexamethasone] / 7 if the last dose is administered on Days 1, 8, 15, and 22; or [date of last dose of dexamethasone + 6 days - first dose of dexamethasone] / 7 if the last dose is administered on Days 2, 9, 16, and 23.
- Cumulative dose: The cumulative dose is the sum of all doses administered from first to last dose.
- Actual dose intensity: Defined as the cumulative dose divided by the duration of exposure.
- Relative dose intensity (RDI): Defined as the ratio of the actual dose intensity to the planned dose intensity. The RDI is an indicator of the feasibility of the chosen schedule of administration.
- Number of infusions (excluding dexamethasone).
- Infusion interruption (excluding dexamethasone): An infusion is considered to be interrupted if the administration is stopped during an infusion before it is completed regardless it is further restarted or not.
- Infusion/dose delay within cycle: An infusion/dose is deemed to have been delayed if the actual start date is >1 day beyond the theoretical day of treatment. Infusion/dose delay does not apply to the first infusion/dose of each cycle, in which case it is considered as cycle delay.
- 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. In addition, if the dose of carfilzomib is not increased to 56 mg/m2 from C1D8 as planned per protocol, this will be also considered as a dose reduction. Although not allowed in the study protocol for isatuximab, potential dose reduction will be screened and reported in the clinical study report.
- Dose omission: A dose is considered omitted if the dose is not administered for the scheduled visit and there are positive dose(s) afterwards.

11.4.2 Analyses of efficacy endpoints

11.4.2.1 Analysis of primary efficacy endpoint

Primary analysis will consist of PFS comparison between IKd arm versus Kd arm through a log-rank test procedure stratified by stratification factors as entered in the IRT (ie, number of previous lines of therapy and R-ISS). The significance levels at the interim and final analyses will be determined using alpha-spending function (see Section 11.5).

This analysis will be performed on the ITT population.

The analysis of PFS will be based on the following censoring rules:

- If progression and death are not observed before the PFS analysis cut-off date or the date of initiation of further anti-myeloma treatment, 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.
- A patient without an event (death or disease progression) and without any valid post-baseline disease assessments will be censored at the day of randomization (Day 1).

The date of disease progression is the date of the first documented (that is subsequently confirmed, if based on paraprotein) progression according to IMWG criteria as assessed by IRC (see Appendix F).

The final PFS analysis cut-off date will be the date when the 159th event (first occurrence of either disease progression or death due to any cause) assessed by the IRC has been observed.

The estimates of the hazard ratio and corresponding (1-2α) % CI (α being the one-sided nominal significance level: α=0.023 at final analysis and 0.005 at PFS interim analysis) will be provided using a Cox proportional hazard model stratified by the stratification factors as entered in the IRT. The median PFS and probabilities of being progression free at different time points calculated using the Kaplan-Meier method as well as corresponding CI will be presented by treatment arm. The Kaplan-Meier PFS curves will also be presented.

Sensitivity analyses of PFS will be performed (eg, different censoring rules and PFS assessed by the Investigator). In particular, a sensitivity analysis has been added to evaluate the impact of late progressions and deaths. In this sensitivity analysis, progressions or deaths occurring more than 8 weeks after the last disease assessment (corresponding to two consecutive missed assessments) will be censored at the earliest of the date of last valid disease assessment without evidence of progression before initiation of new anti-myeloma treatment and the cut-off date. Subgroup analyses of PFS (eg, by high risk cytogenetic status, number of prior lines of treatment) will also be conducted.

11.4.2.2 Analyses of secondary efficacy endpoints

11.4.2.2.1 Analysis of key secondary efficacy endpoints

Key secondary endpoints other than OS will be analyzed in the ITT population at the time of the primary and/or the final analysis of PFS (based on data collected up to the PFS analysis cut-off date). The CR rate will only be tested for comparison when the antibody-capture interference assay will be available.

Key secondary endpoints other than OS will be summarized with descriptive statistics per treatment arm. The (1-2α) % 2-sided CI will be computed using the Clopper-Pearson method. These endpoints will be compared between treatment arms using Cochran Mantel Haenszel stratified method.

For analysis purpose, subjects in the ITT population without MRD assessment will be considered as having positive MRD. In addition, analyses on MRD negativity rate will be also performed on the ITT population but restricted to patients with VGPR or better as per investigator, as exploratory analyses.

The OS analysis will be similar to what is described for PFS and will be performed approximately 3 years after the primary PFS analysis cut-off date. The analysis of OS will consist of comparison between the IKd arm versus Kd arm through a log-rank test procedure stratified by stratification factors as entered in the IRT (ie, number of previous lines of therapy and R-ISS) at the 1-sided level of 0.025. The analysis will be based on the following censoring rule:

- Patients without death prior to the OS analysis cut-off date will be censored at the last date the patient was known to be alive or the OS analysis cut-off date, whichever comes first.

The estimates of the hazard ratio and corresponding 95% CI will be provided using a Cox proportional hazard model stratified by the stratification factors as entered in the IRT. The median OS and probabilities of being surviving at different time points calculated using the Kaplan-Meier method as well as corresponding CI will be presented by treatment arm. The Kaplan-Meier OS curves will also be provided.

Subgroup analyses of OS (eg, by high risk cytogenetic status, number of prior lines of treatment) will also be conducted.

11.4.2.2.2 Analysis of other secondary efficacy endpoints

Other secondary endpoints will be analyzed at the time of the primary analysis and/or the final PFS analysis.

The analyses of TTP, PFS2, DOR, time to first response and time to best response will be similar to what is described for PFS and will be based on the following censoring rules:

- TTP: If progression is not observed before the PFS analysis cut-off date or the date of initiation of further anti-myeloma treatment, TTP 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.
- PFS2: For patients alive without a progression after initiation of further anti-myeloma treatment before the PFS analysis cut-off date, PFS2 will be censored at the date of the last follow-up visit not showing disease progression after initiation of further anti-myeloma treatment or the analysis cut-off date, whichever comes first.
- DOR: In the absence of the confirmation of subsequent disease progression or death before the analysis cut-off date, the DOR will be censored at the date of the last valid disease assessment not showing disease progression performed prior to initiation of a further antimyeloma treatment or the analysis cut-off date, whichever is earlier.
- Time to first response: in the absence of response, patients will be censored at the earliest of the date of the last valid disease assessment before disease progression or death, the date of the last valid disease assessment before initiation of a further anti-myeloma treatment (if any) or the analysis cut-off date, whichever comes first.
- Time to best response: The same censoring rules as time to first response will be used

11.4.2.3 Multiplicity considerations

Hypothesis testing of the key secondary efficacy endpoints will be carried out. A closed test procedure will be used to control the type I error rate meaning that no further testing will be performed unless the significance level had been reached on PFS. The hierarchical procedure will be then performed according to the following order:

- ORR at the time of the primary PFS analysis and/or the final PFS analysis.
- Rate of VGPR or better at the time of the primary PFS analysis on and/or the final PFS analysis.

- Rate of VGPR or better with MRD negativity at the time of the primary PFS analysis and/or the final PFS analysis.
- CR rate will only be tested for comparison when the antibody-capture interference assay will be available
- OS tested at End-of-Study.

The significance levels at the interim and final analyses will be determined using alpha-spending function specific to each endpoint (see Section 11.5). The primary analysis of PFS corresponds either to the positive interim analysis or the final PFS analysis.

No update of PFS, ORR, rate of VGPR or better, VGPR or better with MRD negativity rate, and rate of CR will be provided at the time of OS analysis.

11.4.3 Analyses of safety data

All safety analyses will be performed on the safety population unless otherwise specified. The summary of safety results will be presented by actual treatment group. The analysis of the safety variables will be essentially descriptive and no systematic testing is planned.

For each of the safety parameters, a baseline value will be defined as the last value or measurement taken up to the first dose in the study.

The observation period will be divided into 3 periods:

- The pre-treatment period is defined as the time form the signed informed consent date up to the first dose of study treatment.
- The treatment period is defined as the time from the first dose of study treatment up to the last dose of study treatment +30 days.
- The post-treatment period is defined as the period of time starting the day after the end of the treatment period up to the end of the study.

11.4.3.1 Adverse events

Adverse event observation period:

- Pre-treatment AEs are defined as any AE reported during the pre-treatment period.
- TEAEs are defined as AEs that developed or worsened or became serious during the treatment period.
- Post-treatment AEs are defined as AEs that developed or worsened or become serious during the post-treatment period.

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

All AEs will be graded according NCI-CTCAE v4.03 (Appendix E) and coded to a lower-level term, preferred term (PT), high-level term (HLT), high-level group term (HLGT), and associated primary system organ class (SOC) using the version of Medical Dictionary for Regulatory Activities currently in effect at Sanofi at the time of database lock.

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

Method for handling incomplete dates of onset will be described in SAP.

Regarding treatment discontinuation, following definitions will be used:

- **Premature** treatment discontinuation is defined as the discontinuation of at least 1 of the study treatments but at least 1 is continued.
- **Definitive** treatment discontinuation is defined as the discontinuation of all the study treatments.

11.4.3.2 Treatment-emergent adverse events

An overview table summarizing the number (%) of patients with the following TEAEs will be generated for the safety population:

- TEAEs any grade.
- TEAEs of Grade ≥3.
- TEAEs of Grade 3 or 4.
- TEAEs of Grade 5 (any TEAE with a fatal outcome during the treatment period).
- Serious TEAEs.
- Serious treatment-related TEAEs.
- TEAE leading to definitive (all study drugs) discontinuation.
- TEAE leading to premature discontinuation of isatuximab.
- TEAE leading to premature discontinuation of carfilzomib.
- TEAE leading to premature discontinuation of dexamethasone.
- IARs of Grade ≥3.
- Treatment-related TEAEs.
- Treatment-related TEAEs of Grade ≥3.

The number and percentage of patients experiencing TEAEs by primary SOC and PT will be summarized by NCI CTCAE grade (all grades and Grade ≥3). Similar tables will be prepared for treatment-related TEAEs, AESIs, TEAEs leading to permanent/premature discontinuation, TEAEs leading to dose modification, serious TEAEs, TEAEs with fatal outcome, and AEs/SAEs occurring during the post-treatment dosing period.

Sorting within tables should ensure the same presentation for the set of all AEs within the observation period (pre-treatment, on-treatment, and post-treatment). For that purpose, the table of all TEAEs presented by SOC and PT sorted by internationally agreed order and decreasing frequency of PTs within SOCs will define the presentation order for all other tables unless otherwise specified. Sorting will be based on results for the IKd arm.

The number and percentage of patients experiencing TEAEs presented by primary SOC, HLGT, HLT, and PT sorted by SOC internationally agreed order, then by alphabetic order of HLGT, HLT, and PT will be provided. This table will be provided for all TEAEs, serious TEAEs, and TEAEs leading to permanent/premature treatment discontinuation.

11.4.3.3 Deaths

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

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

The following death summaries will be generated for the safety population:

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

11.4.3.4 Other safety evaluation

11.4.3.4.1 Laboratory data

Clinical laboratory values will be analyzed after conversion into standard international units. International units will be used in all listings and tables. Hematological and biochemistry results will be graded according to NCI-CTCAE v4.03, when applicable. For patients with multiple occurrences of the same laboratory variable during the treatment period, the maximum grade (worst) per patient will be used.

For hematological parameters and for some selected biochemistry parameters, Sanofi generic ranges (lower limit of normal, ULN) are defined and will be used for grading. For other biochemistry parameters (eg, for hepatic enzymes ALT, AST, alkaline phosphatase, total bilirubin), grading will be derived using local laboratory normal ranges.

The number and proportion of patients with abnormal laboratory tests at baseline (ie, last assessment before the first dose of study treatment administration) will be presented by grade and all grades together. A similar table showing abnormalities during the treatment period will be provided. The denominator used for percentage calculation is the number of patients with at least 1 evaluation of the laboratory test during the considered observation period.

For laboratory tests for which NCI-CTCAE v4.03 scale is not applicable, potentially clinically significant abnormality (PCSA) values are defined as abnormal values considered medically important by the Sponsor according to predefined criteria/thresholds based on literature review. The PCSA criteria will determine which patients had at least 1 PCSA during the treatment period, taking into account all evaluations performed during the on-treatment period, including nonscheduled or repeated evaluations. The incidence of PCSA any time during the on-treatment period will be summarized by treatment group irrespective of the baseline level.

11.4.3.4.2 ECOG Performance Status

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

11.4.3.4.3 Vital signs

For blood pressure/heart rate parameters, the incidence of PCSAs prior to study treatment administration at any cycle during the on-treatment period will be summarized by treatment group whatever the baseline level and/or according to the following baseline categories:

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

The incidence of PCSAs during and after isatuximab administration at any cycle during the treatment period in the IKd arm will also be summarized.

11.4.3.4.4 Electrocardiogram

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

- Normal/missing.
- Abnormal.

11.4.4 Analyses of pharmacokinetic and pharmacodynamic variables

11.4.4.1 Analysis of pharmacokinetic variables

Individual concentrations and PK parameters of carfilzomib will be summarized by descriptive statistics (such as mean, geometric mean, median, standard deviation, standard error of the mean [SEM], coefficient of variation [CV], minimum, and maximum).

The population PK of isatuximab will be characterized in the population of patients in the IKd arm, using a nonlinear mixed effect model based on PK data from Phase I/II studies and III in

which intensive and sparse blood sampling protocols were used. The population estimates from this analysis will provide a prior distribution from which individual Bayesian estimates of the PK parameters for each patient in this study will be derived.

Pharmacokinetic parameters of isatuximab will be summarized by descriptive statistics (such as mean, geometric mean, median, standard deviation, SEM, CV, minimum, and maximum).

11.4.5 Analysis of immunogenicity variables

The observation period for ADAs will be divided into 2 periods:

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

Patients with at least 1 evaluable ADA result during the ADA pre-treatment period will be considered as evaluable at baseline. Patients with at least 1 evaluable ADA result during the ADA on-study observation period will be considered evaluable during the on-study observation period.

The immunogenicity for isatuximab will be assessed by summarizing the number (%) of patients with pre-existing ADA and ADA negative at baseline, and by summarizing the number (%) of ADA positive patients (including treatment-induced ADA and treatment boosted ADA) during the on-study observation period.

Anti-drug antibody prevalence and ADA incidence will be also described.

The impact of positive immune response will be evaluated on efficacy, PK, and safety endpoints, when relevant.

11.4.6 Analyses of biomarker variables

Biomarker endpoints will be analyzed using patients from the ITT population who have at least 1 evaluable assessment on the biomarker of interest.

Each genetic biomarker will be summarized with descriptive statistics by treatment group and overall. Further analyses will be described in the SAP.

11.4.7 Analyses of PRO (health-related quality of life/health economics variables)

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

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

A descriptive summary at each visit and change from baseline will be provided for each group for the following variables:

- EORTC QLQ-C30: GHS/quality of life scale, the 5 functional scales (physical, emotional, cognitive, role, and social), the 3 symptom scales (fatigue, nausea/vomiting, and pain) and the 6 additional single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial impact).
- QLQ-MY20: Future perspective, body image, disease symptoms and side effects of treatment.
- EQ-5D-5L: Health state utility value and VAS scores.

11.5 INTERIM ANALYSIS

An interim analysis for efficacy assessment of PFS is planned when 65% of the 159 PFS events have been observed. The interim PFS cut-off date is expected approximately 24 months after the FPI.

An O'Brien and Fleming α-spending function will be used to obtain the nominal significance levels for the interim and final analyses of survival on PFS. The 1-sided nominal significance level to terminate the study for efficacy at 65% information fraction (103 PFS events) is 0.005 (corresponding to a HR of 0.6). The 1-sided nominal significance level to declare superiority of IKd at the final analysis (159 events) is 0.023 (corresponding to a HR of 0.725). In case of positive results at interim analysis, PFS results will be updated in a descriptive way (non-inferential analysis) at the analysis cut-off date when 159 PFS events are observed.

For the key secondary endpoints, the significance levels at the interim and final analyses will be determined using α-spending function specific to each endpoint, except if the information fraction is 100% at the interim analysis of PFS (ie, information on secondary endpoints available for every patient). For ORR and rate of VGPR or better, a Pocock-type boundary will be used. For rate of VGPR or better and MRD negative rate, the O'Brien-Fleming alpha-spending function will be used. OS will be tested only at End-of-Study (ie, 3 years after the primary PFS analysis cut-off date).

12 ETHICAL AND REGULATORY CONSIDERATIONS

12.1 ETHICAL AND REGULATORY STANDARDS

This clinical trial will be conducted by the Sponsor, the Investigator, and delegated Investigator staff and Subinvestigator, in accordance with consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki, and the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines for Good Clinical Practice (GCP), all applicable laws, rules, and regulations.

This clinical trial will be recorded in a free, publicly accessible, internet-based registry, no later than 21 days after the first patient enrollment, in compliance with applicable regulatory requirements and with Sanofi public disclosure commitments.

The Investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC Determining whether an incidental finding should be returned to a participant and, if it meets the appropriate criteria, to ensure the finding is returned (an incidental finding is a previously undiagnosed medical condition that is discovered unintentionally and is unrelated to the aims of the study for which the tests are being performed). The following should be considered when determining the return of an incidental finding:
    - The return of such information to the study participant (and/or his/her designated healthcare professional, if so designated by the participant) is consistent with all applicable national, state, or regional laws and regulations in the country where the study is being conducted, and
    - The finding reveals a substantial risk of a serious health condition or has reproductive importance, AND has analytical validity, AND has clinical validity.
    - The participant in a clinical study has the right to opt out of being notified by the Investigator of such incidental findings. In the event that the participant has opted out of being notified and the finding has consequences for other individuals, eg, the finding relates to a communicable disease, Investigators should seek independent ethical advice before determining next steps.
    - In case the participant has decided to opt out, the Investigator must record in the site medical files that she/he does not want to know about such findings.

According to the Regulation No 536/2014 of the European Parliament and the Council of the European Union and as specified by the applicable regulatory requirements in non-European Union/European Economic Area countries, Sanofi, as the clinical trial Sponsor, needs to report to the concerned regulatory agency/ies serious breaches without undue delay but not later than 7 calendar days of becoming aware of that breach. A serious breach is defined as a deviation of the version of the protocol applicable at the time of the breach or the applicable clinical trial regulation that is likely to affect to a significant degree the safety and rights of a subject or the reliability and robustness of the data generated in the clinical trial.

The Sponsor shall ensure that all parties involved in the conduct of the clinical trial promptly report any events that might meet the definition of a serious breach.

Therefore, Investigators shall within 48 hours after being aware of a deviation that might meet the definition of a serious breach, report to the Sponsor any suspected serious breach to enable the Sponsor to carry out the required assessment and notify the regulatory agency/ies in the event of a confirmed serious breach. To that extent, the principal Investigator must have a process in place to ensure that the site staff or service providers engaged by the principal Investigator/institution are able to identify the occurrence of a (suspected) serious breach and that a (suspected) serious breach is promptly reported to the Sponsor through the contacts (e-mail address or telephone number) provided by the Sponsor.

12.2 INFORMED CONSENT

The Investigator (according to applicable regulatory requirements), or a person designated by the Investigator, and under the Investigator's responsibility, should fully inform the patient of all pertinent aspects of the clinical trial including the written information giving approval/favorable opinion by the ethics committee (IRB/IEC). All participants should be informed to the fullest extent possible about the study, in language and terms they are able to understand.

Prior to a patient’s participation in the clinical trial, the written informed consent form should be signed, name filled in and personally dated by the patient or by the patient’s legally acceptable representative, and by the person who conducted the informed consent discussion. A copy of the signed and dated written informed consent form will be provided to the patient.

The informed consent form used by the Investigator for obtaining the patient's informed consent must be reviewed and approved by the Sponsor prior to submission to the appropriate ethics committee (IRB/IEC) for approval/favorable opinion.

For a regional or national emergency declared by a governmental agency, contingency measures refer to Appendix N.

12.3 HEALTH AUTHORITIES AND INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE (IRB/IEC)

As required by local regulation, the Investigator or the Sponsor must submit this clinical trial protocol to the health authorities (competent regulatory authority) and the appropriate IRB/IEC, and is required to forward to the respective other party a copy of the written and dated approval/favorable opinion signed by the chairman with IRB/IEC composition.

The clinical trial (study number, clinical trial protocol title and version number), the documents reviewed (clinical trial protocol, informed consent form, Investigator’s Brochure with any addenda or labeling documents (summary of product characteristics, Investigator’s curriculum vitae, etc.) and the date of the review should be clearly stated on the written (IRB/IEC) approval/favorable opinion.

The study treatment will not be released at the study site and the Investigator will not start the study before the written and dated approval/favorable opinion is received by the Investigator and the Sponsor.

During the clinical trial, any amendment or modification to the clinical trial protocol should be submitted to the health authorities (competent regulatory authority), as required by local regulation, in addition to the IRB/IEC before implementation, unless the change is necessary to eliminate an immediate hazard to the patients, in which case the health authorities (competent regulatory authority) and the IRB/IEC should be informed as soon as possible. They should also be informed of any event likely to affect the safety of patients or the continued conduct of the clinical trial, in particular any change in safety. All updates to the Investigator's Brochure will be sent to the IRB/IEC and to health authorities (competent regulatory authority), as required by local regulation.

13 STUDY MONITORING

13.1 RESPONSIBILITIES OF THE INVESTIGATOR(S)

The Investigator is required to ensure compliance with all procedures required by the clinical trial protocol and with all study procedures provided by the Sponsor (including security rules). The Investigator agrees to provide reliable data and all information requested by the clinical trial protocol (with the help of the eCRF, Discrepancy Resolution Form [DRF], or other appropriate instrument) in an accurate and legible manner according to the instructions provided and to ensure direct access to source documents by Sponsor representatives.

If any circuit includes transfer of data particular attention should be paid to the confidentiality of the patient's data to be transferred.

The Investigator may appoint such other individuals as he/she may deem appropriate as Subinvestigators to assist in the conduct of the clinical trial in accordance with the clinical trial protocol. All Subinvestigators shall be appointed and listed in a timely manner. The Subinvestigators will be supervised by and work under the responsibility of the Investigator. The Investigator will provide them with a copy of the clinical trial protocol and all necessary information.

13.2 RESPONSIBILITIES OF THE SPONSOR

The Sponsor of this clinical trial is responsible to regulatory authorities for taking all reasonable steps to ensure the proper conduct of the clinical trial as regards ethics, clinical trial protocol compliance, and integrity and validity of the data recorded on the eCRFs. Thus, the main duty of the monitoring team is to help the Investigator and the Sponsor maintain a high level of ethical, scientific, technical, and regulatory quality in all aspects of the clinical trial.

At regular intervals during the clinical trial, the site will be contacted, through monitoring visits, letters, or telephone calls, by a representative of the monitoring team to review study progress, Investigator and patient compliance with clinical trial protocol requirements, and any emergent problems. These monitoring visits will include but not be limited to review of the following aspects: patient informed consent, patient recruitment and follow-up, SAE documentation and reporting, AESI documentation and reporting, AE documentation, study treatment allocation, patient compliance with the study treatment regimen, study treatment accountability, concomitant therapy use, and quality of data. Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote or on-site monitoring) are provided in separate study documents.

13.3 SOURCE DOCUMENT REQUIREMENTS

According to the ICH GCP, the monitoring team must check the eCRF entries against the source documents, except for the pre-identified source data directly recorded in the eCRF. The informed consent form will include a statement by which the patient allows the Sponsor's duly authorized personnel, the ethics committee (IRB/IEC), and the regulatory authorities to have direct access to original medical records which support the data on the eCRFs (eg, patient's medical file, appointment books, original laboratory records, etc.). These personnel, bound by professional secrecy, must maintain the confidentiality of all personal identity or personal medical information (according to confidentiality and personal data protection rules).

13.4 USE AND COMPLETION OF CASE REPORT FORMS (CRFS) AND ADDITIONAL REQUEST

It is the responsibility of the Investigator to maintain adequate and accurate eCRFs (according to the technology used) designed by the Sponsor to record (according to Sponsor instructions) all observations and other data pertinent to the clinical investigation in a timely manner. All eCRFs should be completed in their entirety in a neat, legible manner to ensure accurate interpretation of data.

Should a correction be made, the corrected information will be entered in the eCRF overwriting the initial information. An audit trail allows identifying the modification.

Data are available within the system to the Sponsor as soon as they are entered in the eCRF.

The computerized handling of the data by the Sponsor may generate additional requests (DRF) to which the Investigator is obliged to respond by confirming or modifying the data questioned. The requests with their responses will be managed through the eCRF.

13.5 USE OF COMPUTERIZED SYSTEMS

The complete list of computerized systems used for the study is provided in a separate document which is maintained in the Sponsor trial master file.

14 ADDITIONAL REQUIREMENTS

14.1 CURRICULUM VITAE

A current copy of the curriculum vitae describing the experience, qualification and training of each Investigator and Subinvestigator will be signed, dated, and provided to the Sponsor prior to the beginning of the clinical trial.

14.2 RECORD RETENTION IN STUDY SITES

The Investigator must maintain confidential all study documentation, and take measures to prevent accidental or premature destruction of these documents.

The Investigator should retain the study documents at least 15 years after the completion or discontinuation of the clinical trial.

However, applicable regulatory requirements should be taken into account in the event that a longer period is required.

The Investigator must notify the Sponsor prior to destroying any study essential documents following the clinical trial completion or discontinuation.

If the Investigator's personal situation is such that archiving can no longer be ensured by him/her, the Investigator shall inform the Sponsor and the relevant records shall be transferred to a mutually agreed upon designee.

14.3 CONFIDENTIALITY

All information disclosed or provided by the Sponsor (or any company/institution acting on their behalf), or produced during the clinical trial, including, but not limited to, the clinical trial protocol, personal data in relation to the patients, the CRFs, the Investigator's Brochure, and the results obtained during the course of the clinical trial is confidential, prior to the publication of results. The Investigator and any person under his/her authority agree to undertake to keep confidential and not to disclose the information to any third party without the prior written approval of the Sponsor.

However, the submission of this clinical trial protocol and other necessary documentation to the ethics committee (IRB/IEC) is expressly permitted, the IRB/IEC members having the same obligation of confidentiality.

The Subinvestigators shall be bound by the same obligation as the Investigator. The Investigator shall inform the Subinvestigators of the confidential nature of the clinical trial.

The Investigator and the Subinvestigators shall use the information solely for the purposes of the clinical trial, to the exclusion of any use for their own or for a third party's account.

14.4 PROPERTY RIGHTS

All information, documents, and study treatment provided by the Sponsor or its designee are and remain the sole property of the Sponsor.

The Investigator shall not and shall cause the delegated Investigator staff/Subinvestigator not to mention any information or the Product in any application for a patent or for any other intellectual property rights.

All the results, data, documents, and inventions, which arise directly or indirectly from the clinical trial in any form, shall be the immediate and exclusive property of the Sponsor.

The Sponsor may use or exploit all the results at its own discretion, without any limitation to its property right (territory, field, continuance). The Sponsor shall be under no obligation to patent, develop, market, or otherwise use the results of the clinical trial.

As the case may be, the Investigator and/or the Subinvestigators shall provide all assistance required by the Sponsor, at the Sponsor's expense, for obtaining and defending any patent, including signature of legal documents.

14.5 DATA PROTECTION

- The patient's personal data, which are included in the Sponsor database shall be treated in compliance with all applicable laws and regulations.
- When archiving or processing personal data pertaining to the Investigator and/or to the patients, the Sponsor shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.
- The Sponsor also collects specific data regarding Investigator as well as personal data from any person involved in the study which may be included in the Sponsor’s databases, shall be treated by both the Sponsor and the Investigator in compliance with all applicable laws and regulations.

Patient race or ethnicity (including ‘Caucasian/white, Black, Asian/Oriental’) will be collected in this study because these data are required by several regulatory authorities (eg, on Afro-American population for the Food and Drug Administration, on the Japanese population for the Pharmaceuticals and Medical Devices Agency in Japan, or on the Chinese population for the China Food and Drug Administration in China).

The data collected in this study will only be used for the purpose(s) of the study and to document the evaluation of the benefit/risk ratio, efficacy, and safety of the product(s). They may be further processed if they have been anonymized.

The contract between Sponsor, Investigators, and study sites specifies responsibilities of the parties related data protection, including handling of data security breaches and respective communication and cooperation of the parties. Accordingly, the Investigator and the institution will promptly notify the Sponsor about any data security breaches and detail in the notification the nature of the breach, the categories (eg, Sponsor’s personnel, study participants or their relatives,

healthcare professionals, etc.), the approximate number of subjects concerned, the type and approximate number of data records concerned and the likely consequences of the breach. The institution and/or Investigator will investigate the causes of the data security breach and take actions to minimize the effects of said breach. The institution and/or Investigator will record all information relating to the breach, including the results of their own investigations and investigations by authorities, as applicable, and will take all measures as necessary to prevent future data security breaches.

14.6 INSURANCE COMPENSATION

The Sponsor certifies that it has taken out a liability insurance policy covering all clinical trials under its sponsorship. This insurance policy is in accordance with local laws and requirements. The insurance of the Sponsor does not relieve the Investigator and the collaborators from any obligation to maintain their own liability insurance policy. An insurance certificate will be provided to the IECs/IRBs or regulatory authorities in countries requiring this document.

14.7 SPONSOR AUDITS AND INSPECTIONS BY REGULATORY AGENCIES

For the purpose of ensuring compliance with the clinical trial protocol, GCP, and applicable regulatory requirements, the Investigator should permit auditing by or on the behalf of the Sponsor and inspection by regulatory authorities.

The Investigator agrees to allow the auditors/inspectors to have direct access to his/her study records for review, being understood that these personnel is bound by professional secrecy, and as such will not disclose any personal identity or personal medical information.

The Investigator will make every effort to help with the performance of the audits and inspections, giving access to all necessary facilities, data, and documents.

As soon as the Investigator is notified of a planned inspection by the authorities, he will inform the Sponsor and authorize the Sponsor to participate in this inspection.

The confidentiality of the data verified and the protection of the patients should be respected during these inspections.

Any result and information arising from the inspections by the regulatory authorities will be immediately communicated by the Investigator to the Sponsor.

The Investigator shall take appropriate measures required by the Sponsor to take corrective actions for all problems found during the audit or inspections.

14.8 PREMATURE DISCONTINUATION OF THE STUDY OR PREMATURE CLOSE-OUT OF A SITE

14.8.1 By the Sponsor

The Sponsor has the right to terminate the participation of either an individual site or the study at any time, for any reason, including but not limited to the following:

- The information on the product leads to doubt as to the benefit/risk ratio.
- Patient enrollment is unsatisfactory.
- The Investigator has received from the Sponsor all study treatment, means, and information necessary to perform the clinical trial and has not included any patient after a reasonable period of time mutually agreed upon.
- Noncompliance of the Investigator or Subinvestigator, delegated staff with any provision of the clinical trial protocol, and breach of the applicable laws and regulations or breach of the ICH GCP.
- The total number of patients are included earlier than expected.

In any case the Sponsor will notify the Investigator of its decision by written notice.

14.8.2 By the Investigator

The Investigator may terminate his/her participation upon 30 days' prior written notice if the study site or the Investigator for any reason becomes unable to perform or complete the clinical trial.

In the event of premature discontinuation of the study or premature close-out of a site, for any reason whatsoever, the appropriate IRB/IEC and regulatory authorities should be informed according to applicable regulatory requirements.

14.9 CLINICAL TRIAL RESULTS

The Sponsor will be responsible for preparing a clinical study report and to provide a summary of study results to the Investigator.

14.10 PUBLICATIONS AND COMMUNICATIONS

The Investigator undertakes not to make any publication or release pertaining to the study and/or results of the study prior to the Sponsor’s written consent, being understood that the Sponsor will not unreasonably withhold its approval.

As the study is being conducted at multiple sites, the Sponsor agrees that, consistent with scientific standards, a primary presentation or publication of the study results based on global study outcomes shall be sought. However, if no multicenter publication is submitted, underway, or planned within 12 months of the completion of this study at all sites, the Investigator shall have the right to publish or present independently the results of this study in agreement with other

Investigators and stakeholders. The Investigator shall provide the Sponsor with a copy of any such presentation or publication for review and comment at least 30 days in advance of any presentation or submission for publication. In addition, if requested by the Sponsor, any presentation or submission for publication shall be delayed for a limited time, not to exceed 90 days, to allow for filing of a patent application or such other justified measures as the Sponsor deems appropriate to establish and preserve its proprietary rights.

The Investigator shall not use the name(s) of the Sponsor and/or its employees in advertising or promotional material or publication without the prior written consent of the Sponsor.
The Sponsor shall not use the name(s) of the Investigator and/or the collaborators in advertising or promotional material or publication without having received his/her and/or their prior written consent(s).

The Sponsor has the right at any time to publish the results of the study.

15 CLINICAL TRIAL PROTOCOL AMENDMENTS

All appendices attached hereto and referred to herein are made part of this clinical trial protocol.

The Investigator should not implement any deviation from, or changes to the clinical trial protocol without agreement by the Sponsor and prior review and documented approval/favorable opinion from the IRB/IEC and/or notification/approval of health authorities (competent regulatory authority) of an amendment, as required by local regulation, except where necessary to eliminate an immediate hazard(s) to clinical trial patients, or when the change(s) involves only logistical or administrative aspects of the trial. Any change agreed upon will be recorded in writing, the written amendment will be signed by the Investigator and by the Sponsor and the signed amendment will be filed with this clinical trial protocol.

Any amendment to the clinical trial protocol requires written approval/favorable opinion by the IRB/IEC prior to its implementation, unless there are overriding safety reasons.

In case of substantial amendment to the clinical trial protocol, approval from the health authorities (competent regulatory authority) will be sought before implementation.

In some instances, an amendment may require a change to the informed consent form. The Investigator must receive an IRB/IEC approval/favorable opinion concerning the revised informed consent form prior to implementation of the change and patient signature should be re-collected if necessary.

16 APPENDICES

Appendix A Revised international staging system

Disease staging is to be done according to R-ISS (12).

R-ISS will be classified undetermined in case of inconclusive FISH, unless Stage can be determined on lactate dehydrogenase, albumin, and β2 microglobulin only.

Table 1. Standard Risk Factors for MM and the R-ISS

Prognostic Factor	Criteria
ISS stage	
I	Serum β_2-microglobulin < 3.5 mg/L, serum albumin ≥ 3.5 g/dL
II	Not ISS stage I or III
III	Serum β_2-microglobulin ≥ 5.5 mg/L
CA by iFISH	
High risk	Presence of del(17p) and/or translocation t(4;14) and/or translocation t(14;16)
Standard risk	No high-risk CA
LDH	
Normal	Serum LDH < the upper limit of normal
High	Serum LDH > the upper limit of normal
A new model for risk stratification for MM	
R-ISS stage	
I	ISS stage I and standard-risk CA by iFISH and normal LDH
II	Not R-ISS stage I or III
III	ISS stage III and either high-risk CA by iFISH or high LDH

Abbreviations: CA, chromosomal abnormalities; iFISH, interphase fluorescent in situ hybridization; ISS, International Staging System; LDH, lactate dehydrogenase; MM, multiple myeloma; R-ISS, revised International Staging System.

Appendix B Modification of diet in renal disease (MDRD) equation

Glomerular filtration rate (mL/mins/1.73 m^2) = 175 x $(Scr)^{-1.154}$ x $(Age)^{-0.203}$ x (0.742 if Female) x (1.212 if African-American)

Appendix C Contraceptive guidance and collection of pregnancy information

No reproductive toxicology studies have been conducted with isatuximab, so the most conservative contraceptive recommendation has to be followed. Females of childbearing potential or male subjects with female partners of childbearing potential shall be required to use effective contraceptive methods starting 2 weeks before first study treatment administration, while on therapy and for 12 weeks for Kd and 5 months for IKd following the last dose of study treatment.

DEFINITIONS

Nonreproductive potential

1. Premenopausal female with 1 of the following:
    - Documented hysterectomy.
    - Documented bilateral salpingectomy.
    - Documented bilateral oophorectomy.
2. Postmenopausal:
    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
    - Females on HRT and whose menopausal status is in doubt will be required to use 1 of the highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrolment.

Reproductive potential

A woman is considered of reproductive potential (WOCBP), ie, fertile, following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy.

CONTRACEPTIVE GUIDANCE

Male subjects

- Male subjects with heterosexual partners of reproductive potential (WOCBP) are eligible to participate if they agree to use the following during the protocol defined timeline:
    - Refrain from donating sperm
      and
    - At least 1 of the following conditions applies:
    - Are and agree to remain abstinent from penile-vaginal intercourse on a long term and persistent basis, when this is their preferred and usual lifestyle
      or
    - Agree to use a male condom plus an additional contraceptive method with a failure rate of <1% per year (see table for female subjects).
- Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom for the time defined in the protocol.

Female subjects:

Highly Effective Contraceptive Methods That Are User Dependent *Failure rate of <1% per year when used consistently and correctly*[a]
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b] - Oral. - Intravaginal. - Transdermal. • Progestogen-only hormone contraception associated with inhibition of ovulation[b] - Oral. - Injectable.
Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[b] • IUD • IUS • Bilateral tubal occlusion • Vasectomized partner *(Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method(s) of contraception should be used. Spermatogenesis cycle is approximately 90 days.)* • Sexual abstinence *(Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the subject.)*

NOTES:

a Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for subjects participating in clinical studies.

b Hormonal contraception may be susceptible to interaction with the study treatment, which may reduce the efficacy of the contraceptive method. In this case 2 highly effective methods of contraception should be used during the treatment period and for at least 3 months for Kd and 5 months for IKd after the last dose of study treatment.

COLLECTION OF PREGNANCY INFORMATION

Male subjects with partners of reproductive potential who become pregnant

- The Investigator will attempt to collect pregnancy information on any female partner of a male study subject who becomes pregnant while participating in this study. This applies only to subjects who receive study treatment.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the partner's pregnancy.
- Partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor.
- Generally, follow-up will be no longer than 1 year following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for procedure.

Female subjects who become pregnant

- The Investigator will collect pregnancy information on any female subject, who becomes pregnant while participating in this study.
- Information will be recorded on the appropriate form and submitted to the Sponsor within 24 hours of learning of a participant's pregnancy.
- Participant will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on participant and neonate, which will be forwarded to the Sponsor. Generally, follow-up will not be required for longer than 1 year beyond the estimated delivery date.
- Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE.
- A spontaneous abortion is always considered to be an SAE and will be reported as such.
- Any SAE occurring as a result of a post-study pregnancy which is considered reasonably related to the study treatment by the Investigator, will be reported to the Sponsor as it will be described in the full protocol. While the Investigator is not obligated to actively seek this information in former study subjects, he or she may learn of an SAE through spontaneous reporting.

Appendix D Eastern Cooperative Oncology Group performance status scale

Performance Status	Description
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work, office work.
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours.
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours.
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair.
5	Dead.

Developed by the Eastern Cooperative Oncology Group, [redacted], Group Chair (23).

Appendix E National Cancer Institute Common Terminology Criteria for Adverse Events

Refer to NCI-CTCAE v4.03 in the Study Reference Manual, or online at the following NCI website:

https://www.eortc.be/services/doc/ctc/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf

Toxicity grade should reflect the most severe degree occurring during the evaluated period, not an average.

When 2 criteria are available for similar toxicities, the one resulting in the more severe grade should be used.

The evaluator must attempt to discriminate between disease/treatment and related signs/symptoms.

Appendix F International Myeloma Working Group Response Criteria

Disease response will be assessed using the updated International Myeloma Working Group Response Criteria (IMWG) (24). A confirmation assessment for disease response within 4 weeks is required in this protocol (either PR or better, or PD).

As a reminder, patients with measurable FLC only at screening are not eligible in the study.

M protein value on Cycle 1 Day 1 will be taken as baseline value for response assessment.

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

Adapted from updated International Myeloma Working Group Response Criteria

IMWG MRD criteria (requires CR as defined below)	
Sustained MRD-negative	MRD negativity in the marrow (NGF or NGS, or both) and by imaging as defined below, confirmed minimum of 1 year apart. Subsequent evaluations can be used to further specify the duration of negativity (eg, MRD-negative at 5 years)
Flow MRD-negative	Absence of phenotypically aberrant clonal plasma cells by NGF on BMAs using the EuroFlow standard operation procedure for MRD detection in multiple myeloma (or validated equivalent method) with a minimum sensitivity of 1 in 10^5 nucleated cells or higher
Sequencing MRD-negative	Absence of clonal plasma cells by NGS on BMA in which presence of a clone is defined as less than two identical sequencing reads obtained after DNA sequencing of BMAs using the LymphoSIGHT platform (or validated equivalent method) with a minimum sensitivity of 1 in 10^5 nucleated cells or higher
Imaging-positive MRD-negative	MRD negativity as defined by NGF or NGS plus disappearance of every area of increased tracer uptake found at baseline or a preceding PET/CT or decrease to less mediastinal blood pool SUV or decrease to less than that of surrounding normal tissue
Standard IMWG response criteria	
Response	**IMWG criteria**
CR	• Negative immunofixation on the serum and urine and • disappearance of any soft tissue plasmacytomas and • <5% plasma cells in BMAs. **Two consecutive assessments are needed. No known evidence of progressive disease or new bone lesions if radiographic studies were performed**
sCR	CR as defined above plus: • Normal FLC ratio (0.26 to 1.65) and • Absence of clonal cells in BM by immunohistochemistry (κ/λ ratio ≤4:1 or ≥1:2 for κ and λ patients, respectively, after counting ≥100 plasma cells). **Two consecutive assessments of laboratory parameters are needed. No known evidence of progressive disease or new bone lesions if radiographic studies were performed**
VGPR	• Serum and urine M protein detectable by immunofixation but not on electrophoresis or • ≥90% reduction in serum M protein plus urine M protein level <100 mg/24 hour. • ≥90% decrease in the sum of the products of maximal perpendicular diameter compared to baseline in soft tissue plasmacytoma. **Two consecutive assessments are needed. No known evidence of progressive disease or new bone lesions if radiographic studies were performed.**

PR	• ≥50% reduction of serum M protein and reduction in 24 hours urinary M protein by ≥90% or to <200 mg/24 hour • In addition to the above listed criteria, if present at baseline, a ≥50% reduction in the size (sum of the products of the maximal perpendicular diameters) of soft tissue plasmacytomas is also required **Two consecutive assessments are needed. No known evidence of progressive disease or new bone lesions if radiographic studies were performed.**
MR	≥25% but ≤49% reduction in serum M protein and reduction in 24h urine M protein by 50 to 89%, which still exceed 200 mg/24 hour. In addition to the above listed criteria, if present at baseline, ≥50% reduction in size (SPD) of soft tissue plasmacytomas is also required. **Two consecutive assessments are needed. No known evidence of progressive disease or new bone lesions if radiographic studies were performed.**
Stable Disease	• Not meeting criteria for CR, VGPR, PR, MR or progressive disease. **No known evidence of progressive disease or new bone lesions if radiographic studies were performed.**
Progressive disease	Any 1 or more of the following criteria: Increase of ≥25% from lowest confirmed value in any 1 of the following criteria: • Serum M protein (the absolute increase must be ≥0.5 g/dL). • Serum M protein increase ≥1 g/dL if the lowest M component was ≥5 g/dL. • Urine M-component (the absolute increase must be ≥200 mg/24 hour). Appearance of new lesion(s), ≥50% increase from nadir in SPD of >1 lesion, or ≥50% increase in the longest diameter of a previous lesion >1 cm in short axis. **Two consecutive assessments are needed for PD on M protein.**

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

Patients with disease only measurable by FLC are not allowed.

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

For patients achieving VGPR by other criteria, a soft tissue plasmacytoma must decrease by more than 90% in the sum of the products of the maximal perpendicular diameters of measured lesions (SPD) compared with baseline.

For IgA and IgD myeloma, quantitative immunoglobulin measurements are preferred for assessments, the same percentage changes apply fornserum M-spike (see table above).

Definite increase in the size of existing bone lesions or soft tissue plasmacytomas is defined as below:

- ≥50% increase in the size of at least one bidimensionally measurable lesion (in comparison with the measurements at Nadir) or appearance of a new lesion.
- Pathological fracture or collapse of bone are not necessarily evidence of disease progression.

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

- Any response (sCR, CR, VGPR, PR) or progression needs to be confirmed by two consecutive disease assessments according to the Study Flow Chart. A disease assessment at one time point not matched by the same disease assessment at the next time point will be considered unconfirmed (except for progression by imaging, BM plasma cell counts, where one time point is adequate for confirmed progression).
- Urine M protein is not needed to document PR or minor response if baseline urine M protein was not measurable; however, it is still required for CR and very good PR.
- Documentation of response requires two consecutive readings of the applicable disease parameter (serum M protein, urine M protein), performed at any time (no minimum interval is required, it can be done the same day); however, to confirm response or progressive disease, 2 discrete samples are required; testing cannot be based upon the splitting of a single sample.
- Patients will continue in the last confirmed response category until there is confirmation of progression or improvement to a higher response status; patients cannot move to a lower response category.
- Percent decreases for response calculations are from baseline values (Cycle 1 Day 1).
- Percent increases for progression calculations are from lowest response values or baseline values, whichever is the smaller number. The lowest value does not need to be confirmed.
- The lowest confirmed value before suspected progression will be used as baseline for calculation of progression; if a serum and/or urine spike is considered too low to quantitate, this value can be assigned as 0 as a baseline for documentation of subsequent progressive disease. Patients will be considered to have progressive disease if they meet the criteria for progression by a variable that was not considered measurable at baseline; however, for patients who had a measurable serum or urine M-spike at baseline, progression cannot be defined by increases in serum FLC alone.

Patients with serum and urine M protein below level of eligibility on efficacy laboratory performed on Cycle 1 Day 1 (eg, patients with only FLC measurable disease according to IMWG, M-protein value >0 [or IF positive] and <0.5 g/dL):

- These patients can have only 2 possible overall response: **CR, non-PD** or **PD**.
- Patients with M-protein (urine and/or serum) below the level of measurability (M protein value >0 [or IF positive] and <0.5 g/dL) can have CR, non-PD, or PD responses only according to the increase or decrease of M protein or extramedullary disease if applicable, following the IMWG criteria.
- Patients with FLC measurable disease only (M protein = 0 and IF negative), can have either non-PD or PD responses (PD will be an absolute increase of >10 mg/dL in the difference between involved and uninvolved FLC).
- Patients with serum M protein value >0 g/dL (or serum IF positive) and <0.5 g/dL, independently of FLC can only be qualified as: CR, non-PD, or PD.

  AND/OR

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

  OR

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

Appendix G Guidelines for the determination of the number of prior lines of therapy in Multiple Myeloma

Line of Therapy

A line of therapy consists of ≥1 complete cycle of a single agent, a regimen consisting of a combination of several drugs, or a planned sequential therapy of various regimens (eg, 3 to 6 cycles of initial therapy with bortezomib-dexamethasone followed by stem cell transplantation [SCT] consolidation, and lenalidomide maintenance is considered 1st line).

New line of Therapy

A treatment is considered a new line of therapy if any 1 of the following 3 conditions are met:

Start of a new line of treatment after discontinuation of a previous line. If a treatment regimen is discontinued for any reason and a different regimen is started, it should be considered a new line of therapy. A regimen is considered to have been discontinued if all the drugs in that given regimen have been stopped. A regimen is not considered to have been discontinued if some of the drugs of the regimen, but not all, have been discontinued.

The reasons for discontinuation, addition, substitution, or SCT do not influence how lines are counted. It is recognized that reasons for change may include end of planned therapy, toxicity, progression, lack of response, inadequate response.

The unplanned addition or substitution of 1 or more drugs in an existing regimen. Unplanned addition of a new drug or switching to a different drug (or combination of drugs) due to any reason is considered a new line of therapy.

SCT: In patients undergoing >1 SCT, except in the case of a planned tandem SCT with a predefined interval (such as 3 months), each SCT (autologous or allogeneic) should be considered a new line of therapy regardless of whether the conditioning regimen used is the same or different. It is recommended that data on type of SCT also be captured.

Planned tandem SCT is considered 1 line. Planned induction and/or consolidation, maintenance with any SCT (frontline, relapse, autologous, or allogeneic) is considered 1 line.

Interruptions and dose modifications

- If a regimen is interrupted or discontinued for any reason and the same drug or combination is restarted without any other intervening regimen, then it should be counted as a single line.
- However, if a regimen is interrupted or discontinued for any reason, and then restarted at a later time point but 1 or more other regimens were administered in between, or the regimen is modified through the addition of 1 or more agents, then it should be counted as 2 lines.
- Modification of the dosing of the same regimen should not be considered a new line of therapy.

Based on Rajkumar, Richardson and San Miguel, 2015 (25).

Appendix H Definition of relapsed and refractory myeloma

Refractory Myeloma:

Refractory myeloma is defined as disease that is non-responsive (failure to achieve MR or develops PD while on therapy) while on primary or salvage therapy, or progresses within 60 days of last therapy. There are 2 categories of refractory myeloma:

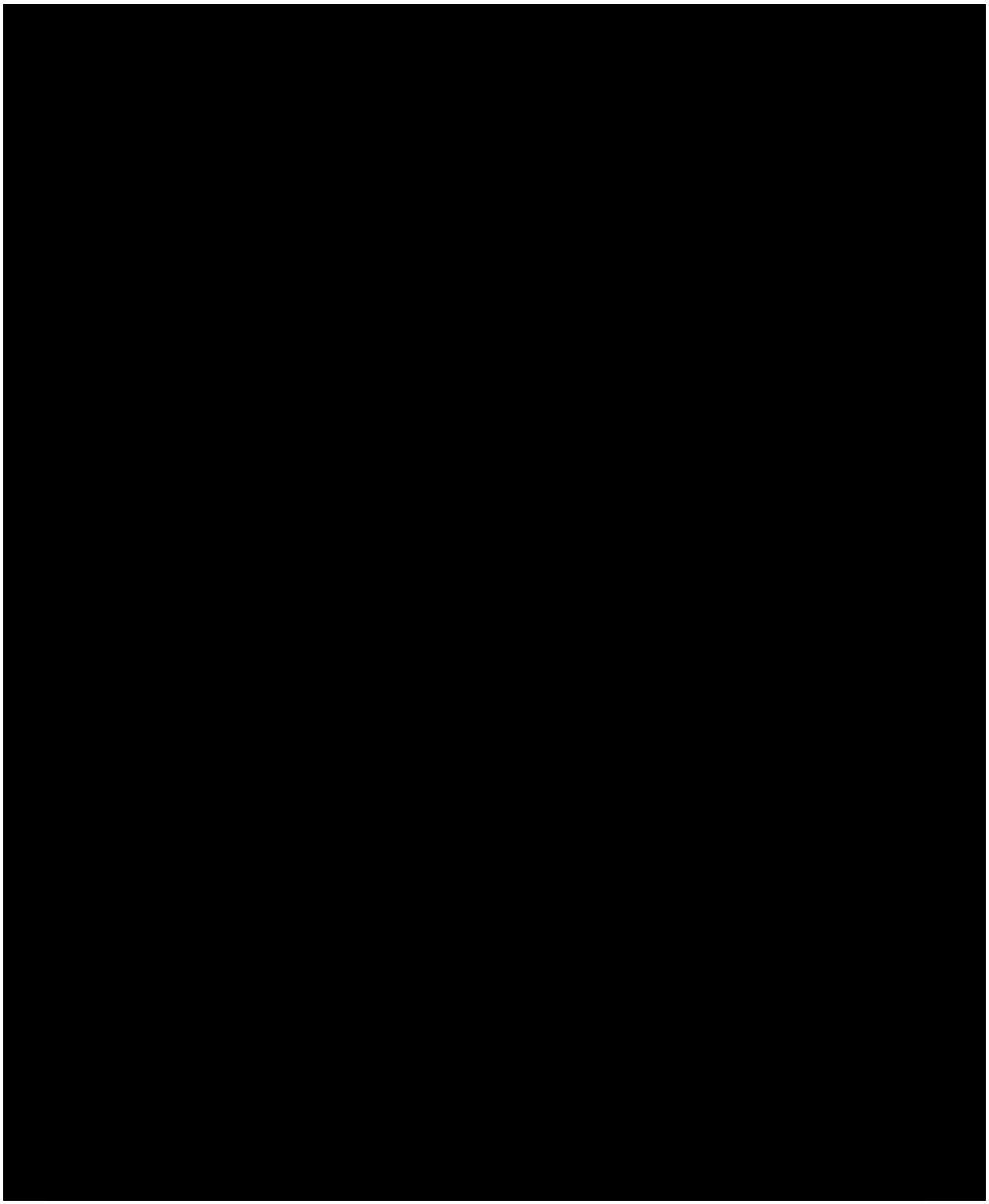
- Relapsed and refractory myeloma: Defined as disease that is non-responsive while on salvage therapy or progresses within 60 days of last therapy in patients who have achieved MR or better at some point previously to then progressing in their disease course.
- Primary refractory myeloma: Defined as disease that is non-responsive in patients who have never achieved MR or better with any therapy. It includes patients who never achieve MR or better in whom there is no significant change in M protein and no evidence of clinical progression; as well as primary refractory, progressive disease where patients meet criteria for true progressive disease.

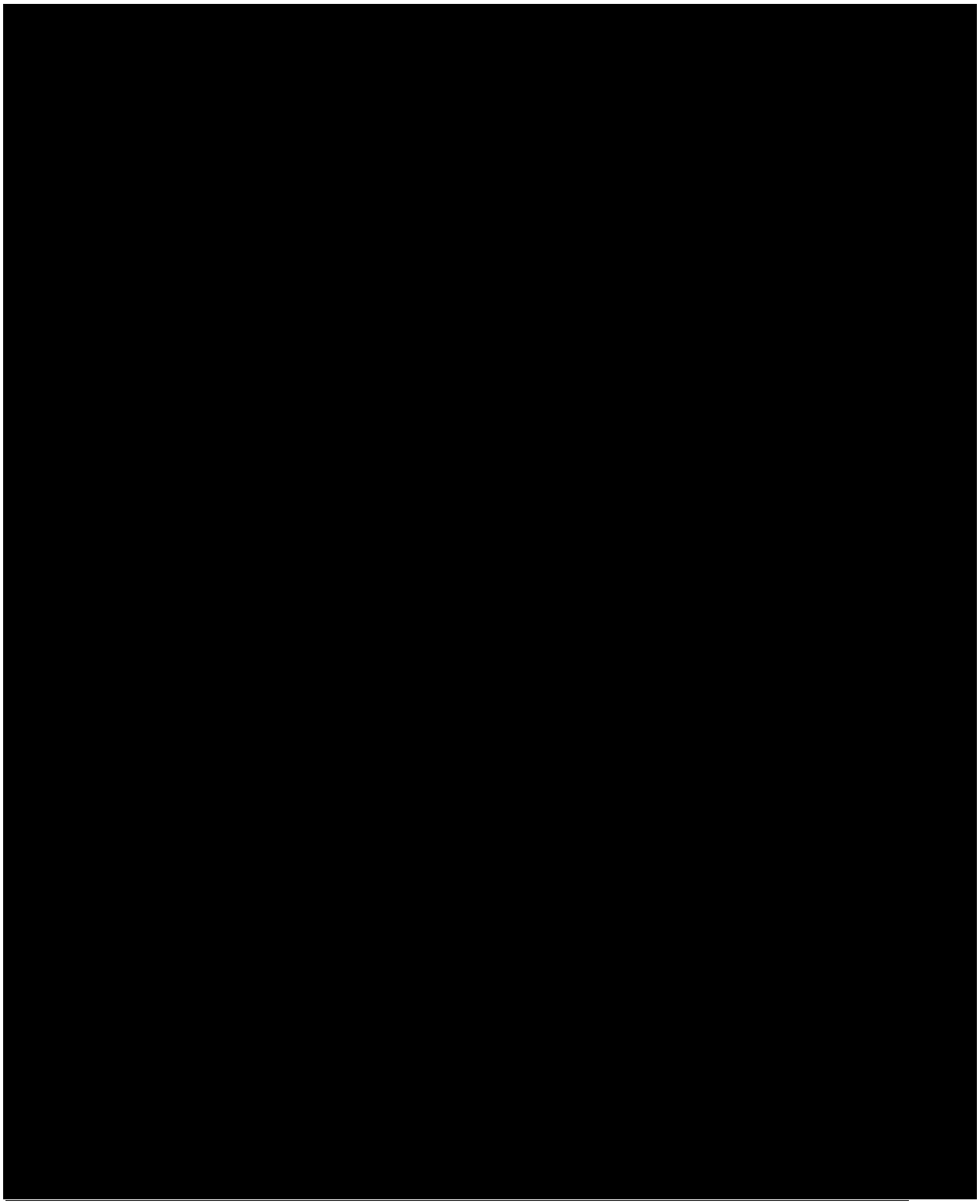
Relapsed myeloma

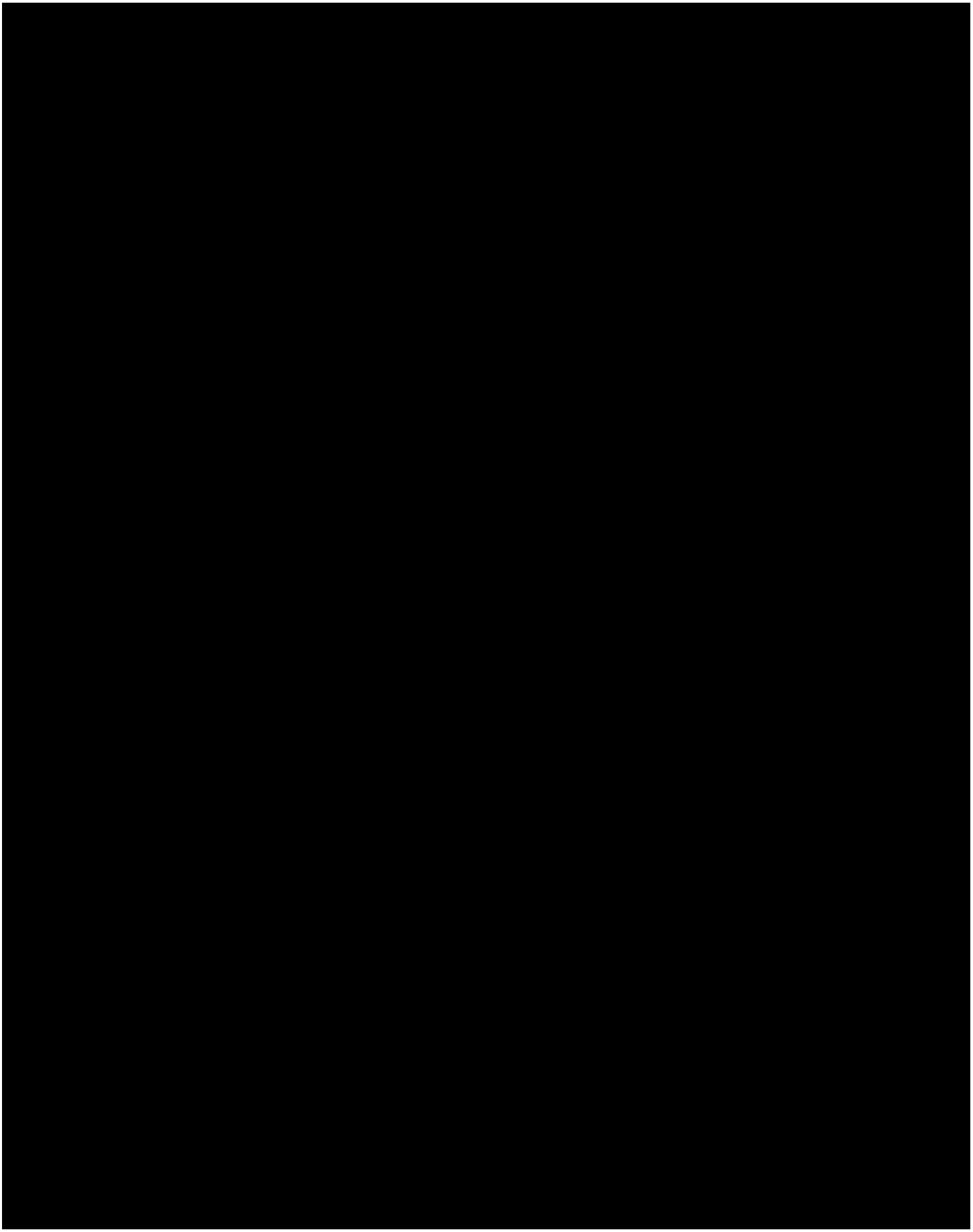
Relapsed myeloma is defined as previously treated myeloma which progresses and requires the initiation of salvage therapy but does not meet the criteria for either primary refractory myeloma or relapsed and refractory myeloma.

Adapted from Rajkumar et al, 2011 (26).

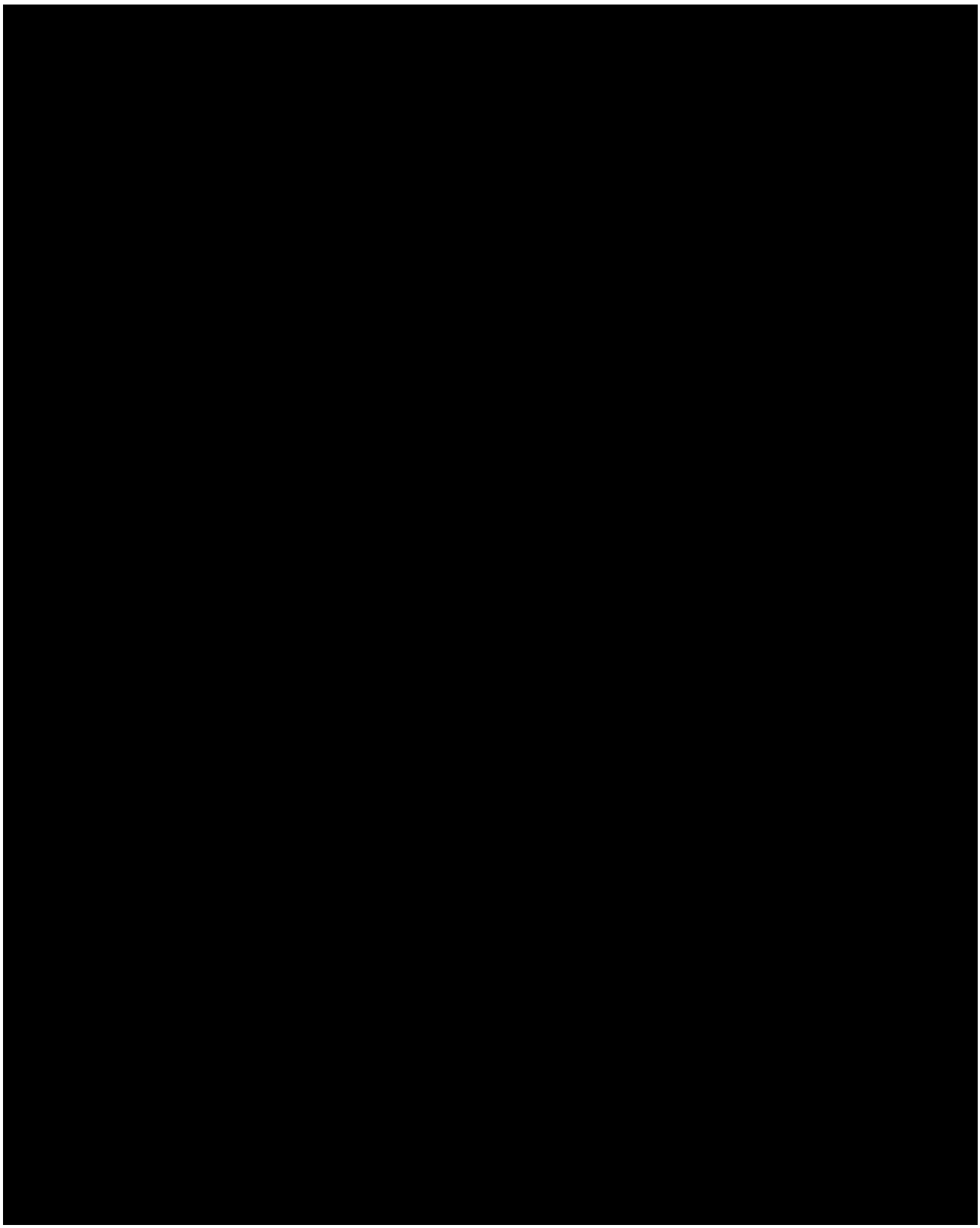
Appendix I EORTC-QLQ-C30 scales, items, and clinically important differences

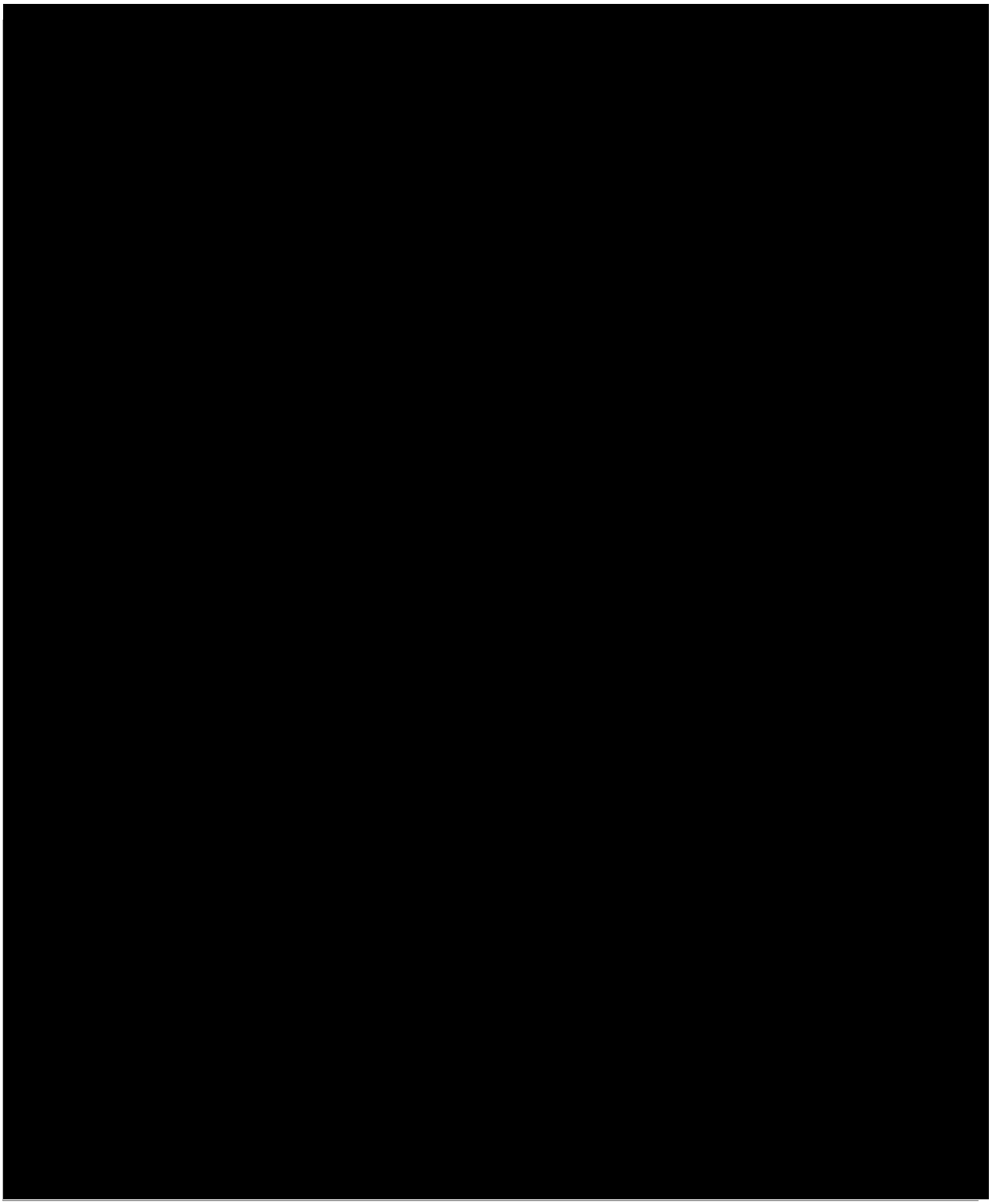


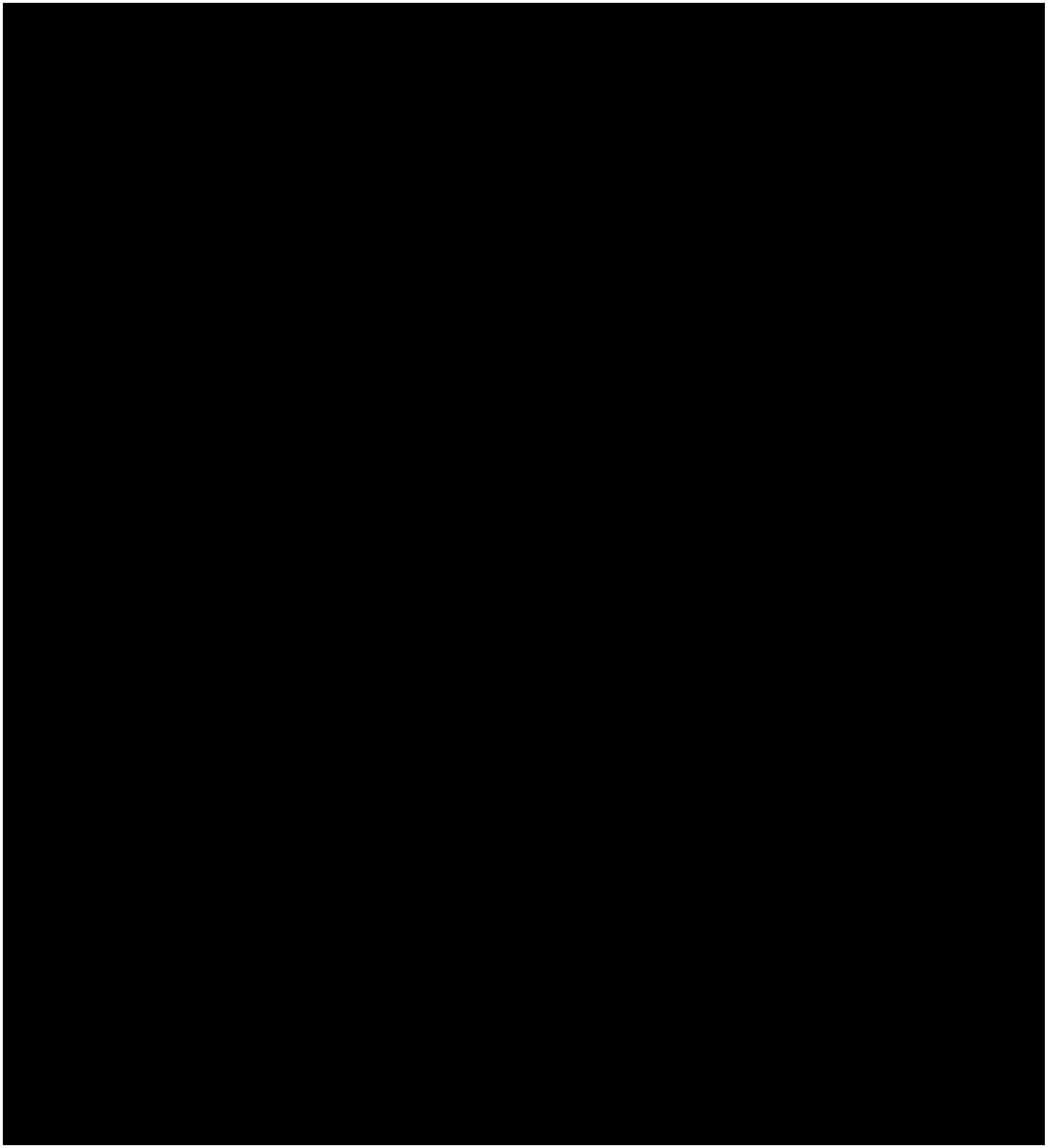




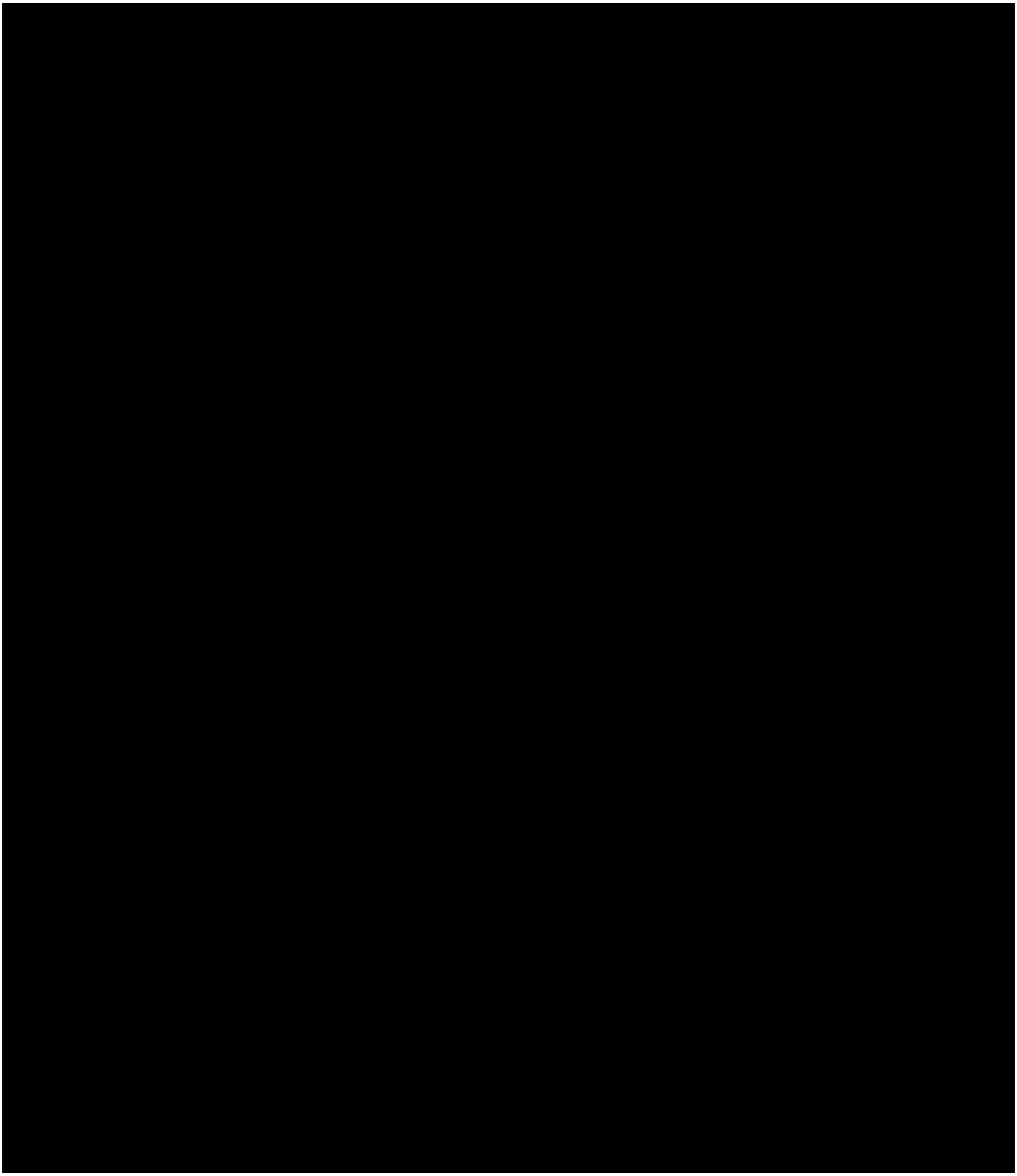
Appendix J QLQ-MY20 scales, items, and clinically important differences

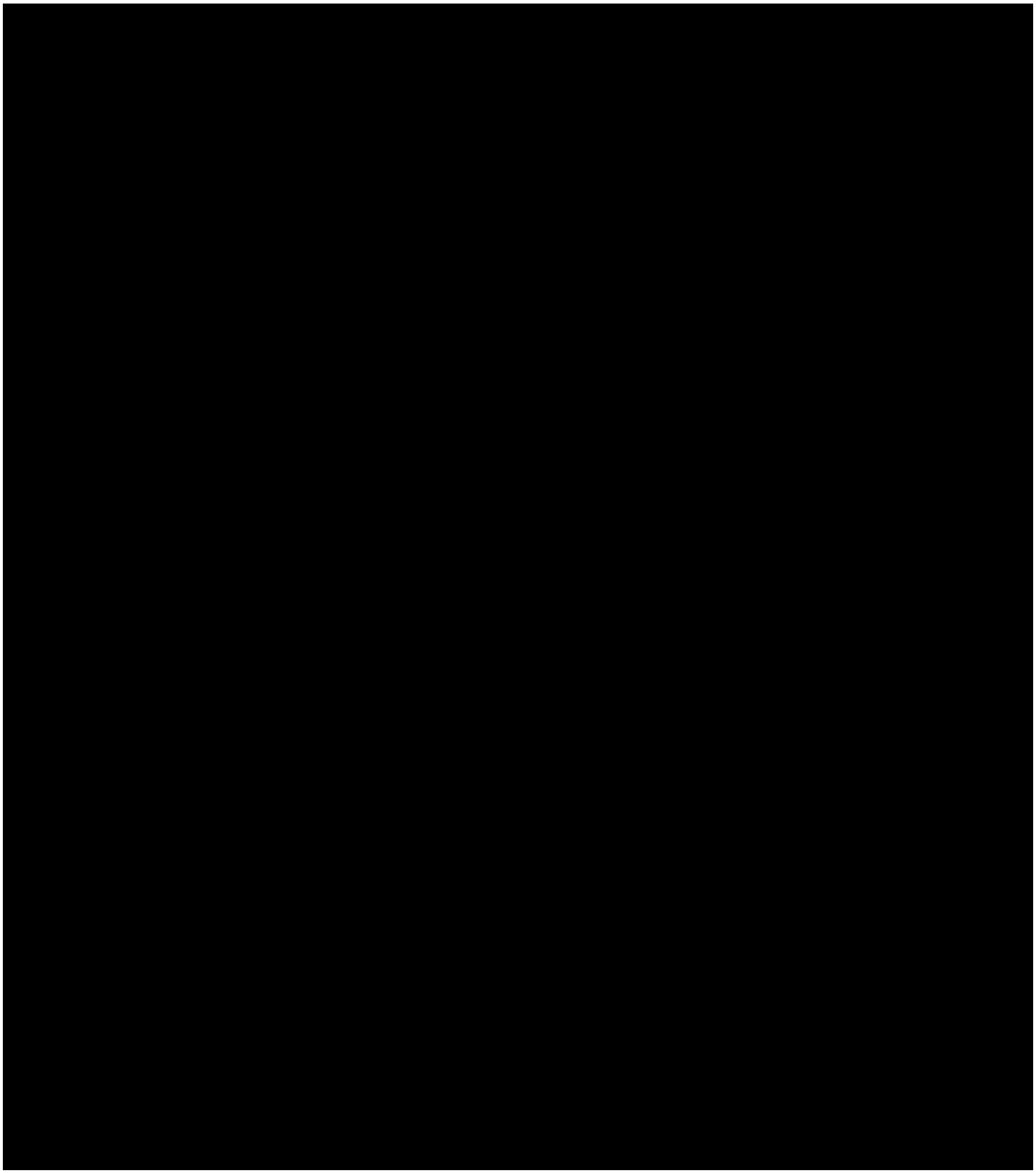


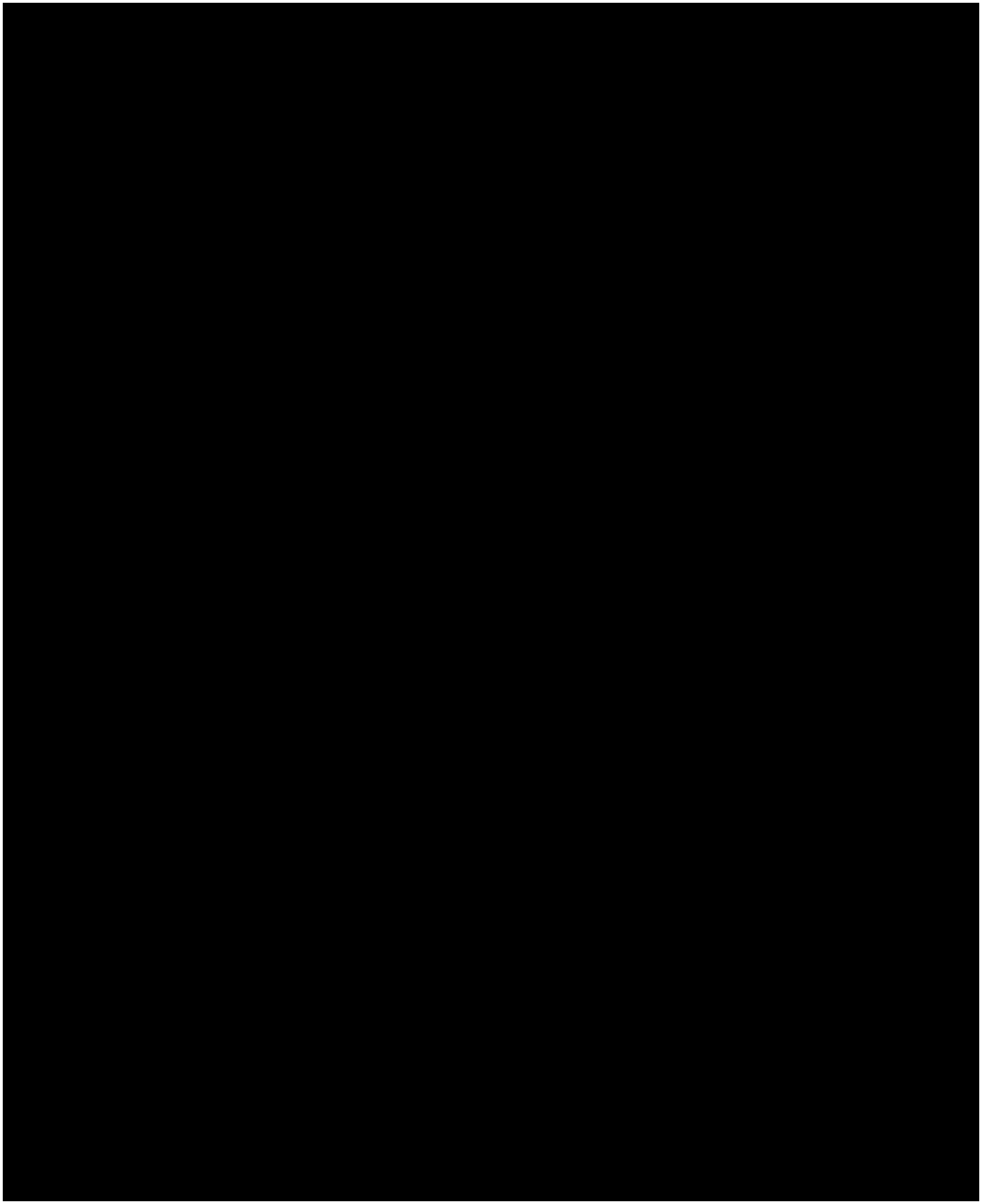




Appendix K EQ-5D-5L scales, items, and clinically important differences







Appendix L CD38 blood test interference guideline AABB2016

Advancing Transfusion and Cellular Therapies Worldwide

Association Bulletin #16-02

Date: January 15, 2016
To: AABB Members
From: [redacted]—President
[redacted]—Chief Executive Officer
Re: Mitigating the Anti-CD38 Interference with Serologic Testing

Summary
A new class of therapeutic agents for multiple myeloma, CD38 monoclonal antibodies, can result in interference with blood bank serologic tests and thereby cause delays in issuing Red Blood Cell (RBC) units to patients receiving these agents. To minimize these delays, hospitals should set up procedures to inform the transfusion service when patients start receiving these agents. Considerations for the transfusion service, both before and after initiation of anti-CD38 therapy, are detailed below.

The AABB Clinical Transfusion Medicine Committee has developed this bulletin to provide background information and guidance to members regarding anti-CD38 interference with serologic testing. The bulletin includes recommendations for its prevention and treatment.

Association Bulletins, which are approved for distribution by the AABB Board of Directors, may include announcements of standards or requirements for accreditation, recommendations on emerging trends or best practices, and/or pertinent information. This bulletin contains information and recommendations. No new standards are proposed.

Background

CD38 monoclonal antibodies are a new treatment for multiple myeloma

CD38, an integral membrane protein that is highly expressed on myeloma cells, has been identified as an effective target antigen for monoclonal antibody therapies. In November 2015, the first therapeutic CD38 monoclonal antibody [daratumumab (Darzalex, Janssen Biotech, Horsham, PA)] was approved by the Food and Drug Administration.[1] Other CD38 monoclonal antibodies are under development.

CD38 monoclonal antibodies interfere with blood bank serologic tests

CD38 is weakly expressed on red cells. Anti-CD38 binds to CD38 on reagent RBCs, causing panreactivity in vitro.[2,3] Plasma samples from anti-CD38-treated patients consistently cause positive reactions in indirect antiglobulin tests (IATs), antibody detection (screening) tests, antibody identification panels, and antihuman globulin (AHG) crossmatches. Agglutination due to anti-CD38 may occur in all media (eg, saline, low ionic strength saline, polyethylene glycol),

and with all IAT methods (eg, gel, tube, solid phase). Agglutination reactions caused by anti-CD38 are usually weak (1+), but stronger reactions (up to 4+) may be seen in solid-phase testing. However, anti-CD38 does NOT interfere with ABO/RhD typing or with immediate-spin crossmatches.

Other notes on anti-CD38 serologic interference:

- Adsorptions using either untreated or ZZAP-treated cells fail to eliminate the interference.
- Anti-CD38 variably interferes with direct antiglobulin tests (DATs) and antibody identification panel autocontrols.
- Some rare Lu(a–b–) cells are not reactive in the presence of anti-CD38, potentially giving the false impression that the patient has a Lutheran-related antibody.[4,5]
- Positive IATs can be observed for up to six months after anti-CD38 is discontinued.[1,3]
- Anti-CD38 may cause a small decrease in hemoglobin in vivo (~1 g/dL), but severe hemolysis has not been observed among treated patients.[3,6]

Anti-CD38 interference can cause delays in issuing RBCs

If the transfusion service is unaware that a patient has received anti-CD38, the following scenario may occur when the patient's sample is tested:

1. ABO/RhD typing: no issues.
2. Antibody detection (screening) test: all cells positive.
3. Antibody identification panel: all cells positive (autocontrol may be negative).
4. DAT: positive or negative.
5. AHG crossmatches: positive with all RBC units tested.
6. Adsorptions: panreactivity cannot be eliminated.

This leads to delays in issuing RBCs to the patient. In some cases, the anti-CD38 interference could mask the presence of a clinically significant alloantibody.

Recommendations

To avoid problems with transfusion, hospitals should set up procedures to inform the transfusion service whenever any patient is scheduled to begin taking anti-CD38.

BEFORE a patient begins taking anti-CD38:

- A baseline type and screen should be performed.
- In addition, a baseline phenotype or genotype is recommended.

AFTER a patient begins taking anti-CD38:

- ABO/RhD typing can be performed normally.
- For antibody detection (screening) and identification, dithiothreitol (DTT)-treated cells can be used to eliminate the interference.[2,7]
    - Because DTT treatment destroys Kell antigens, K-negative units should be provided unless the patient is known to be K-positive.
    - Antibodies against other DTT-sensitive blood group antigens (anti-k, anti-Yt^a, anti-Do^a/Do^b, etc) will not be detectable when the antibody screen with DTT-

treated cells is performed; such antibodies are encountered infrequently, however.

Crossmatch

- For patients with a negative antibody screen using DTT-treated cells, an electronic or immediate-spin crossmatch with ABO/RhD-compatible, K-matched units may be performed.
- For patients with known alloantibodies, phenotypically or genotypically matched RBC units may be provided.[6,8]
    - As some typing antisera require the use of AHG, phenotyping should be performed before the patient receives anti-CD38.
    - Genotyping can be performed either before or after the patient receives anti-CD38.
    - AHG crossmatches with phenotypically or genotypically matched units will still be incompatible.
    - Some clinically significant antibodies may be missed with the use of uncrossmatched phenotypically or genotypically matched units, although this will occur infrequently.
- Alternatively, an AHG crossmatch may be performed using DTT-treated donor cells.
- If an emergency transfusion is required, uncrossmatched ABO/RhD-compatible RBCs may be given per local blood bank practices.

Future/alternative approaches to mitigating the anti-CD38 interference

It is possible to neutralize anti-CD38 in plasma and eliminate the interference using either recombinant soluble human CD38 or daratumumab idiotype antibody.[2,3] Neither reagent is widely available at this time, and additional validation would be needed. In principle, soluble CD38 could be used to neutralize any anti-CD38, while different idiotype antibodies would be needed to neutralize different CD38 therapeutic antibodies. Finally, antigen-typed cord cells have been used for the antibody screen as an alternative to DTT-treated cells.[9]

References

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8. Hannon JL, Caruk B, Clarke G. Serological findings related to treatment with a human monoclonal antibody (daratumumab) in patients with advanced plasma cell myeloma (abstract). Transfusion 2014;54(2S):162A.

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Appendix M Low dose whole body CT scan

Low dose whole body CT scan (LDWB CT) allows radiation dose reduction compared to conventional exam and lasts usually no more than 2 minutes. It is done without oral or IV contrast and patient position is supine, head first, arms at the side (32, 33).

Example of parameters used to perform a LDWB CT:

- FOV – mm (small) adapted to subject's circumference
- Technical Factors – 16 x 1.5 collimation/0.5 rotation time
- Tube current – 50-70 mAs (could exceed 70 mAs for larger subjects)
- Image Reconstruction – Bone kernel/512 x 512 matrix
- Long bones should be covered: through knees and elbows

All sites have the option of adapting this protocol or using their own local LDWB or manufacturer's recommended protocol.

PET CT scan are not allowed for assessment of the disease.

Appendix N Contingency measures for a regional or national emergency that is declared by a governmental agency

COVID-19 Pandemic Contingency Measures:

Continuation of the study in the event of a regional or national emergency declared by a governmental agency:

A regional or national emergency declared by a governmental agency (eg, public health emergency, natural disaster, pandemic, and terrorist attack) may prevent access to the clinical trial site.

Contingency procedures are suggested for an emergency that prevents access to the study site, to ensure the safety of the participants, to consider continuity of the clinical study conduct, protect trial integrity, and assist in maintaining compliance with GCP in Conduct of Clinical Trials Guidance. Sponsor agreement MUST be obtained prior to the implementation of these procedures for the duration of the emergency.

The decision for each individual participant to remain and/or start in the study should be made on a case by case basis based on best Investigator medical judgment. The clinical judgment of the treating physician should guide the management plan of each participant based on individual benefit/risk assessment and the evolving situation at the site.

When participants are already randomized and/or treated, attempts should be made to perform all assessments in accordance with the protocol to the extent possible.

When possible, the focus should be on IMP administration and safety blood collection (eg, biochemistry and hematology). However, all efforts should be made to perform the measurements of key parameters for efficacy endpoints (eg, tumor assessments). The deviations from the study protocol (eg, treatment delay, omission, tests not performed…) should be documented in the source document and collected in the appropriate pages of the eCRF.

Procedures to be considered in the event of a regional or national emergency declared by a governmental agency:

- If onsite visits are not possible, remote visits (eg, with home nurses, home health vendor, etc) may be planned for the collection of possible safety data.
- If onsite visits are not possible visit windows may be extended for assessment of safety and/or efficacy data that cannot be obtained remotely.
- The Direct-to-Patient supply of oral dexamethasone from the site/sponsor where allowed by local regulations and agreed upon by participant (Section 8.1).

Contingencies implemented due to emergency will be documented.

The impact of the regional or national emergency declared by a governmental agency on study conduct will be assessed. Additional analyses may be performed to evaluate the impact on efficacy (eg, missing data due to the emergency) and safety.

For a regional or national emergency declared by a governmental agency, contingency procedures may be implemented for the duration of the emergency. The participant or their legally authorized representative should be verbally informed prior to initiating any changes that are to be implemented for the duration of the emergency (eg, study visit delays/treatment extension, use of local labs) (Section 12.2).

Appendix O Protocol amendment history

The "Protocol Amendment Summary of Changes Table" for the current amendment is located directly before the Clinical Trial Summary section of this amended protocol.

Amended Protocol 09 (14-September-2021)

Last patient in (LPI) occurred in March 2019, so patients randomized in the study and still on treatment are now treated for at least 2 years and half with a regimen requiring coming to the study site 2 days weekly 3 out of 4 weeks. The purpose of this amendment was to allow to omit carfilzomib dosing on Days 8 and 9 in case a patient requests for a more convenient schedule and in case Investigator judges that the maximum benefit is reached.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
8.2.1 Study treatments (IMP)	Addition of the possibility to omit carfilzomib dosing on Days 8 and 9 if a patient asks for a more convenient schedule and Investigator agrees because she/he judges that the maximum benefit is reached.	Two administrations per week for a duration of more than 2 years can become tiring for the patients.
8.2.4.1 General rules	If dexamethasone dosing is maintained on Days 8 and 9 while carfilzomib on Days 8 and 9 is omitted, possibility to re-increase the dose of dexamethasone if dose previously reduced, based on Investigator judgement.	Omission of carfilzomib on Days 8 or 9 could allow in some cases re-increase the dose of dexamethasone previously decreased.
Appendix O (Protocol amendment history)	Amendments to amended protocol 08 are summarized.	History of amendments to this protocol added.

Amended Protocol 08 (11-March-2021)

Based on the positive interim PFS data, the treatment effect of IKd is expected to be better than initially anticipated in comparison to Kd. A descriptive PFS analysis is added when approximately 180 PFS events have been reached. Based on more PFS events accumulated, this additional analysis would help to better characterize the distribution of PFS in a descriptive way for the IKd arm. With approximately 180 PFS events planned, the possibility of observing the median PFS time for the IKd arm is expected to be increased.

Clarification of accidental or intentional overdose of isatuximab and carfilzomib is defined by each administration and dexamethasone will be defined by cycle.

Appendix N is added for contingency measures for a regional or national emergency declared by a governmental agency.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Names and Addresses Page	Sponsor information added	Sponsor information added according to regulatory requirements
Clinical Trial Summary: Assessment Schedule, Other examinations for disease assessment:	"additional" and "twice a year until death, or OS analysis cut-off date, whichever comes first" were added. The word final was changed to "additional"	Frequency of survival status collection have been increased from once to twice a year to better follow the occurrence of the events
Clinical Trial Summary: Statistical Considerations, Primary Analysis	"An additional PFS analysis will be performed when approximately 180 events assessed by the IRC have been observed to better characterize the distribution of PFS in the IKd arm in a descriptive way. This analysis will be performed at the latest 15 months after the 159 PFS event analysis cut-off date in case of the approximately 180 PFS events are not observed at that time" was added	To better characterize the distribution of PFS in a descriptive way for the IKd arm, including the increased possibility of observing median PFS
Clinical Trial Summary: Statistical Considerations, Interim Analysis, Planned PFS and OS cut-of dates	"Efficacy results will be updated in a descriptive way (non-inferential analysis) at the time of the PFS additional analysis (approximately 180 events)" and "The cut-off date for the additional PFS analysis will be the date when approximately 180 PFS events assessed by the IRC have occurred or 15 months after 159 PFS events analysis cut-off date, whichever comes first" were added	To better characterize the distribution of PFS in a descriptive way for the IKd arm, including the increased possibility of observing median PFS
Clinical Trial Summary: Duration of Study Period (per patient)	"Approximately 180" was added to the cut-off date for the additional PFS analysis	The last PFS analysis being the additional PFS analysis, the cut-off for this analysis has been added
	"or 15 months after 159 PFS events analysis cut-off date, whichever comes first" was added Survival status collection was changed from "one" to "twice a year" and "additional PFS analysis cut-off date for all patients still alive at the additional PFS analysis cut-off date, until death, or OS analysis cut-off date, whichever comes first" was added	Frequency of survival status collection have been increased from once to twice a year to better follow the occurrence of the events
	The word "final" was changed to "additional"	The last PFS analysis being the additional PFS analysis, "final" has been updated by "additional" in the document where it was necessary
Section 6.2.1 Duration of study participation for each patient	The word "final" was changed to "additional"	The last PFS analysis being the additional PFS analysis, "final" has been updated by "additional"
	"twice a year" and "until death, or OS cut-off date, whichever comes first" were added	Frequency of survival status collection have been increased from once to twice a year to better follow the occurrence of the events

Section # and Name	Description of Change	Brief Rationale
Section 6.2.2 Determination of end of clinical trial (all patients)	"An additional PFS analysis will be performed at approximately 180 events. The additional analysis will be performed at the latest 15 months after the 159 PFS event analysis cut-off date in case of the approximately 180 PFS events are not observed at that time" was added	To better characterize the distribution of PFS in a descriptive way for the IKd arm, including the increased possibility of observing median PFS
	"The end of the study is defined as the date of the last visit of the last participant in the study" was added	To clarify definition of end of the study visit
Section 6.4 Study Committees	The words "primary" and "final" were changed to "additional"	The last PFS analysis being the additional PFS analysis, "final" has been updated by "additional"
Section 8.2.1 Study treatments (IMP): IKd arm (experimental arm)	The infusion maximum rate was changed from "200" to "150" mL/hr for the first infusion done with fixed volume	Typo was fixed
Section 10.1.6 Post additional PFS analysis cut-off date (approximately 180 PFS events as per IRC)	"(approximately 180 PFS events as per IRC)" was added to the section title	To better characterize the distribution of PFS in a descriptive way for the IKd arm, including the increased possibility of observing median PFS
	Survival status collection was changed from "once" to "twice" a year "Death date will be collected when site is informed of death. In addition," was added and "at approximately the anniversary date of the final PFS analysis cut-off date" was removed	Frequency of survival status collection have been increased from once to twice a year to better follow the occurrence of the events. Redundant text was removed.
	The word "final" was changed to "additional"	The last PFS analysis being the additional PFS analysis, "final" has been updated by "additional"
Section 10.4.1.5 Overdose	"…of isatuximab and carfilzomib at each administration, at least 30% above the intended administered dose of dexamethasone at each cycle" was added to the definition of overdose for isatuximab and carfilzomib	To clarify that overdose of isatuximab and carfilzomib is defined by administration and not on the total dose administered on over the cycle. Overdose definition of dexamethasone is based on all the dose over the cycle based on different therapeutic index of dexamethasone and the two other IMPs

Section # and Name	Description of Change	Brief Rationale
Section 11.4.2.1 Analysis of primary efficacy endpoint	"In particular, a sensitivity analysis has been added to evaluate the impact of late progressions and deaths. In this sensitivity analysis, progressions or deaths occurring more than 8 weeks after the last disease assessment (corresponding to two consecutive missed assessments) will be censored at the earliest of the date of last valid disease assessment without evidence of progression before initiation of new anti-myeloma treatment and the cut-off date" and	This analysis has been requested by United States Food and Drug Administration as post-hoc PFS analysis
	"An additional PFS analysis (non-inferential analysis) will be performed when approximately 180 events assessed by the IRC have been observed to better characterize the distribution of PFS in the Ikd arm in a descriptive way. The additional analysis will be performed at the latest 15 months after the 159 PFS event analysis cut-off date in case of the approximately 180 PFS events are not observed at that time." were added	To better characterize the distribution of PFS in a descriptive way for the IKd arm, including the increased possibility of observing median PFS
Section 11.4.2.3 Multiplicity considerations	It is added that "efficacy results will be updated at the time of the PFS additional analysis (approximately 180 events) but will be only descriptive (non-inferential analysis)"	Description of the PFS analysis added to better characterize the distribution of PFS in a descriptive way for the IKd arm, including the increased possibility of observing median PFS
Section 11.5 Interim analysis	It is clarified that "in case of positive results at interim analysis, PFS results will be updated in a descriptive way (non-inferential analysis) at the analysis cut-off date when 159 PFS events are observed"	Clarification added in the protocol but already specified in the SAP.
	"Efficacy results will be updated at the time of the PFS additional analysis (approximately 180 events) but will be only descriptive (non-inferential analysis). No α-spending or formal testing is planned for the PFS additional analysis" was added	Description of the PFS analysis added to better characterize the distribution of PFS in a descriptive way for the IKd arm, including the increased possibility of observing median PFS
Section 12.2 Informed consent	"For a regional or national emergency declared by a governmental agency, contingency measures refer to Appendix N" was added	To refer to the added Appendix for procedures to inform patient in case of regional or national emergency declared by governmental agency
Section 13.2 Responsibilities of the Sponsor	"Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote or on-site monitoring) are provided in separate study documents" was added to the section	To clarify where the monitoring techniques are located.
Appendix N (Contingency measures for a regional or national emergency that is declared by a government agency, COVID-19 Pandemic Contingency Measures)	Appendix N "Contingency measures for a regional or national emergency that is declared by a government agency, COVID-19 Pandemic Contingency Measures" was added	To clarify the procedure during National Emergencies
Appendix O (Protocol amendment history)	Amendments to protocol v7.0 are summarized. This section was shifted down from Appendix N	History of amendments to this protocol added

Amended Protocol 07 (10-August-2020)

Instruction for collecting hospitalization report and exams reports in case of serious adverse events section is updated.

Option of direct supplies of oral investigational medicinal products (IMPs) to patients has been added in case of regional or national emergency declared by a governmental agency that results in travel restrictions, confinement, or restricted site access.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Section 8.1 (Study treatments)	Option of direct supplies of investigational medicinal products (IMPs) to patient has been added	In emergency situations, when patient cannot conduct on-site visits, a Sponsor-approved courier company could deliver the IMPs from the site to the patient.
Section 8.1.1.1, Section 8.2.1, Section 8.2.5	Improvement in isatuximab administration implementing the approved administration mode with fixed volume.	Switching to faster infusion schedule with a fixed distribution volume will reduce hospital chair time (particularly in some specific challenging situations like pandemic restrictions) and increase convenience for patients and sites).
Section 8.2.2 and Section 8.2.2.1	Use of ranitidine or equivalent will be considered as an optional premedication and will be based on Investigators; judgement.	To provide option to adapt the premedication depending on individual situation
Section 10.4.3	Instruction for collecting hospitalization report and exams reports in case of serious adverse events has been updated.	Only necessary copies of medical records are to be shared with the Sponsor
Appendix N (Protocol amendment history)	Amendments to protocol v6.0 are summarized.	History of amendments to this protocol added

Amended Protocol 06 (13-November-2019)

Censoring rules for the Progression-free survival (PFS) analysis were changed following interaction with Health Authorities. PFS2 definition was updated according to this change.

Hepatitis B virus (HBV) DNA testing by polymerase chain reaction was added for patients with a positive hepatitis B surface antigen (HBsAg) test and/or anti-Hepatitis B core (HBc) antibody test.

Second primary malignancies, if any, should be reported also in follow-up period.

Statistical sections were updated in line with the changes made in the Statistical Analysis Plan (SAP) amendment of July 2019.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Clinical trial summary, 9.2.2 Other secondary efficacy endpoints, 11.4.2.1 Analysis of primary efficacy endpoint, 11.4.2.2.2 Analysis of other secondary efficacy endpoints	Change in censoring rules for the primary PFS analysis and update of PFS2 definition related to this change.	According to Health Authorities feedback
Clinical trial summary, 5.2 Secondary, 9.2.1 Key secondary efficacy endpoints, 9.2.2 Other secondary efficacy endpoints, 11.4.1 Extent of study treatment exposure and compliance, 11.4.2.2.1 Analysis of key secondary efficacy endpoints, 11.4.2.2.2 Analysis of other secondary efficacy endpoints, 11.4.2.3 Multiplicity considerations, 11.4.7 Analyses of patient reported outcomes (health-related quality of life/health economics variables), 11.5 Interim analysis	Update of statistical sections in order to reflect the changes made in the SAP amendment of July 2019: Update of definitions and analysis of minimal residual disease (MRD) negativity rate and complete response (CR) rate • Update of the handling of multiplicity and spending functions for secondary endpoints • Addition of other secondary endpoints (time to first response and time to best response) • Update of the definition of overall number of cycles started • Update of the analysis of electronic patient-reported outcomes (ePROs)	To clarify the definitions and the analyses of efficacy endpoints To clarify the analyses of efficacy endpoints To further characterize the efficacy of study treatments To clarify the definition To clarify the analysis
1.2 Study flow chart, 8.2.7 Hepatitis B virus infection, 10.1.3.2 Subsequent cycles (Days 1-2, Days 8-9, Days 15-16, and Days 22-23)	Hepatitis B virus DNA testing by polymerase chain reaction was added for patients with a positive HBsAg test and/or HBc antibody test	To complement HBV investigations
Clinical trial summary, 1.2 Study flow chart, 6.2.1 Duration of study participation for each patient, 10.1.5 Post study treatment follow-up, 10.1.6 Post final PFS analysis cut-off date	Second primary malignancies occurring during the follow-up period should be reported	To secure to collect any second primary malignancy during follow-up period
12.1 Ethical and regulatory standards	Description of Investigator's responsibility regarding incidental findings	To clarify Investigator's responsibility regarding incidental findings
Entire document	Editorial changes	Correction of typographical errors and inconsistencies between different sections, and clarifications

Amended Protocol 05 (11 September 2019)

Implementation of safety monitoring measures following identification of 2 new risks related to carfilzomib:

- Carfilzomib may increase risk of progressive multifocal leukoencephalopathy (4 cases reported as of 17 July 2019 among 4,156 patients in Amgen Sponsored clinical trials and estimated 126, 638 patients in post marketing).
- Carfilzomib may increase risk of hepatitis B virus reactivation (frequency of Hepatitis B virus [HBV] reactivation is 0.1% in Amgen Sponsored clinical trials).

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Clinical Trial Summary, 1.2 Study Flow Chart 8.2.7 Hepatitis B virus Infection 8.8 Concomitant Medication 10.1.3.2 Subsequent cycles (Days 1-2, Days 8-9, Days 15-16, and Days 22-23)	Addition of HBV serology assessment in patients with unknown HBV status including safety measures.	Implementation of safety monitoring measures following identification of new risk (hepatitis B virus reactivation) related to carfilzomib
8.2.6 Posterior reversible encephalopathy syndrome and progressive multifocal leukoencephalopathy	Addition of measures for management of progressive multifocal leukoencephalopathy	Implementation of safety monitoring measures following identification of new risk (progressive multifocal leukoencephalopathy) related to carfilzomib

Amended Protocol 04 (11 June 2019)

REASON FOR AMENDMENT:

Based on updated pharmacokinetic characterization of isatuximab, the plasma half-life has been re-estimated to 28 days. As duration of contraceptive measures is required to last for 5 half-lives, a revised duration of contraceptive measures of 5 months after the last dose of isatuximab is required.

* Contraception duration after end of isatuximab changed from 3 months (12 weeks) to 5 months

In sections: Appendix C Contraceptive Guidance and Collection of Pregnancy Information.

Rationale: Duration of contraception has been impacted by the updated pharmacokinetic characterization of the isatuximab half-life leading to an increase by 2 months (ie, 12 weeks to 5 months), the time for continuing contraception after the last dose of isatuximab.

* Pregnancy test will be performed before each cycle and then monthly during the follow-up period up to 3 months (12 weeks) in the Kd arm and up to 5 months in the IKd arm

In sections: Clinical Trial Summary, 1.2 Study Flow Chart, 10.1.3.1 Cycle 1 (Days 1-2, Days 8-9, Days 15-16, and Days 22-23), 10.1.3.2 Subsequent cycles (Days 1-2, Days 8-9, Days 15-16, and Days 22-23), 10.1.5 Post study treatment follow-up, 10.1.6 Post final PFS analysis cut-off date, 10.1.7 Post OS analysis cut-off date.

Rationale: To detect any pregnancy during relevant systemic exposure of study treatment.

Amended Protocol 03, Amended Protocol 04 (GB) based on Protocol Amendment 04: (02 July 2018)

REASON FOR AMENDMENT:

The main reason of this amendment is to modify Appendix N, to clarify timing for minimal residual disease (MRD) assessment in patient reaching very good partial response (VGPR), and to leave possibility to IRC to consider clinical progression as event. Editorial changes, corrections of inconsistencies and typographic errors, clarifications, and deletion of redundancies were also done.

* To add Czech Republic in the Appendix N

In sections: Appendix N.

Rationale: Due to local requirement, Czech Republic is adding in the list of countries where pregnancy test is to be performed before each cycle initiation in addition to before study treatment initiation and end of treatment.

* To clarify timing for BMA samplings

In sections: clinical trial summary, Section 1.2, Section 9.2.1, Section 10.1.3.2, Section 10.1.4, Section 10.1.5.

Rationale: Bone marrow aspiration (BMA) is an invasive procedure and study allow up to 6 BMA. In order to limit as much as possible the number of BMA, wording to trigger BMA has been clarified.

* To include possibility for Independent Response Committee (IRC) to consider clinical progression as PD event

In sections: Section 9.1.

Rationale: In absence of radiological and M protein progression, if clinical and biological data all together provide with clear evidence of clinical progression based on IRC judgement, in this case IRC could consider clinical progression as PFS event.

* To clarify 2 exclusion criteria

In sections: tabulated Clinical Trial Summary, Section 7.2.

Rationale: To clarify which type of radiotherapy is allowed within 14 days prior to randomization and that therapy (not only chemotherapy) should be completed by at least 5 years in case of prior other cancer in medical history.

* Miscellaneous

In sections: Title page, Section 1.1, Section 3, Section 6.1, Section 8.2.2, Section 8.2.3, Section 8.2.4.1, Section 8.2.8, Section 8.8, Appendix K.

* Typo on version date of amended protocol 02 GB and protocol amendment 02 GB.

* Typo in graphical study design.

* Addition of 2 definitions in abbreviation list.

* To allow per os diphenhydramide or equivalent in country where the is no longer iv formulation.

* To mention possibility to keep same volume of hydration on a longer time of administration in case of cardiac decompensation risk.

* To clarify some rules of dose modifications.

* To add protocol recommendations regarding antibacterial prophylaxis and thromboprophylaxis, and to add caution regarding co-treatment of dexamethasone with CYP3A inhibitor in concomitant medications section.

* To add copyrights information at the bottom of the EQ-ED questionnaire.

* Correction of inconsistencies.

Amended protocol 02, Amended protocol 03 (GB) based on Protocol Amendment 03:
(08 February 2018)

REASON FOR AMENDMENT:

The main reasons of this amendment are to add minimal residual disease (MRD) assessment in patients reaching very good partial response (VGPR) and to remove local laboratory disease assessment from the protocol. Editorial changes, corrections of inconsistencies and typographic errors, clarifications, and deletion of redundancies were also done.

Modifications implemented through local amendment for United Kingdom (amendment02-gb) is included in this global amendment (amendment #3) specifying when changes are applicable for UK only, to go back to a unique protocol version for all participating countries.

* To add MRD assessment in VGPR patients

In sections: tabulated Clinical Trial Summary, 1.1, 1.2, 5.2, 9.1, 9.2.1, 10.1.1, 10.1.3.1, 10.1.3.2, 10.1.4, 10.1.5, 11.4.2.2.1, 11.4.2.3, 11.5, 16.

Rationale: Addition of MRD assessment in VGPR patients is based on recent data strongly suggesting MRD negativity as prognostic factor for PFS and OS in patients with CR or not. Indeed, this has been reported also in patients MRD-negative despite a persistent M-component who showed similar PFS and OS to patients with MRD-negative disease in CR (Lahuerta et al, JCO 2017). Because the sample size of patients MRD negativity increases, the order of the key secondary endpoints is also modified: patients with at least VGPR with MRD negativity will be tested prior to patients with CR.

* To remove local laboratory efficacy samples:

In sections: tabulated Clinical Trial Summary, 1.2, 8.4, 9.1, 10.1.1, 10.1.2, 10.1.3.1, 10.1.3.2, 10.1.4, 10.1.5.

Rationale: PFS being the primary endpoint and in order to limit the risk of inconsistency in date of progression as per investigator assessment versus as per IRC assessment and to reduce the number of blood samples drawn by patient, local laboratory efficacy assessments are removed. Investigator will assess disease response using the central laboratory results.

* To clarify what will be done with the samples collected for the interference of isatuximab with M protein measurement by adding a formal exploratory objective.

In sections: tabulated Clinical Trial Summary, 5.3.

Rationale: Assessment of potential interference was listed in endpoint assessment in section 9.3.1, but was not listed in exploratory objectives and exploratory endpoints.

* To add a Coombs test after initiation of isatuximab

In sections: tabulated Clinical Trial Summary, 1.1, 1.2, 10.1.3.2.

Rationale: Interference in Coombs test has been reported with anti CD38 agents. Coombs test is currently planned to be assessed before study initiation for all patients randomized in isatuximab arm. A systematic Coombs test is added after initiation of study treatment to describe incidence of patients with interference in Coombs test after isatuximab initiation.

* To change to the frequency of pregnancy test depending on country requirements

In sections: tabulated Clinical Trial Summary, 1.2, 10.1.1, 10.1.3.2.

Rationale: To provide clarity when the serum pregnancy should be performed. Carfilzomib having shown possible fetal harm in preclinical studies, pregnancy test (urine or serum) is to be done before each new cycle administration in addition to effective contraception, according to country requirement (list of country provided in Appendix N, which is added in this amendment).

* To allow urine pregnancy test

In sections: tabulated Clinical Trial Summary, 1.2, 10.1.1, 10.1.4, 10.1.3.2.

Rationale: pregnancy test may be requested before each cycle administration according to local requirement; urine test is added as an allowed procedure.

* To allow semi-quantitative urinalysis

In sections: 1.2, 10.1.1.

Rationale: to allow semi-quantitative instead of quantitative urinalysis if semi-quantitative method used at site level can provide with an absolute numeric value of the parameters.

* To correct rounding error in required number of PFS

In sections: Clinical trial summary, sections 6.2.2, 6.3, 11.1, 11.4.2.1, 11.5

Rationale: number of required PFS events has been corrected from 158 to 159 events. All sections impacted and modified in the study protocol are listed above but all are not in the detailed description of changes in the amendment.

* To add grade 5 IARs and symptomatic NIMP overdose as AESI for Adverse Event of Special Interest (AESI) reporting

In section(s): 10.4.1.3.

Rationale: Grade 5 IARs are to be considered as AESIs, for reporting purposes.

* To add duration of contraceptive measure during the study

In section: Appendix C

Rationale: to have clear instruction on duration of contraceptive measures.

* Miscellaneous clarifications, correction of inconsistencies

In sections: title page, tabulated Clinical Trial Summary, Sections 1.2, 6.1, 6.4, 7.2, 8.1.1.1, 8.1.1.2, 8.2.1, 8.2.3, 8.2.4.1, 8.2.4.4, 8.2.5, 8.4, 8.8.1, 10.1.3.1, 10.1.6, 12.3, 16, Appendix A, Appendix F, Appendix M, Appendix N.

Rationale: include but not limited to:

* Correction typo in IND number.

* Correction that in case of FISH unknown, for some patients the possibility to assess R-ISS is not limited to stage III.

* To provide serologic definition of active hepatitis B and C.

* To clarify that further anti myeloma therapies will continue to be collected after final PFS analysis until OS analysis.

* Correction of inconsistency between protocol and pharmaceutical manual regarding pharmaceutical form.

* Clarification in instruction of hydration prior carfilzomib and to allow less than 500 mL (remaining above 250 mL) during the 2 first infusions for patients at risk of cardiac decompensation (as per carfilzomib labelling).

* Clarification and correction of inconsistencies in dose modifications.

* G-CSF use is not limited to the first 3 cycles.

* To correct in which CRF page to report ongoing signs and symptoms related to multiple myeloma.

* To specify that re-screening of patient in case of screen failure is allowed.

* Editorial correction in IMWG criteria Appendix.

* To provide clarification on low dose whole body CT scan in a specific Appendix and provide with 2 supporting bibliographic references.

* To specify which countries will have pregnancy test during study treatment in Appendix N

Amended protocol 02 (GB) based on Protocol Amendment 02 (GB): (30 August 2017)

* **Change to the frequency of pregnancy test**

In section(s): study flow chart (with footnote “i”), and sections 10.1.1 and 10.1.3.2 of the protocol

Rationale: carfilzomib having shown possible fetal harm in preclinical studies, pregnancy test (urine or serum) is to be done before each new cycle administration in addition to effective contraception, according to country requirement.

* **To add duration of contraceptive measure during the study**

In section(s): Appendix C

Rationale: to have clear instruction on duration of contraceptive measures.

Amended protocol 01 based on Protocol Amendment 01: (21 August 2017)

REASON FOR AMENDMENT:

* Rectification of error in the infusion time of carfilzomib to be consistent with SMPC/PI

In section(s): tabulated Clinical Trial Summary (Investigational product(s)), sections 1.2, 1.3.1 and 8.2.1 of the protocol.

Rationale: Rectification of an error in the infusion time of carfilzomib to be consistent with SmPC/PI. As a consequence information on indicative clock time and relative nominal time in PK flowchart have also been corrected.

* Typographical corrections

In section(s): 1.2, 3, 6.1, 8.2.4.3, 8.2.4.4, 8.2.5 and 9.2.3 of the protocol.

Rationale: deletion of duplicate abbreviation, grammatical and cosmetic corrections will not be described.

In addition, other minor changes are listed in the description of changes (next section).

* Deletion of wording of Absolute neutrophil count

In section(s): sections 1.2, 10.1.1, 10.1.3.1, 10.1.3.2 and 10.1.4 of the protocol.

Rationale: The wording of ANC is a redundancy when it is with the White Blood Count differential.

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