NCT Number: NCT02990338

AMENDED CLINICAL TRIAL PROTOCOL NO. 05

COMPOUND: isatuximab/SAR650984

A Phase 3 randomized, open-label, multicenter study comparing Isatuximab (SAR650984) in Combination with pomalidomide And low-dose dexamethasone veRsus pomalidomide and low-dose dexamethasone In patients with refractory or relapsed And refractory Multiple Myeloma

STUDY NUMBER: EFC14335

STUDY NAME: ICARIA-MM

VERSION DATE / STATUS: Approval date (11-Jun-2019) / APPROVED

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PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY

Document	Country/countries impacted by amendment	Date, version
Amended Clinical Trial Protocol 05	All	11-Jun-2019, version 1 (electronic 5.0)
Amended Clinical Trial Protocol 04	All	25-Oct-2018, version 1 (electronic 4.0)
Amended Clinical Trial Protocol 03	Japan	13-Sep-2018, version 1 (electronic 3.0)
Protocol Amendment 03	All	18-May-2017, version 1 (electronic 1.0)
Amended Clinical Trial Protocol 02	All	18-May-2017, version 1 (electronic 2.0)
Protocol Amendment 02 (GB)	United Kingdom	24-Feb-2017, version 1 (electronic 1.0)
Amended Clinical Trial Protocol 01 (GB)	United Kingdom	24-Feb-2017, version 1 (electronic 1.0)
Amended Clinical Trial Protocol 01	All	01-Nov-2016, version 1 (electronic 1.0)
Protocol Amendment 01	All	01-Nov-2016, version 1 (electronic 1.0)
Clinical Trial Protocol	All	04-Aug-2016, version 1 (electronic 2.0)

AMENDED PROTOCOL 05 (11-JUN-2019)

This amended protocol (amendment 05) is considered to be 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 because it significantly impacts the safety or physical/mental integrity of participants.

OVERALL RATIONALE FOR THE 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 and pregnancy testing of 5 months after the last isatuximab dose is required.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Tabulated clinical trial summary and Section 7.2 Exclusion criteria	E27 and E28 amended to indicate that females of child-bearing potential will be required to use contraception and to be tested for pregnancy for 3 or 5 months after discontinuation of study treatment for Pd and IPd respectively; and that male patients will be required to use contraception for 3 or 5 months after discontinuation of study treatment, for Pd and IPd respectively.	Change from 3 months due to re-estimation of isatuximab plasma half-life
Flow Chart foot note j	Amended to indicate that females of child-bearing potential will be required to be tested for pregnancy for 3 or 5 months after discontinuation of study treatment for Pd and IPd respectively.	Change from 3 months due to re estimation of isatuximab plasma half-life
Section 8.9.4 Contraceptive measures and pregnancy counseling	Amended to indicate that females of child-bearing potential will be required to use contraception, abstain from breastfeeding or blood donation and to be tested for pregnancy for 3 or 5 months after discontinuation of study treatment for Pd and IPd respectively; and that male patients will be required to use contraception and abstain from sperm or blood donation for 3 or 5 months after discontinuation of study treatment for Pd and IPd respectively.	Change from 3 months due to re-estimation of isatuximab plasma half-life
Section 10.1.5.1 60 days visit	Amended to indicate that females of child-bearing potential will be required to be tested for pregnancy for 3 or 5 months after discontinuation of study treatment for Pd and IPd respectively.	Change from 3 months due to re estimation of isatuximab plasma half-life
Section 10.1.5.2 Further follow-up visits	Amended to indicate that females of child-bearing potential will be required to be tested for pregnancy for 3 or 5 months after discontinuation of study treatment for Pd and IPd respectively.	Change from 3 months due to re estimation of isatuximab plasma half-life

CLINICAL TRIAL SUMMARY

COMPOUND: SAR650984 (isatuximab)	**STUDY No.: EFC14335** **STUDY NAME: ICARIA-MM**
TITLE	A Phase 3 randomized, open-label, multicenter study comparing isatuximab in combination with pomalidomide and low-dose dexamethasone versus pomalidomide and low-dose dexamethasone in patients with refractory or relapsed and refractory multiple myeloma
INVESTIGATOR/TRIAL LOCATION	Worldwide
PHASE OF DEVELOPMENT	3
STUDY OBJECTIVE(S)	**Primary objective:** To demonstrate the benefit of isatuximab in combination with pomalidomide and low-dose dexamethasone in the prolongation of Progression Free Survival (PFS) as compared to pomalidomide and low-dose dexamethasone in patients with refractory or relapsed and refractory multiple myeloma (MM). **Key Secondary objective(s):** • To evaluate the Overall Response Rate (ORR) as per International Myeloma Working Group (IMWG) criteria in each arm • To compare the Overall Survival (OS) between the two arms **Other Secondary objective(s):** • To evaluate the Time to Progression (TTP) in each arm • To evaluate the PFS in high risk cytogenetic population defined as patients carrying del(17p), t(4;14), t(14;16) in each arm • To evaluate the Duration of Response (DOR) in each arm • To evaluate safety in both treatment arms • To determine the pharmacokinetic (PK) profile of isatuximab in combination with pomalidomide • To evaluate the immunogenicity of isatuximab • To assess disease-specific and a generic health-related quality of life (HRQL), disease and treatment-related symptoms, health state utility and health status. **Exploratory objective(s):** • [redacted] • To explore PK and pharmacodynamic (PDy) relationships • To explore the minimal residual disease (MRD) rate in both treatment arms

STUDY DESIGN	This is a prospective, multicenter, multinational, randomized, open-label, parallel group, 2-arm study evaluating the clinical benefit of isatuximab in combination with pomalidomide and low-dose dexamethasone as compared to pomalidomide and low-dose dexamethasone for the treatment of patients with refractory or relapsed and refractory multiple myeloma who have received at least two prior lines including lenalidomide and a proteasome inhibitor (bortezomib, carfilzomib or ixazomib) alone or in combination, and have demonstrated disease progression on or within 60 days of completion of the last therapy. **Randomization/treatment arms:** After confirmation of eligibility criteria, patients will be randomly assigned using interactive response technology (IRT) in a 1:1 ratio to one of the two arms: • Isatuximab in combination with pomalidomide and low-dose dexamethasone (IPd, experimental arm) • Pomalidomide and low-dose dexamethasone (Pd, control arm) Isatuximab, pomalidomide and dexamethasone are defined in this protocol as "study treatments". Randomization will be stratified by age (<75 years versus ≥75 years) and number of previous lines of therapy (two or three versus more than three). A complete transplant procedure (induction, mobilization, conditioning, transplant, consolidation and maintenance) will be considered as one line. Each other regimen will be considered as one line, whatever the reason of discontinuation (progression, adverse event or patient request). **Duration of therapy** Patients will be allowed to continue therapy until disease progression, unacceptable adverse events (AEs) or patient wish, whichever comes first.
STUDY POPULATION **Selection criteria**	**Inclusion criteria:** Eligible patients will be considered for inclusion in this study if they meet all of the following criteria: I 01. Age ≥18 years or country's legal age of majority if the legal age is >18 years old I 02. Patients must have a documented diagnosis of multiple myeloma with evidence of 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. Patients must have received at least 2 prior lines of anti-myeloma therapy, which must include at least 2 consecutives cycles of lenalidomide and a proteasome inhibitor (bortezomib, carfilzomib or ixazomib) given alone or in combination. Note: An induction treatment followed by autologous stem cell transplantation (ASCT) and consolidation/maintenance is considered as one line of treatment

	I 04. Patients must have failed treatment with lenalidomide and a proteasome inhibitor (bortezomib, carfilzomib or ixazomib) alone or in combination, defined by any of the following (failure to lenalidomide and a proteasome inhibitor can have occurred at any line of therapy): • Progression has occurred while on or within 60 days from end of the treatment with lenalidomide and/or a proteasome inhibitor • In case of previous response ≥partial response (PR) to lenalidomide and/or a proteasome inhibitor, patient must have progressed within 6 months after discontinuation of the treatment • Patients who have developed intolerable toxicity after a minimum of 2 consecutive cycles of a regimen containing lenalidomide and a proteasome inhibitor (bortezomib, carfilzomib or ixazomib) alone or in combination. Intolerance is defined as below: - For proteasome inhibitor containing regimens: any toxicity leading to discontinuation of a proteasome inhibitor, like ≥G2 peripheral neuropathy or ≥G2 neuropathic pain. Peripheral neuropathy must be ≤G1 before study entry (according to NCI-CTCAE v4.03) - For lenalidomide containing regimens: any toxicity leading to discontinuation of lenalidomide, like G3 rash. Rash must not have been G4 and other non-hematologic toxicities should not have been G4. All non-hematologic toxicities must be ≤G1 before study entry I 05. Patients must have progressed on or within 60 days after end of previous therapy before to study entry, ie, refractory to the last line of treatment. This patient population includes the following two categories: • Refractory disease: patients who were refractory to all previous lines of treatment but should have achieved at least a minimal response (MR) in one previous line • Relapsed and refractory disease: patients who were relapsed from at least one previous line of treatment and refractory to the last line of treatment. Patients can be refractory to other previous line/lines of treatment Note: Patients must have achieved a minimal response (MR) or better to at least one of the previous lines of treatment (ie, primary refractory disease is not eligible) I 06. Patient has given voluntary written informed consent before performance of any study related procedures not part of normal medical care, with the understanding that consent may be withdrawn by the patient at any time without prejudice to his/her medical care **Exclusion criteria:** Patients who have met all the inclusion criteria will be screened for the following exclusion criteria: E 01. Primary refractory multiple myeloma defined as: patients who have never achieved at least a MR with any treatment during the disease course E 02. Free Light Chain measurable disease only

	E 03.	Patient with prior anti-CD38 monoclonal antibody treatment with progression on or within 60 days after end of anti-CD38 monoclonal antibody treatment or failure to achieve at least MR to treatment (ie, refractory to anti-CD38)
	E 04.	Prior therapy with pomalidomide
	E 05.	Any anti-myeloma drug treatment within 14 days before randomization, including dexamethasone
	E 06.	Prior allogenic hematopoietic stem cell (HSC) transplant with active graft versus host disease (GvHD) (GvHD any grade and/or being under immunosuppressive treatment within the last 2 months)
	E 07.	Any major procedure within 14 days before the initiation of the study treatment: plasmapheresis, major surgery (kyphoplasty is not considered a major procedure), radiotherapy
	E 08.	Patient who has received any other investigational drugs or prohibited therapy for this study within 28 days or 5 half-lives from randomization, whichever is longer
	E 09.	ECOG status >2
	E 10.	Platelets <75 000 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 three days before the screening hematological test
	E 11.	ANC <1000 µ/L (1 x 10^9/L). The use of G-CSF is not allowed to reach this level
	E 12.	Creatinine clearance <30 mL/min (MDRD Formula, see Appendix A)
	E 13.	Total bilirubin >2 x ULN
	E 14.	Corrected serum calcium >14 mg/dL (>3.5 mmol/L)
	E 15.	AST and/or ALT>3 x ULN
	E 16.	Ongoing toxicity (excluding alopecia and those listed in eligibility criteria) from any prior anti-myeloma therapy >G1 (NCI-CTCAE v4.03)
	E 17.	Hypersensitivity to IMiDs (thalidomide or lenalidomide) defined as any hypersensitivity reaction leading to stop IMiDs within the 2 first cycles or toxicity, which does meet intolerance definition (see I 04)
	E 18.	Hypersensitivity to dexamethasone, sucrose histidine (as base and hydrochloride salt) and polysorbate 80 or any of the components of study therapy that are not amenable to premedication with steroids, or H2 blockers that would prohibit further treatment with these agents
	E 19.	Significant cardiac dysfunction; myocardial infarction within 12 months; unstable, poorly controlled angina pectoris
	E 20.	Diagnosed or treated for another malignancy within 3 years prior to randomization with the exception of complete resection of basal cell carcinoma or squamous cell carcinoma of the skin, an in situ malignancy, or low risk prostate cancer after curative therapy
	E 21.	Known to be HIV+ or to have hepatitis A, B or C active infection

	E 22. Malabsorption syndrome or any condition that can significantly impact the absorption of pomalidomide E 23. Active primary amyloid-light (AL) amyloidosis (evidence of end organ damage or receiving treatment for amyloidosis) E 24. Concomitant plasma cell leukemia E 25. Unable or unwilling to undergo to thromboprophylaxis E 26. Daily requirement for corticosteroids (equivalent to ≥10 mg/day of prednisone) for more than 7 days (except for inhalation corticosteroids) E 27. Pregnant or breastfeeding female or female who intends to become pregnant during the participation in the study. Females of childbearing potential (FCBP) unwilling to prevent pregnancy by the use of 2 reliable methods of contraception for ≥4 weeks before the start of study treatment, during treatment (including dose interruptions), and up to 3 or 5 months following the last dose of study treatment for Pd and IPd respectively, and/or who are unwilling or unable to be tested for pregnancy before study treatment initiation (2 negative tests), weekly during 1st month of treatment and then prior each treatment cycle administration or every 2 weeks in case or irregular menstrual cycles up to 3 or 5 months following the last dose of study treatment for Pd and IPd respectively E 28. Male participants who disagree to practice true abstinence or disagree to use a condom during sexual contact with a pregnant female or a FCBP while participating in the study, during dose interruptions and at least 3 or 5 months following study treatment discontinuation for Pd and IPd respectively, even if has undergone a successful vasectomy Note 1: a FCBP is a female who: 1) has achieved menarche at some time point, 2) has not undergone a hysterectomy or bilateral oophorectomy or 3) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (ie, has had menses at any time in the preceding 24 consecutive months) Note 2: True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception. E 29. All patients who disagree to refrain from donating blood while on study treatment and for 4 weeks after discontinuation from this study treatment E 30. All patients who do not agree to keep study treatment for their personal use only E 31. Any country-related specific regulation that would prevent the patient from entering the study E 32. 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 study results (eg, systemic infection unless specific anti-infective therapy is employed) or patient unable to comply with the study procedures

Total expected number of patients	Approximately 300 patients (150 patients per arm). Enrollment will be stopped after PFS analysis or when approximately 300 patients will have been randomized, whichever is first.
Expected number of sites	Approximately 150
STUDY TREATMENT(s)	
Investigational medicinal product(s)	**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 at pH 6.0. 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(s) of administration:	IV
Dose regimen:	Isatuximab dosed at 10 mg/kg will be given IV on Days 1, 8, 15, and 22 in the first cycle, then Days 1 and 15 in subsequent cycles. Each cycle will be 28 days in duration. Dose modifications will be applied in case of toxicity.
Investigational medicinal product(s)	**Pomalidomide**
Formulation:	The drug product is presented as capsules, 1 mg, 2 mg, 3 mg and 4 mg.
Route(s) of administration:	PO
Dose regimen:	Pomalidomide will be given at 4 mg on Days 1 to 21 in a 28-day cycle. Patients will be asked to maintain a diary to record the doses of pomalidomide to document all oral administration (except those administered by the study nurse/doctor). Dose modifications will be applied in case of toxicity
Investigational medicinal product(s)	**Dexamethasone**
Formulation:	The drug product is presented as tablets, 4 mg and 8 mg; and 3.3 mg/mL (6.6 mg/2mL) ampoules for all countries except US, and 10 mg/mL vials for US, for intravenous injection
Route(s) of administration:	PO/IV
Dose regimen:	Dexamethasone will be given at 40 mg for patients <75 years of age and at 20 mg for patients ≥75 years of age, on Days 1, 8, 15 and 22 in a 28-day cycle. Patients will be asked to maintain a diary to record the doses of dexamethasone PO to document all oral administration (except those administered by the study nurse/doctor). Dose modifications will be applied in case of toxicity Dexamethasone will have also intent of premedication for infusion acute reaction in IPd arm
Non investigational medicinal product(s) (NIMP) Premedication (IPd arm only)	
Product	**Acetaminophen (paracetamol)**
Route(s) of administration:	PO

Dose regimen:	Acetaminophen (paracetamol) will be given 650 to 1000 mg 15-30 minutes (but no longer than 60 minutes) before isatuximab infusion
Product	**Ranitidine or equivalent** (other approved H2 antagonists [eg, cimetidine], oral proton pump inhibitors [eg, omeprazole, esomeprazole])
Route(s) of administration:	IV
Dose regimen:	Ranitidine or equivalent will be given 50 mg 15-30 minutes (but no longer than 60 minutes) before isatuximab infusion
Product	**Diphenhydramine or equivalent** (eg, cetirizine, promethazine, dexchlorpheniramine, according to local approval and availability. Intravenous route is preferred for at least the first 4 infusions)
Route(s) of administration:	IV
Dose regimen:	Diphenhydramine or equivalent will be given 25 to 50 mg 15-30 minutes (but no longer than 60 minutes) before isatuximab infusion
ENDPOINT(S)	**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 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 International Myeloma Working Group (IMWG) criteria (1). Progression will be confirmed based on two consecutive assessments. **Key Secondary endpoint(s):** • Overall Response Rate (ORR): defined as the proportion of patients with stringent complete response (sCR), complete response (CR), very good partial response (VGPR), and partial response (PR) as assessed by the IRC using the IMWG response criteria • Overall Survival (OS): defined as the time from the date of randomization to death from any cause **Other Secondary Endpoints** • Time to Progression (TTP) defined as time from randomization to the date of first documentation of PD (as determined by the IRC) • PFS as defined above in the high risk cytogenetic population patients carrying del(17p), t(4;14), t(14;16) determined by fluorescence in situ hybridization (FISH) • Duration of response (DOR): defined as the time from the date of the first IRC determined response to the date of first IRC-PD or death, whichever happens first. DOR will not be calculated for patients that do not achieve a response • Safety in terms of treatment-emergent AEs/serious adverse events (TEAE/SAE), laboratory parameters, and vital signs and assessment of physical examination, infusion associated reactions (IAR), second primary malignancies. TEAEs are defined as AEs that develop, worsen (according to the Investigator opinion), or become serious during the TEAE period. The TEAE period is defined as the time from first dose of study treatments up

	to 30 days after last dose of study treatments. Adverse events and laboratory parameters will be graded using NCI-CTCAE v4.03 • Pharmacokinetic evaluation: blood samples will be collected in 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, inter-occasion PK variability, the population PK parameters estimates and the assessment of pomalidomide and pathophysiologic covariate effects on the main PK parameters. Empirical Bayesian estimation of individual parameters and of individual exposure (AUC: Area Under the Curve) will also be performed • Presence of isatuximab Anti-Drug Antibodies (ADA) in the IPd arm will be assessed throughout the study • The QLQ-C30, MY20 and EQ-5D-5L assessments will be captured electronically throughout the study. All patient reported outcomes (PRO) are to be completed by the patients at the centers prior to discussing their health/disease status, and prior to administration of study treatments, or other study-related procedures during treatment, at end of treatment visit (EOT; 30 [±5] days after last study treatment administration) and 60 days (±5 days) after last study treatment administration: - Disease-specific HRQL will be assessed using the EORTC QLQ-C30 - Disease- and treatment-related symptoms will be assessed using the EORTC QLQ-C30 and the EORTC MY20 questionnaires - Health state utility and health status will be assessed using the EQ-5D-5L **Exploratory Endpoints** • [redacted] • PK estimates will be investigated as prognostic factors for clinical outcome including safety and efficacy endpoints if possible • Bone marrow aspiration will be collected to assess minimal residual disease (MRD) in CR patients, as clinically indicated
ASSESSMENT SCHEDULE	The following evaluations will be performed at baseline only: • Demographic characteristics and medical history • Prior multiple myeloma history (diagnosis, stage at diagnosis and at study entry, prior anti multiple myeloma therapies) • Molecular analysis on blood [redacted]) and bone marrow samples (FISH for high risk cytogenetic and MRD) • Complete blood phenotyping including information of cross-matching and antibody screening if not yet available (local laboratory) (IPd arm only)

	Safety evaluation will be performed continuously throughout the study period and will include the following: • Vital signs and physical exam • Adverse event evaluation. Severity grade will be determined according to the NCI CTCAE v4.03 • Laboratory tests in blood and urine, including pregnancy tests (urine or serum; with a minimum sensitivity of 25 mIU/mL) prior to each cycle in females with childbearing potential (local laboratory) • ECOG PS • Cytokines (tumor necrosis factor alpha (TNF-α), IL-1-β, interleukines (IL) IL-4, IL-6 and interferon gamma (IFN)), markers of complement activation (C3a, C4, CH50), serum tryptase in the IPd arm (central laboratory) • Tumor Lysis Syndrome (TLS) markers (uric acid, creatinine, potassium, phosphate, calcium and corrected calcium) if needed (local laboratory) • Level of human anti-drug antibodies (ADA) in the IPd arm (central laboratory) • Second primary malignancies during and any time after treatment until the end of the study The following disease assessment procedures will be performed at screening (for eligibility) and again at Cycle 1 Day 1 prior to study treatment administration (baseline for response assessment) and then Day 1 of every cycle during treatment up to progression and for patients who discontinue study treatment for reasons other than progression, every 4 weeks during follow-up until PD (even for patients who would initiate further anti-myeloma therapy without PD): • M-protein quantification (serum and 24-hour urine, protein immunoelectrophoresis and immunofixation) (local and central laboratory) • Free light chains quantification (local and central laboratory) • Quantitative immunoglobulins (local and central laboratory) Other examinations for disease assessment will be done as below: • Bone marrow aspiration (or biopsy as clinically indicated) at baseline, and then to confirm response or progression as clinically indicated (local laboratory for plasma cells involvement, and in case of CR central laboratory will be done to assess MRD) • Bone disease assessment: - Skeletal survey or low-dose whole-body 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 or documented extramedullary disease (plasmacytoma) at baseline, CT scan or MRI is to be done at baseline and to be repeated every 12 weeks (±1 week), 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 assessment or extramedullary disease, the same modality (skeletal survey or low-dose whole-body CT; CT or MRI) should be used throughout the study for each individual patient All imaging to be sent for central review. Further anti-myeloma therapies will be collected. PROs 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), and 60 days (±5 days) after last study treatment administration. PK samples will be collected in all patients receiving isatuximab using a sparse sampling strategy as depicted in the PK/PDy Flow Chart in Section 1.3 (central laboratory).
STATISTICAL CONSIDERATIONS	**Sample size determination:** Progression Free Survival: Assuming proportional hazards, a total of 162 PFS events will be needed to detect a hazard ratio of 0.6 using a log rank test at the one sided 0.025 level with a 90% power. Based on an anticipated median PFS time of 4 months in the Pd arm; this is expected to correspond to a median PFS of 6.67 months in the IPd arm. Overall Survival: Assuming proportional hazards, a total of 220 death events will be needed to detect a hazard ratio of 0.685 using a log rank test at the one sided 0.025 level with 80% power. Calculation takes into account an interim analysis on OS at the time of PFS analysis. Based on an anticipated median OS time of 13 months in the Pd arm; this is expected to correspond to a difference of 6 months in median OS between the Pd arm and the IPd arm. A maximum of 300 patients (150 in each arm) would be adequate to achieve the targeted number of events for both PFS and OS. Assuming a uniform accrual rate of 15 patients per month, cut-off dates for primary analyses of PFS and OS will be approximately 18 and 51 months after first patient in (FPI) respectively. **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. **All treated (AT)/ safety population:** this population will include ITT patients who have actually received at least one dose or a part of a dose of the 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 treatment actually received. **PRO population:** is defined as the AT population who have completed the baseline (Cycle 1 Day 1) and at least 1 post baseline assessment for each of the three selected ePROs (EORTC QLQ-C30, MY20 and EQ-5D-5L).

	Analysis of Primary Efficacy endpoint: The primary analysis of PFS will be based on the following censoring rules: If progression and death are not observed before the analysis cut-off date, PFS will be censored at the date of the last valid disease assessment not showing disease progression performed prior to initiation of a new anti-myeloma treatment (if any) and the analysis cut-off date, whichever comes first. PFS in the IPd arm will be compared to the Pd arm using the log-rank test procedure stratified by stratification factors as entered in the IRT at the one sided level of 0.025. The estimates of the hazard ratio and corresponding 95% 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 provided. Sensitivity analyses of PFS will be performed (eg, different censoring rules and PFS assessed by the Investigator). Cut-off date for primary analysis of PFS will be the date when 162 PFS events are observed. **Analysis of secondary endpoints:** Best overall response, ORR and clinical benefit rate (CBR) will be summarized with descriptive statistics by treatment arm. The 95% two-sided CI will be computed for ORR and CBR using the Clopper-Pearson method. Overall response rate will be compared between treatment groups using the Cochran Mantel Haenszel stratified method. Clinical benefit rate is defined as the proportion of patients with sCR, CR, VGPR, PR or minimal response (MR) according to IMWG criteria, as determined by the IRC. The analysis of OS will be similar to that described for PFS and will be based on the following censoring rules: Patients without death prior to the analysis cut-off date will be censored at the last date the patient was known to be alive or the cut-off date, whichever is first. The final OS analysis (based on 220 deaths) is expected to be performed approximately 33 months after the final PFS analysis cut-off date (ie, 51 months after first patient in). The analysis of DOR will be similar to that described for PFS. The same censoring rules as PFS will be used. **Analysis of PRO endpoints:** • [redacted]

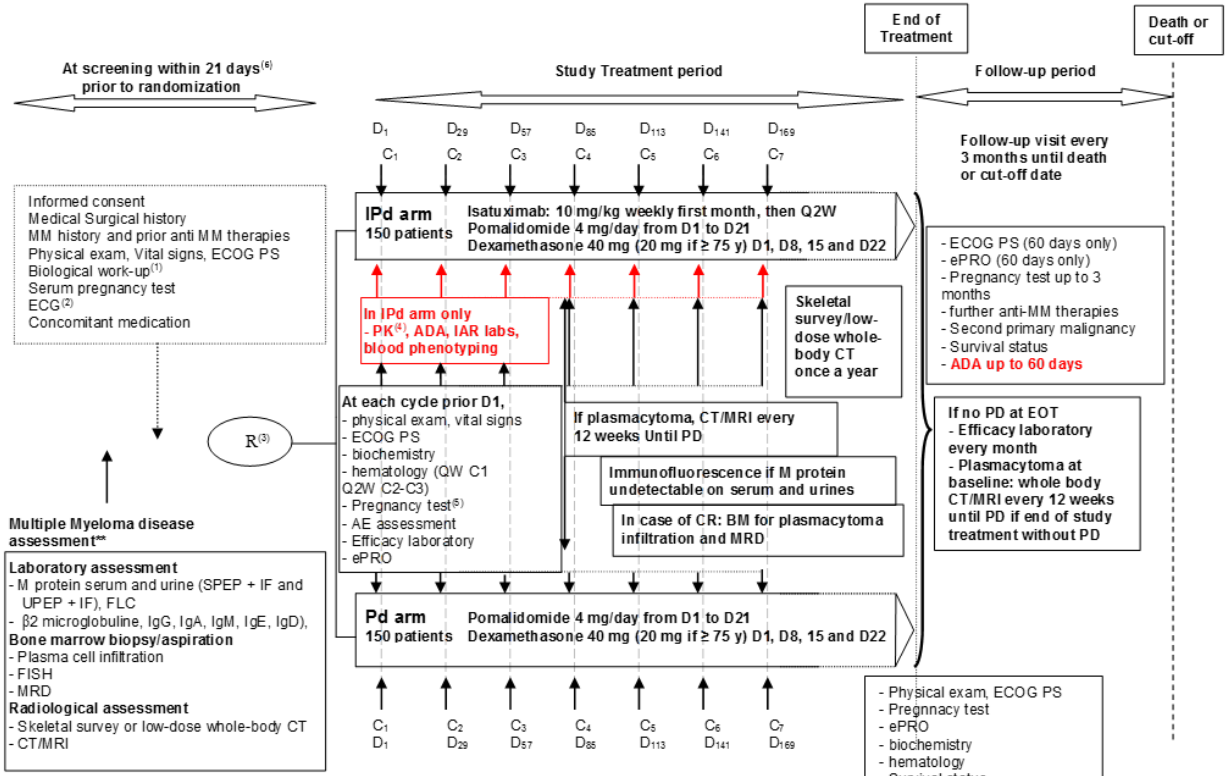
	• [redacted] • [redacted]. • [redacted]. • Clinically meaningful improvements for each PRO are defined (based on CIDs) in Appendix H, Appendix I and Appendix J. **Analysis of the Safety Endpoints:** Number (%) of patients experiencing TEAEs by primary system organ class and preferred term will be summarized by CTCAE grade (all grades and ≥Grade 3) for the safety population. The same summaries will be prepared for drug-related TEAEs, TEAEs leading to treatment discontinuation, TEAEs leading to dose modification, serious TEAEs and TEAEs with fatal outcome. For patients with multiple occurrences of the same AE within the on-treatment period, the worst grade will be used. Hematology and biochemistry results will be graded according to the CTCAE v4.03, when applicable. Number (%) of patients with laboratory abnormalities (ie, all grades and ≥Grade 3) using the worst grade during the on-treatment period will be provided for the safety population. Second primary malignancies will be analyzed throughout the study. **Interim Analysis** An interim analysis for efficacy assessment on OS is planned at the time of primary analysis on PFS which is estimated to occur when about 42% of the OS 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. **Planned Database Lock Date:** Estimated cut-off date for primary analysis of PFS will be approximately 18 months after FPI. The estimated final analysis cut-off date for OS analysis will be approximately 51 months after FPI.

DURATION OF STUDY PERIOD (per patient)	The duration of the study for a patient will include a period for screening of up to 21 days (or up to 28 days for FCBP). The cycle duration is 28 days. Patients will continue study treatment until disease progression, unacceptable AEs, patient wish, or any other reason. After study treatment discontinuation, patients will return to the study site 30 days after the last dose of study treatment for EOT assessments, and 60 days after the last dose of study treatment for assessments including ADA (IPd arm only). If ADA test at Day 60 is positive or inconclusive, ADA testing will be repeated every 30 days until negative. If isatuximab is stopped prior to pomalidomide and dexamethasone, ADA will be tested on D1 of the 2 next cycles. If ADA test at the second cycle administered without isatuximab is positive or inconclusive, ADA testing will be repeated every cycle until negative. During follow-up (FU), patients who discontinue the study treatment due to PD will be followed every 3 months (12 weeks) for further anti-myeloma therapy, second primary malignancies, and survival until death or OS cut-off date, whichever comes first. Patients who discontinue the study treatment prior to documentation of PD will be followed-up monthly until confirmation of PD (even for patients who would initiate further anti-myeloma therapy without PD), and then after confirmation of disease progression, every 3 months (12 weeks) for further anti-myeloma therapy, second primary malignancies, and survival, until death or OS cut-off date, whichever comes first. Cut-off date for PFS analysis will be the date when the 162 PFS events have occurred. Cut-off date for OS will be the date when 220 deaths have occurred. If a patient is still on treatment at the time of the cut-off date for OS and benefitting from the study treatment, the patient can continue the study treatment until disease progression, unacceptable AEs, patient wish, or any other reason. For cycles completed after the cut-off date, study treatment administration, pregnancy tests for FCBP, all related AEs, all serious AEs (regardless of relationship to study treatment), laboratory abnormalities if applicable, and reason of end of treatment will continue to be collected. For patients in the IPd arm, 1 ADA sample should be drawn 60±5 days after last study treatment administration. If ADA is positive or inconclusive at 60 days, the repeat samples will be taken every 30±7 days until the results become negative.
STUDY COMMITTEES	**Steering Committee:** ☒ Yes ☐ No The Steering Committee (SC) will include Study Chairmen, investigators and Sponsor's representatives. The SC will provide guidance on study conduct to the study team and will evaluate recommendations by the Data Monitoring Committee **Data Monitoring Committee:** ☒ Yes ☐ No Independent from the Sponsor and the investigators, the Data Monitoring Committee (DMC) role will be to monitor the safety of the patients enrolled in the study (ie, exposed to study treatment and/or to study procedures) and to provide the SC with appropriate recommendations in due time to ensure the safety of the patients. During this exercise, the DMC will also institute any measures that may be required for ensuring the integrity of the study results during the execution of its primary mission.

	Independent Response Committee: ☒ Yes ☐ No The Independent Response Committee (IRC) will determine disease response and progression according to laboratory data for MM disease assessment (central laboratory results), bone marrow, and imaging as per IMWG criteria

1 FLOW CHARTS

1.1 GRAPHICAL STUDY DESIGN



(1) biological work-up: hematology, biochemistry, quantitative urinalysis, coagulation, thyroid function
(2) ECG also pre-dose at C2D1
(3) First cycle should start within 3 working days after randomization
(4) Prior each isa infusion up end of treatment + at end of infusion on C1D1 and D15, C2D1 and C4D1; + EOI +1h at C1D1 and C4D1
(5) Weekly during first cycle, and then Q4W if regular menstruation of Q2W if irregular menstruation
(6) Or 28 days for women of childbearing potential

SPEP = serum protein immunoelectrophoresis, UPEP; urine protein immunoelectrophoresis; MRD= minimal residual disease, IAR = infusion associate reaction

1.2 STUDY FLOW CHART

Evaluation[a]		Screening/ Baseline	Cycle 1[c]				Subsequent Cycles[c]		End of Treatment (EOT)	Post treatment Follow-up Period[ee]	
		D-21 to D-1	D1	D8	D15	D22	D1	D15	30 days after last study treatment administration	60±5 days after last study treatment administration	Every 3 months (±7 days) after last study treatment administration
Informed Consent, Inclusion/Exclusion Criteria		X									
Contraception counselling for FCBP and partner		≤Day-28	X				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		
12-Lead ECG[h]		X	As clinically indicated				C2D1[h] and as clinically indicated		X		
Performance status (ECOG PS)		X	X	X	X	X	X		X	X	
Electronic patient reported outcomes (ePRO)	QLQ-C30[i]		X				X		X	X	
	MY20[i]		X				X		X	X	
	EQ-5D-5L[i]		X				X		X	X	
LOCAL LAB Assessments	Pregnancy test[j]	X	X	X	X	X	X		X	X[j]	X[j]
	Blood chemistry[k]	X	X	X	X	X	X		X		
	Hematology[l]	X	X	X	X	X	X	C2, C3	X		
	Antibody screening test (IPd arm only)[m]	X					C2[m]				
	Coagulation[n]	X	As clinically indicated								
	Urinalysis[o]	X	As clinically indicated								
	Thyroid function tests[p]	X	Once a year thereafter until EOT or as clinically indicated.						X		
	Serum β2-microglobulin[q]	X									
	Markers of potential TLS[r]		As clinically indicated								

Evaluation[a]		Screening/ Baseline	Cycle 1[c]				Subsequent Cycles[c]		End of Treatment (EOT)	Post treatment Follow-up Period[ee]	
		D-21 to D-1	D1	D8	D15	D22	D1	D15	30 days after last study treatment administration	60±5 days after last study treatment administration	Every 3 months (±7 days) after last study treatment administration
CENTRAL LAB Assessments[s]	Experimental arm only:										
	PK[t]		X	X	X	X	X	C2-C4	X		
	ADA [u]		X		X		X		X	X	X
	Isatuximab IAR Labs[v]		Prior C1D1 then if IAR ≥G2								
	PD/Exploratory:										
	FISH (Bone Marrow)[w]	X									
	MRD assessment (Bone Marrow)[w]	X	in case of CR								
	[redacted]		X								
	Pharmacogenetics (blood, optional)[y]		X								
CENTRAL LAB[s] & LOCAL LAB Assessment	Disease assessment labs:										
	Serum M-Protein Immunoelectrophoresis and Immunofixation[z]	X	X				X		X	if EOT without PD, disease assessment as during study treatment up to PD[ee]	
	Urine M-Protein (24-hour urine) Immunoelectrophoresis and Immunofixation[z]	X	X				X		X	if EOT without PD, disease assessment as during study treatment up to PD[ee]	
	Serum Free light chains[z]	X	X				X		X	if EOT without PD, disease assessment as during study treatment up to PD[ee]	
	Immunoglobulins: IgG, IgA, IgM, IgD, IgE[z]	X	X				X		X	if EOT without PD, disease assessment as during study treatment up to PD[ee]	
Other Disease assessments											
Bone Marrow for disease assessment[w]		X	To confirm CR and as clinically indicated								
Bone disease assessment[aa]		X	As clinically indicated							if EOT without PD disease assessment as during study treatment up to PD[ee]	
Extramedullary disease (plasmacytoma) assessment (CT scan/MRI)[aa]		X	If present at baseline[aa]							if EOT without PD disease assessment as during study treatment up to PD[ee]	

Evaluation[a]	Screening/ Baseline	Cycle 1[c]				Subsequent Cycles[c]		End of Treatment (EOT)	Post treatment Follow-up Period[ee]	
	D-21 to D-1	D1	D8	D15	D22	D1	D15	30 days after last study treatment administration	60±5 days after last study treatment administration	Every 3 months (±7 days) after last study treatment administration
Study Treatments:										
Isatuximab premedication (IPd arm only)		X	X	X	X	X	X			
Isatuximab infusion: 10 mg/kg IV (IPd arm only)		X	X	X	X	X	X			
Pomalidomide administration: 4 mg daily PO[bb]		D1-21								
Dexamethasone administration: 40 (20) mg PO/IV)[bb]		D1, 8, 15, 22								
Thromboprophylaxis		Continuously throughout study period								
AE Assessment[cc]	X	Continuously throughout study period						X	X (related AEs, all SAEs)	
Prior/Concomitant Medication[dd]	X	Continuously throughout study period						X		
Further anti-myeloma therapy									X	X
Survival status									X	X
Second primary malignancies		X						X	X	X

a **Evaluation**: Assessments are to be performed prior to study treatment administration and prior to premedication in the IPd arm unless otherwise indicated.

b **Randomization**: To take place once the consented patient has completed all the necessary screening procedures and is deemed eligible (based on assessments including myeloma specific results from central laboratory (see footnote "z") and hematology/biochemistry local laboratory results) for study entry by the investigator or designee. All eligible patients must be randomized by contacting the Interactive Response Technology (IRT). All efforts should be made to start treatment within 3 working days even if a maximum up to 5 working days can be allowed.

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. Day 8, Day 15 and Day 22 time window at Cycle 1 is ±1 day. For subsequent cycles, Day 1 and 15 time window is ±2 days and any delay above these time windows or any omission due to AE will be documented in the electronic case report form (eCRF) (please refer to details for dose modification in Section 8.2.3)

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

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

f **Physical Examination**: To be performed at screening, then prior to study treatment administration on Day 1, Day 8, Day 15 and Day 22 of Cycle 1, within 24 hours prior to study treatment administration on Day 1 of each subsequent cycle, and at the EOT visit. Consists of examination of major body systems, including neurological, digestive exam, respiratory (signs and symptoms, respiratory rate), hepatic and spleen span, lymph node examination, weight and height (height at baseline only). Only main diagnoses will be reported in the eCRF as AEs or medical history. Signs and symptoms related to multiple myeloma ongoing at baseline will be recorded in medical history and will be reported in AE page in case they worsen or become serious during study treatment. Laboratory abnormalities at baseline will be recorded in laboratory pages.

g **Vital Signs** : Blood pressure, heart rate and temperature required at screening and then on Day 1, Day 8, Day 15 and Day 22 of Cycle 1 in both arms. For subsequent cycles vital signs are to be taken on Day 1 of each cycle in both arms. In addition, in the IPd arm, vital signs are to be taken just before starting infusion and 1 hour after starting infusion and end of infusion on Day 1, Day 8, Day 15 and Day 22 of Cycle 1 and Day 1 and Day 15 of each subsequent cycle up to and including Cycle 4 and as clinically indicated. The final measurements will be performed at the EOT visit in both arms.

h **12-Lead ECG**: To be performed at screening, C2D1 (pre-dose), EOT, and as clinically indicated.

i **ePRO (EORTC QLQ-C30, MY20 and EQ-5D-5L)**: To be completed by the patient at the center prior to discussing their health/disease status, and prior to study treatment administration, or other study-related procedures on Day 1 of every cycle, at the EOT visit, and 60 days (±5 days) after last study treatment administration. The time estimated to complete the EORTC QLQ-C30 is approximately 10-15 minutes. The time estimated to complete the MY20 and EQ-5D-5L is approximately 5-10 minutes.

j **Pregnancy tests (urine or serum; with a minimum sensitivity of 25 mIU/mL) for FCBP must be performed within 10-14 days and again within 24 hours of initiation of study treatment. Repeat pregnancy test every week for the first 4 weeks and then every 28 days while on** therapy and during interruptions in therapy and 28 days following discontinuation of study treatment and then monthly up to 3 or 5 months after discontinuation of study treatment for Pd and IPd respectively . Females with irregular menstruation must have pregnancy testing weekly for the first 4 weeks of treatment then every 14 days while on therapy and during interruptions in therapy and on Days 14 and 28 following discontinuation of study treatment and then monthly up to 3 or 5 months after discontinuation of study treatment for Pd and IPd respectively. All patients must be counseled about pregnancy precautions, risks of fetal exposure and other risks. All patients enrolled into this trial must comply with all requirements of the Pomalidomide Pregnancy Prevention Plan (Appendix L) or the country specific risk management plan in countries where pomalidomide is not supplied by the Sponsor. FCBP - A female of childbearing potential is a sexually mature female who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 24 consecutive months.

k **Blood Chemistry**: To be done at screening and to be repeated within 24 hours prior to study treatment administration on Cycle 1 Day 1 (prior to premedication in IPd arm and prior to pomalidomide administration in Pd control arm on Day 1), within 24 hours prior to study treatment administration on Day 8, Day 15 and Day 22 of Cycle 1 and within 24 hours prior to study treatment administration on Day 1 of every subsequent cycle, at the EOT visit and as clinically indicated. Blood chemistry includes: SGOT (AST), SGPT (ALT), bilirubin (total and direct), alkaline phosphatase, lactate dehydrogenase (LDH), sodium, potassium, chloride, bicarbonate/carbon dioxide, 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. Biochemistry abnormalities will be recorded as AEs only if they are serious or lead to study treatment modification or discontinuation.

l **Hematology**: To be done at screening and to be repeated within 24 hours prior to study treatment administration on Cycle 1 Day 1 (prior to premedication in IPd arm and prior to pomalidomide administration in Pd arm on Day 1), within 24 hours prior to study treatment administration on Day 8, Day 15 and Day 22 of Cycle 1, within 24 hours prior to study treatment administration on Day 1 and Day 15 at Cycle 2 and Cycle 3, and then within 24 hours prior to study treatment administration on Day 1 of every subsequent cycle, at the EOT visit, and as clinically indicated. Hematology includes: hemoglobin, hematocrit, RBC, WBC with differential, ANC and platelet count. If G4 neutropenia, assess ANC every 2-3 days until ANC ≥0.5 x 10^9/L and at least weekly thereafter until ANC ≥1.0 x 10^9/L. Hematological abnormalities will be recorded as AEs only if they are serious or lead to study treatment modification or discontinuation.

m **Antibody screening test (IPd arm only):** Blood typing and complete blood phenotyping (C,c; E,e; Kell. Kidd; Duffy; S,s is recommended, if not available follow site's standard) if not already done, and antibody screening (Indirect Coombs Test, Indirect Antiglobulin Test [IAT]) to be obtained after randomization prior to Cycle 1 Day 1 study treatment administration. IAT to be repeated at Cycle 2 Day 1; if the test is not performed at this visit, it can be done at the next blood sampling. Results of IAT will be recorded in eCRF, including those performed prior to any transfusion during study treatment. Transfusions are to be recorded in the eCRF. Blood type card will be kept by the patient with the study card and the blood bank needs to be informed that the patient is receiving a treatment with an anti-CD38 and a potential interference with the Indirect Coombs test is possible.

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

o **Urinalysis**: To be done at screening and then as clinically indicated. Quantitative urinalysis at baseline, and qualitative (dipstick) after start of study treatment. This includes for quantitative: red blood cells, protein, glucose, pH, ketones, bilirubin, leucocytes; and for qualitative: blood, protein, glucose, pH, ketones, bilirubin, leucocytes.

p **Thyroid function tests** (TSH, T3 and T4 assessment): To be performed at baseline and once a year thereafter until EOT or as clinically indicated and at EOT.

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

r **Tumor Lysis Syndrome (TLS) markers**: to be done in case of suspicion of TLS (uric acid, creatinine, potassium, phosphate, calcium and corrected calcium).

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

t **Pharmacokinetics** (PK; IPd arm only): Refer to Pharmacokinetics/Pharmacodynamics Flow Chart.

u **ADA** (Anti-Drug Antibodies [IPd arm only]): To be performed on Day 1 of every cycle prior to each isatuximab administration, Day 15 of Cycle 1, at the EOT visit and at 60 days (±5 days) after last study treatment administration. At 60 days, if the test is positive or inconclusive, additional ADA samples are required every 30 days (±7 days) until sample is negative. If isatuximab is stopped prior to pomalidomide and dexamethasone, ADA will be tested on Day 1 of the 2 next cycles. If ADA test at the second cycle administered without isatuximab is positive or inconclusive, ADA testing will be repeated every cycle until negative

v **Isatuximab IAR labs**: (TNF- α, IL-1-β, IL-4, IL-6, and IFN-γ) baseline sample to be drawn prior to first isatuximab administration at Cycle 1. Then if a isatuximab infusion associated reaction (IAR) of ≥Grade 2 occurs, additional blood sampling during the AE is required for analysis of cytokine release (TNF-α, IL-1-β, IL-4, IL-6, and IFN-γ), markers of complement activation (C3a, C4, CH50) and serum tryptase.

w **Bone marrow biopsy/aspirate (as clinically indicated according to site's standard)**.

- 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. BMA or core biopsy (as clinically indicated) will be collected for disease assessment (local laboratory). Central laboratory samples will be collected for all patients but will be analyzed only for randomized patients. If local FISH assessment is done using purified CD138+ plasma cells or by clg FISH, the most recent local FISH report will be collected in patients who fail central laboratory FISH testing, for central review. Baseline MRD sample will be analyzed in patients who achieve a CR.
- During study treatment: to confirm CR (local laboratory), and to assess MRD in case of CR (central laboratory). If the first MRD is positive, BMA collection for MRD is to be repeated 3 months later for late negativity (one additional sample can be collected if patient remains MRD positive). No more than 3 post treatment samples are to be obtained

x [redacted]

y **Pharmacogenetics** (blood): Optional blood sample for pharmacogenetics in both arms in patients who signed the separate pharmacogenetics consent. To be performed within 24 hours prior to study treatment administration on Cycle 1 Day 1 (central lab).

z **Laboratory evaluation of disease assessment** (local and central laboratory for each planned time point): At screening, all lab assessments to be performed within 21 days prior to randomization. Eligibility will be assessed based on central laboratory results. Results for central serum and urine M-protein must be available before the patient may be randomized. In the absence of central lab results, sites may use local laboratory results for eligibility. Central laboratory results may not be available due to (but not limited to) the following reasons: samples were not able to be analyzed by central lab (for various reasons).
All lab assessments to be performed **again** prior to (within 24 hours) first study treatment administration on Cycle 1 Day 1 and response evaluation will be calculated compared to Cycle 1 Day 1 assessments. In IPd arm only, an additional blood sample will be collected at all time-points to evaluate the potential interference of isatuximab with the M protein assessment (central laboratory).
Response will be assessed on the basis of clinical and laboratory findings on Day1 of every cycle, to confirm response and whenever disease progression is suspected. Investigator decision to continue study treatment or not will be taken based on local laboratory results except in selected country(ies) where central laboratory results are available on an ongoing basis (in which case, one sample will be collected at each timepoint). Efficacy analyses will be done according to IRC assessment, which will use central laboratory data.

- Serum M-Protein immunoelectrophoresis (SPEP) and immunofixation: To be performed at screening and **again** prior to (within 24 hours) first study treatment administration on Cycle 1 Day 1, then at Day 1 of every subsequent cycle within 24 hours prior to study treatment administration, and at the EOT visit. After C1D1 immunofixation to be done if SPEP is negative.
- Urine M-Protein (24-hour urine) immunoelectrophoresis (UPEP) and immunofixation: To be performed at screening, sampling collection must be **completed** within 24 hours prior to study treatment administration on Cycle 1 Day 1, then within 24 hours prior to study treatment administration on Day 1 of every subsequent cycle and at the EOT visit. If urine M-protein is negative (negative immunofixation) at screening and Cycle 1 Day 1, this assessment is to be repeated every 3 cycles only (Cycle 4, Cycle 7, Cycle 10, etc.) and to confirm CR. After Cycle 1 Day 1, immunofixation to be done if UPEP is negative in patients whose disease is evaluable in urine.
- Serum free light chains (sFLC, quantification and ratio): To be performed at screening, within 24 hours prior to study treatment administration on Cycle 1 Day 1, then within 24 hours prior to study treatment administration on Day 1 of every subsequent cycle, and at the EOT visit (central lab analysis to be triggered if M protein is undetectable and immunofixation negative after Cycle 1 Day 1).
- Immunoglobulins (IgG, IgA, IgM, IgD and IgE): To be performed at screening, within 24 hours prior to study treatment administration on Cycle 1 Day 1 and within 24 hours prior to study treatment administration on Day 1 of every subsequent cycle, and at the EOT visit (IgD or IgE only if the heavy chain component of the disease is known to be IgE or IgD).

For patients who discontinue study treatment for reasons other than disease progression serum M-protein, urine M-protein (plus or minus sFLCs if needed to confirm sCR) to be performed monthly (central and local laboratory) during the follow-up period until progression.

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

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

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

- If known or documented extramedullary disease (plasmacytoma) at baseline, CT scan or MRI is to be done at baseline and to be repeated every 12 weeks (±1 week), to confirm CR, 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

bb Oral pomalidomide and dexamethasone will be recorded in patient diaries

cc **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, and all new related AEs whatever seriousness, are to be reported and followed up until resolution or stabilization. Severity will be graded according to NCI-CTC v4.03.

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

ee **Post 60-Day Follow-up (Day 60 visit, Day 90 visit, then every 3 months)**

At **60 days (±5 days)** after last treatment administration, the following are to be recorded for **all patients:** ECOG performance status, ePROs, pregnancy test (for FCBP), ADA, AE assessment, further anti-myeloma therapy, survival status, and second primary malignancies.

Patients who discontinue study treatment without PD will be followed monthly (ie, Day 60, Day 90 then every month thereafter) until confirmation of PD (even for patients who would initiate further anti-myeloma therapy). In addition to the above, the following will also be recorded at all monthly visits: disease assessment labs, bone disease assessment, radiological assessment every 12 weeks (±1 week) in case of known or documented extramedullary disease (plasmacytoma) at baseline, and skeletal survey (to be assessed yearly or if clinically indicated).

At **90 days (±5 days)** after last treatment administration, and every 3 months thereafter until death, the following are to be recorded for **patients with PD**: AE assessment, further anti-myeloma therapy, survival status and second primary malignancies.

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 FU 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 all efforts should be made to schedule follow-up visit at clinical center.

1.3 PHARMACOKINETIC/PHARMACODYNAMIC FLOW CHART

IPd arm only

Study Phase	Treatment Phase																		End of Treatment (EOT)	Post treatment Follow-up period	
	Cycle 1							Cycle 2			Cycle 3		Cycle 4				Subsequent Cycles				
Day	D1			D8	D15		D22	D1		D15	D1	D15	D1			D15	D1	D15	30±5 days after last study treatment	60±5 days after last study treatment	Monthly (± 7 days) for approximately 12 months
Time (decimal hours)	0h Start Infusion	EOI	EOI +1h	0h Start Infusion	0h Start Infusion	EOI	0h Start Infusion	0h Start Infusion	EOI	0h Start Infusion	0h Start Infusion	0h Start Infusion	0h Start Infusion	EOI	EOI +1h	0h Start Infusion	0h Start Infusion	0h Start Infusion			
Indicative clock time	8 am	12 pm	1 pm	8 am	8 am	12 pm	8 am	8 am	12 pm	8 am	8 am	8 am	8 am	12 pm	1 pm	8 am	8 am	8 am	8 am	8 am	8 am
Treatment																					
isatuximab (IV infusion)	X-----	----X		X	X-----	----X	X	X-----	----X	X	X	X	X-----	----X		X	X	X			
Pharmacokinetics[e]																					
isatuximab	P00[a]	P01[b]	P02[c]	P03[a]	P04[a]	P05[b]	P06[a]	P00[a]	P01[b]	P02[a]	P00[a]	P01[a]	P00[a]	P01[b]	P02[c]	P03[a]	P00[a]		PF0		
Pharmacodynamics[e]																					
ADA (Immunogenicity)[f]	P00[a]				P01[a]			P00[a]			P00[a]		P00[a]				P00[a]		PF0	PF1[d]	PFX[d]

a Sample collected (within 10 min) strictly before the start of isatuximab infusion (ie, after administration of the isatuximab premedications).
b Sample collected just before actual end of infusion (EOI). A time window of [±10 min] around the actual end of infusion will be allowed for end of infusion sample.
c Sample collected 1 hour [±10 min] after the actual end of infusion.
d At 60 days, if patient is positive or inconclusive for ADA, additional ADA are required every 30 days (± 7 days) until sample is negative (sample ID: PF2, PF3 etc.).
e Refer to laboratory manual for sample collection, processing and shipping.
f The sampling times for ADA detection can be modified based on the updated knowledge of isatuximab on immunogenicity.
If isatuximab is stopped prior to pomalidomide and dexamethasone, ADA will be tested on D1 of the 2 next cycles. If ADA test at the second cycle administered without isatuximab is positive or inconclusive, ADA testing will be repeated every cycle until negative.
After the PFS cut-off date, no further PK samples will be collected.
EOI = End of Infusion; ADA = Anti-Drug Antibody (immunogenicity); P = Plasma; 1 Cycle = 28 days

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3 LIST OF ABBREVIATIONS

ADA:	antidrug antibodies
ADCC:	antibody-dependent cellular-mediated cytotoxicity
AEs:	adverse events
AESI:	adverse event of special interest
ALT:	alanine aminotransferase
ANC:	absolute neutrophil count
ASCO:	American Society of Clinical Oncology
ASCT:	autologous stem cell transplantation
AST:	aspartate aminotransferase
AT:	all treated
AUC:	area under the curve
BM:	bone marrow
BMA:	bone marrow aspirate
cADPR:	cyclic adenosine-diphosphate-ribose
CBR:	clinical benefit rate
CDC:	complement-dependent cytotoxicity
CI:	confidence interval
CID:	clinical important difference
CLL:	chronic lymphocytic leukemia
CR:	complete response
DMC:	Data Monitoring Committee
DOR:	duration of response
DVT:	deep vein thrombosis
ECOG:	Eastern Cooperative Oncology Group
ELISA:	enzyme linked immunoabsorbant assay
EORTC:	European Organisation for Research and Treatment of Cancer
EOT:	end of treatment
ePROs:	electronic patient reported outcomes
EQ-5D-5L:	European Quality of Life Group questionnaire with 5 dimensions and five levels per dimension
FCBP:	female of child-bearing potential
FISH:	fluorescence in situ hybridization
FPI:	first patient in study
GVHD:	graft versus host disease
HDAC:	hystone deacetylase
HLA:	human leukocyte antigen
HLGT:	high level general term
HLT:	high level term
HRQL:	health-related quality of life
HSC:	hematopoietic stem cell
IAR:	infusion associated reaction

IEC:	independent ethics committee
IFN:	interferon
IL:	interleukin
IMiDs:	immunomodulatory drugs
IMWG:	International Myeloma Working Group
IPd:	isatuximab pomalidomide dexamethasone
IRB:	institutional review board
IRC:	Independent Response Committee
IRT:	interactive response technology
ITT:	intent-to-treat
IV:	Intravenous
kDa:	kilodalton
KIR:	killer cell inhibitory receptor
mAb:	monoclonal antibody
MedDRA:	Medical Dictionary for Regulatory Activities
MM:	multiple myeloma
MR:	minimal response
MRD:	minimal residual disease
NAD+:	nicotinamide adenine dinucleotide
NCI-CTCAE:	National Cancer Institute Common Terminology for Adverse Event
NK:	natural killer
NSAIDs:	non steroid anti-inflammatory drugs
ORR:	overall response rate
OS:	overall survival
PBMC:	peripheral blood mononuclear cells
Pd:	pomalidomide dexamethasone
PD:	progressive Disease
PDy:	pharmacodynamic
PE:	pulmonary embolism
PFS:	progression free survival
PIs:	proteasome inhibitors
PK:	pharmacokinetic
PR:	partial response
PRO:	patient reported outcome
PT:	preferred term
QLQ-C30:	quality of life questionnaire with 30 questions
QLQ-MY20:	EORTC myeloma module with 20 items
RBC:	red blood cell
RRMM:	relapsed refractory multiple myeloma
SAE:	serious adverse event
SC:	Steering Committee
SCT:	stem cell transplant
SOC:	system organ class
SPD:	sum of the products of the maximal perpendicular diameters of measured lesions
TEAE:	treatment-emergent adverse event
TLS:	tumor lysis syndrome

TNF:	tumor necrosis factor alpha
TTP:	time to progression
UPEP:	Urine Protein immunoelectrophoresis
URTI:	Upper Respiratory Tract Infection
VAS:	visual analogic scale
VGPR:	very good partial response
WBC:	white blood cell

4 INTRODUCTION AND RATIONALE

4.1 INTRODUCTION

CD38 is a Type II glycosylated 45 kilodalton (kDa) membrane protein that was identified as a lymphocyte marker (2). CD38 has a role in leukocyte homeostasis through modulation of hematopoietic cell survival and differentiation (3). CD38 functions as a receptor binding to CD31 and is involved in cell adhesion and signal transduction. The function of CD38 in signal transduction appears to be versatile depending on the cell lineage, the differentiation stage, and, possibly, the association with different co-receptors (3). CD38 is also an ecto-enzyme catalyzing the synthesis and hydrolysis of cyclic adenosine-diphosphate-ribose (cADPR) from nicotinamide adenine dinucleotide (NAD+) to ADP-ribose (4). These reaction products are implicated in calcium mobilization and intracellular signaling (5).

The expression of CD38 in healthy humans can be detected on natural killer (NK) cells, monocytes, dendritic cells, macrophages, granulocytes, activated T and B cells, and plasma cells. In contrast, expression has not been detected in hematopoietic stem cells (HSC), resting T and B cells, or tissue macrophages. Several hematological malignancies express CD38 including those of B-lymphocyte, T-lymphocyte and myeloid origin. Moreover, CD38 was identified as a negative prognostic marker in some hematological malignancies, such as chronic lymphocytic leukemia (CLL). The expression of CD38 is especially notable in multiple myeloma (MM) as >98% of patients are positive for this protein (6, 7). The strong and uniform expression of CD38 on malignant clonal MM cells contrasts with the restricted expression pattern on normal cells suggesting this antigen may be useful for specific targeting of tumor cells.

4.2 MULTIPLE MYELOMA

Multiple myeloma is a malignant plasma cell disease that is characterized by clonal proliferation of plasma cells in the bone marrow (BM) and the production of excessive amounts of a monoclonal immunoglobulin (usually of the IgG or IgA type or free urinary light chain [paraprotein, M-protein or M-component]). It is a disease predominantly associated with advancing age with more than 80% of patients aged 60 years or older. Patients with MM can experience bone pain, bone fractures, fatigue, anemia, infections, hypercalcemia, and kidney problems (8). The disease course for MM varies with the aggressiveness of the disease and related prognostic factors. Certain chromosomal abnormalities in multiple myeloma have been shown to be associated with poor clinical outcome. High-risk cytogenetic changes include del(17p), t(4;14), and t(14;16), among others. During the 2 last decades, median survival has been improved from 3 to 6 years; however, some patients can live longer than 10 years (8, 9).

Treatment options and survival are based on the patient's age, fitness and disease status. Patients under the age of approximately 65, presenting with symptomatic active disease in good physical health will generally receive initial therapy with autologous stem cell transplantation (ASCT). To achieve cytoreduction of the disease before collecting stem cells, induction chemotherapy is

administered. Induction treatment regimens include alkylating agents, dexamethasone alone, thalidomide plus dexamethasone, and vincristine, Adriamycin® (doxorubicin), and dexamethasone (VAD; or modifications to this regimen); however, the latter 2 regimens are associated with higher toxicity (10). Newer treatments with Velcade® (bortezomib) alone, bortezomib combinations, and Revlimid® (lenalidomide) plus dexamethasone have demonstrated improved outcomes as induction therapy, and these agents demonstrate higher response rates and lower toxicity (9, 10). In addition to these new treatments, daratumumab has been recently approved in US and Europe in single agent based on response rate of 29.2% (95%CI: 20.8-38.9) in late stage relapse and refractory multiple myeloma patients previously treated with IMiDs and PI, supporting the use of CD38 antibody in MM (11).

The current aim of MM therapy is to control the disease as effectively as possible, to maximize quality of life and to prolong survival. Treatments for relapsed and/or refractory disease are often referred to as salvage therapy. The initial chemotherapy regimen (eg, bortezomib plus dexamethasone or bortezomib thalidomide plus dexamethasone or lenalidomide plus dexamethasone, or bortezomib plus melphalan plus prednisone depending if the patient was eligible for stem cell transplantation or not) can be reinstituted for relapsed/refractory disease if the disease relapsed more than 6 months after the last therapy ended. Subsequent treatment decisions are based on whether the patient experiences an indolent or aggressive relapse. In general, MM patients will receive an average of 4 to 8 different regimens during their lifespan utilizing agents such as proteasome inhibitors (eg, bortezomib, ixazomib and carfilzomib) and immune modulatory agents (eg, lenalidomide), monoclonal antibodies (elotuzumab), histone deacetylase (HDAC) inhibitors (panobinostat) alone or in combination. However, once a patient becomes refractory to those agents, survival is limited and newer treatment options are needed to treat patients after they have failed stem cell transplant (SCT), chemotherapy, proteasome inhibitors, and immunomodulatory drugs (IMiDs®). Despite the dramatic improvement in patient outcomes with newer therapies, MM remains an incurable disease. Thus, the treatment of patients who have received at least 2 different lines of therapy including a proteasome inhibitor and an immunomodulatory agent or who are double refractory to a proteasome inhibitor and an IMiD® remains an unmet medical need.

4.3 POMALIDOMIDE

Pomalidomide is a thalidomide analogue indicated for patients with multiple myeloma who have received at least two lines therapies including lenalidomide and a proteasome inhibitor (PI) and have demonstrated disease progression on or within 60 days of completion of the last therapy.

Pomalidomide is an IMiD with multiple cellular effects that inhibit MM cell growth and survival blocking the stromal support from the BM microenvironment that can promote myeloma cell growth; in addition, pomalidomide has potent immunomodulatory effects that enhance the immune response to myeloma cells by stimulating natural killer cell and by inhibiting regulatory T cells (5). Pomalidomide has been approved following the data reported in the MM-003 trial where pomalidomide plus low-dose dexamethasone was compared to high-dose dexamethasone. In the MM-003 trial the most common Grade 3-4 hematological adverse events in the pomalidomide plus low-dose dexamethasone arm were neutropenia (48%), anemia (33%) and thrombocytopenia (22%); Grade 3-4 non-hematological AEs included pneumonia (13%), bone

pain (7%) and fatigue (5%). The ORR in the pomalidomide plus low-dose dexamethasone and high-dose dexamethasone was 31% and 10% respectively, the PFS was 4 months and 1.9 months. The updated OS after crossover showed significant advantage in the pomalidomide arm (12), providing relapsed refractory multiple myeloma (RRMM) patients with a new therapeutic option.

4.4 INVESTIGATIONAL PRODUCT

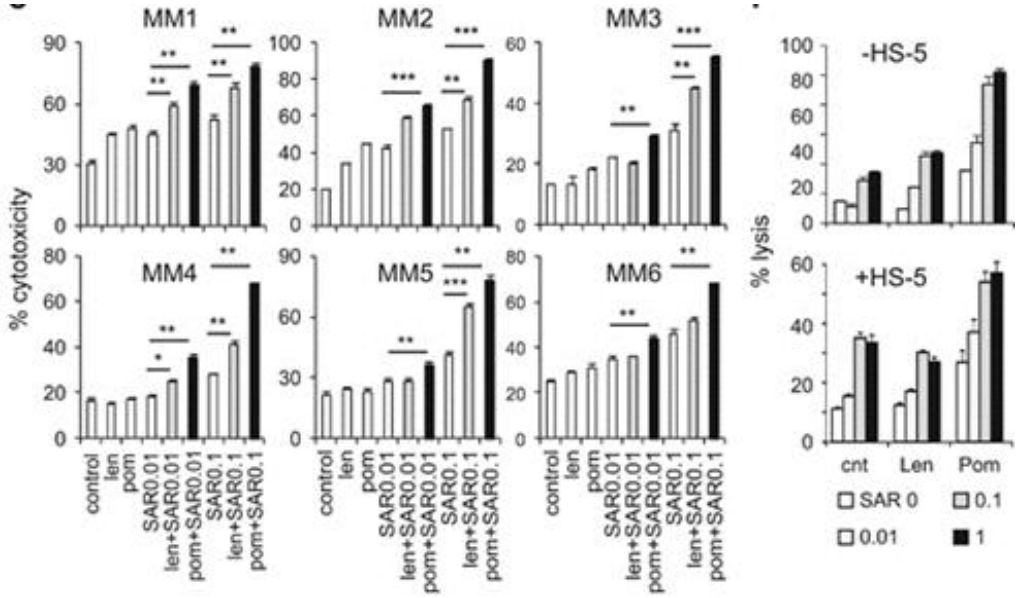
Based on the fact that CD38 is the most strongly and uniformly expressed antigen identified on the malignant clonal populations of myeloma cells compared with its pattern of expression on normal cells this antigen may be a useful target for the in vivo depletion of tumor cells while sparing normal cells (13).

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 (ADCC), complement-dependent cytotoxicity (CDC), direct induction of apoptosis (pro-apoptosis) without crosslinking, and inhibition of CD38 enzymatic activity.

4.4.1 Preclinical data

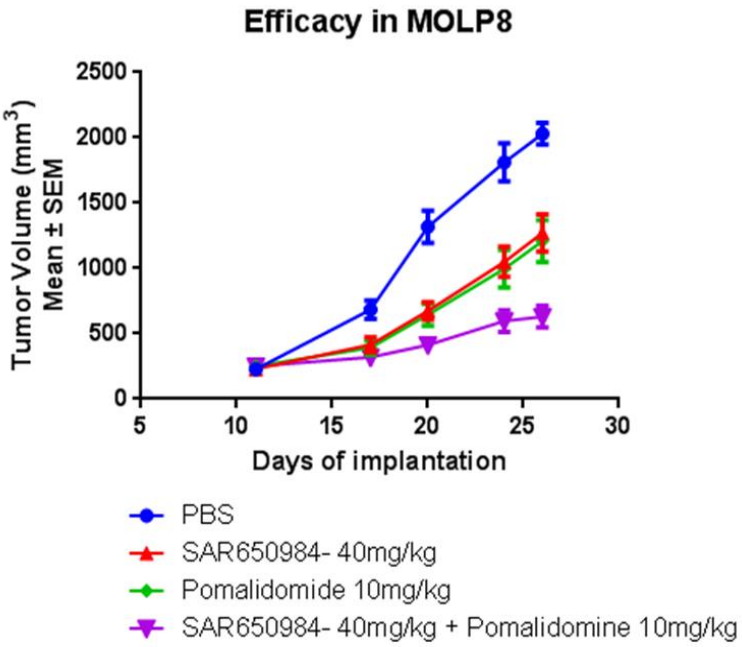
In vitro experiments demonstrate that the combination of isatuximab and pomalidomide results in enhanced direct toxicity and lysis by effector cells (ADCC) of CD38+ MM cells compared to that of isatuximab alone. Pomalidomide significantly increased isatuximab induced toxicity against patient derived MM cell s both sensitive and resistant to pomalidomide or lenalidomide. Pretreatment of peripheral blood mononuclear cells (PBMC) with pomalidomide increased isatuximab induced lysis of MM1S cells from below 40% to above 80% (Figure 1) (14).

Figure 1 - Pomalidomide and isatuximab combination effect on PBMCs



In vivo experiments using a MM xenograft model (MOLP-8) demonstrate that the combination of isatuximab and pomalidomide results in enhanced antitumor activity (T/C=22%) compared to the activity of isatuximab (T/C=56%) and pomalidomide alone (T/C=46%) (Figure 2).

Figure 2 - MOLP xenograft model isatuximab + pomalidomide



4.4.2 Clinical data

Isatuximab has shown promising activity in heavily pretreated relapsed and refractory multiple myeloma (RRMM) patients both as single agent and in combination with lenalidomide and dexamethasone (7, 14).

4.4.2.1 Single agent

The TED10893 (NCT01084252) trial is a Phase I/II single agent trial of isatuximab in RRMM. In the Phase II dose finding part of the trial patients with RRMM (≥3 lines of anti-MM therapy or refractory to IMiDs and proteasome inhibitors [PIs]) were randomized to isatuximab 3 mg/kg Q2W, 10 mg/kg Q2W x 2 cycles then Q4W, or 10 mg/kg Q2W, furthermore a fourth treatment arm was enrolled at 20 mg/kg QW/Q2W. As of November 2015, the observed ORR was: 9% (2/23), 20% (5/25), 29% (7/24) and 24% (6/25) at isatuximab ISA 3 Q2W, 10 Q2W/Q4W, 10 Q2W, and 20 mg/kg QW/Q2W, respectively; 14/20 responders continue without progression. Most common adverse events (AEs) were nausea (33%), fatigue (30%), dyspnea (26%), and cough (24%), which were typically Grade ≤2. Infusion associated reactions (IARs) occurred in 49% of patients, mostly Grade ≤2, 94% during the first infusion. Six patients discontinued therapy due to AEs, 2 due to IARs.

[redacted]

[redacted]

[redacted]

4.4.2.2 Combinations

4.4.2.2.1 Lenalidomide and low dose dexamethasone

The TCD11863 (NCT01749969) trial is evaluating the combination of isatuximab with standard doses of lenalidomide and dexamethasone in RRMM and has enrolled 57 patients as of 30 October 2015. Three dose levels were explored with the Q2W regimen, 3, 5 and 10 mg/kg with ORR of 63% at 10 mg/kg (n=24). Furthermore 2 additional cohorts of patients were enrolled and treated at 10 or 20 mg/kg using the QW/Q2W regimen. Amongst the efficacy evaluable patients the ORR was 50% in both cohorts (10 mg/kg [n=12]: VGPR 25%; PR 25%; 20 mg/kg [n=10]: VGPR 20%; PR 30%) with no difference in the safety profile although 1 DLT (pneumonia) was observed at 20 mg/kg as well as 3 G3 IARs leading to treatment discontinuation. Most frequent AEs were fatigue (46%), pyrexia (35%) and diarrhea (31%). IARs occurred in 65% of patients, mostly Grade ≤2, and >90% during the first infusion. MTD has not been reached.

4.4.2.2.2 Pomalidomide and low dose dexamethasone

The combination of isatuximab with pomalidomide and dexamethasone is being studied in the ongoing TCD14079 trial (NCT02283775). This is a Phase 1b dose escalation trial evaluating the combination in patients with refractory or relapsed and refractory multiple myeloma.
Three isatuximab dose levels are planned to be evaluated, 5, 10 and 20 mg/kg weekly for 4 weeks followed by every other week (QW/Q2W). Pomalidomide is administered at 4 mg per day for 21 days and dexamethasone 40 mg (20 mg if ≥75 years old) once a week as per the current label of pomalidomide, cycles are 28-day each.

As of May 26th 2016, 18 patients were enrolled in the trial; all of them have received at least 2 prior therapies including lenalidomide or proteasome inhibitor and have progressed during or within 60 days of the end of last therapy. Eight patients were treated at 5 mg/kg and 6 at 10 mg/kg. Four patients have been enrolled at 20 mg/kg dose level although the data is not presented here as these is not mature enough for the first hint of efficacy (none of them have completed at least 2 cycles of treatment).

Among the 14 patients for whom the data is available, 8 were treated at the dose of 5 mg/kg (with a median exposure of 21.2 weeks); and 6 patients at the dose of 10 mg/kg QW, then Q2W (with a median exposure of 8.1 weeks). Three patients discontinued treatment, 2 because of PD, and 1 because of a reason classified as “other” (patient wish due to grade 2 infusion associated reaction). The most common TEAEs reported in more than 3 patients consisted of fatigue (all Grade 64.3%, Grade 3-4 in 1 patient, 7.1%), infusion related reaction (all Grade 57.1%, no Grade 3-4), upper respiratory tract infection, tremor, dyspnea, and cough (all Grade 28.6%, no Grade 3-4). Infections occurred in 6 patients (42.9%) with a severity of Grade 3-4 in 1 patient

(7.1%, pneumonia). According to laboratory values, neutropenia was reported in 13 patients (92.9%), with severity of Grade 3-4 in 12 patients (85.7%); lymphopenia was reported in 11 patients (92.9%), with severity of Grade 3-4 in 11 patients (78.6%); thrombocytopenia was reported in 13 patients (92.9%), with severity of Grade 3-4 in 4 patients (56.0%); anemia was reported in all patients (100.0%), with no Grade 3-4. SAEs were reported in 6 patients (42.9%), with the most frequent being neutropenia, reported in 2 patients. DLTs occurred in 2 patients: 1 patient from the 5 mg/kg cohort (Grade 4 neutropenia at C1, related to pomalidomide), and 1 patient from the 10 mg/kg cohort (Grade 4 neutropenic infection consisting of cellulitis at C1, related to pomalidomide). Both DLTs resolved. No patient had AEs leading to death or discontinuation. One patient died while on study because of PD, at C2, 36 days after the last administration of study therapy.

All Grade IARs occurred in 8 patients (57.1%) with no grade 3-4 the majority of them during the first cycle of treatment and further resolved.

At 5 mg/kg one patient was considered not evaluable for efficacy because of treatment discontinuation (due other reason than AE or PD) before completion of the first cycle, eventually 7 patients were considered evaluable for efficacy. Among them and with a follow-up of at least 2 cycles, one confirmed complete response (CR), two confirmed VGPRs and 2 PRs were reported. Four patients are still on treatment and have received 9, 9, 7 and 5 cycles respectively. Two patients have experienced disease progression after 9 and 4 cycles of treatment respectively.

At 10 mg/kg, all patients have completed at least 2 cycles of treatment and have at least 2 consecutive efficacy assessments. Two patients have their myeloma laboratory values with a decrease qualifying them to MR, one is in SD, one patient is in PR, and two are in VGPR. All of them are still on treatment and have completed 2, 3 and 4 cycles respectively.

The dose level of 20 mg/kg is under enrolment.

4.5 RATIONALE

4.5.1 Study rationale

Multiple myeloma is a high unmet medical need and as a result, several agents are currently under clinical investigation in MM. Some of them (including isatuximab) have shown clinical activity as monotherapy, but the clinical avenue for development of most of them is to search for rationally based or pre-clinically oriented combinations of these novel agents with standard of care of MM, looking for potentiation. Monoclonal antibodies are one of the most promising groups of drugs in development in the treatment of MM with several of them demonstrating activity in this disease (13). One of the most important characteristics of this type of agents, apart from the clinical efficacy demonstrated, is the safety profile and the absence of potential cross-resistance with the agents currently utilized. This makes mAb an ideal combination partner with proteasome inhibitors, IMiDs and steroids.

Pre-clinical data demonstrate at least additive activity of isatuximab in combination with the immunomodulatory drug lenalidomide. The ongoing TCD11863 study evaluating this combination showed promising activity. Pomalidomide is the newest immunomodulatory drug which is a derivate from thalidomide. Pomalidomide in combination with low-dose dexamethasone has been studied in Phase I-III trials for patients with RR myeloma. It has shown activity in lenalidomide refractory patients and demonstrates superior OS and PFS compared to high dose dexamethasone. The effect of pomalidomide on the immune system coupled with the mechanism of action of isatuximab, suggests that the combination of both drugs may improve the benefit seen with pomalidomide in combination with low-dose dexamethasone in RRMM patients whose disease have previously failed to 2 or more anti-myeloma treatments. This study (EFC14335) will evaluate the efficacy and safety of isatuximab in combination with pomalidomide and dexamethasone compared to pomalidomide and dexamethasone.

4.5.2 Dose and regimen rationale

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

Although no evident difference is seen for tolerability, the available data in combination with lenalidomide (see Section 4.4.2.2.1) does not demonstrate major differences in efficacy between 10 and 20 mg/kg with comparable response rate in heavily pretreated patients. There is no apparent increase on adverse events with the combination and no DDI was evidenced between isatuximab and lenalidomide. PK/PDy analyses 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 term 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 lenalidomide/isatuximab combination studies is 10 mg/kg QW x 4 administrations followed by 10 mg/kg Q2W.

The data available for the combination of isatuximab with pomalidomide and dexamethasone in the TCD14079 shows no apparent difference in efficacy and tolerability between the two doses currently studied (5 and 10 mg/kg). Isatuximab PK appeared not to be altered by pomalidomide and vice-versa, as it has been shown for isatuximab in combination with lenalidomide. It is not expected to have an increase on response rate with 20 mg/kg as this was not seen in single agent or in combination with lenalidomide, although no data is available yet as the cohort is under enrolment.

[redacted]

The current data show:

- [redacted]
- No effect of pomalidomide or lenalidomide on isatuximab PK parameters and vice versa,

- The combination of isatuximab with lenalidomide and dexamethasone (TCD11863) where there is no benefit in response rate with increasing the dose from 10 to 20 mg/kg.

Based on these data above, the dose of isatuximab 10 mg/kg was selected for the combination with pomalidomide and dexamethasone in this Phase 3 trial.

4.5.3 Benefit/Risk of isatuximab in combination with pomalidomide and low-dose dexamethasone

Based on the safety and efficacy data described above, isatuximab as a single agent has shown clinical benefit in response rate with a favorable safety profile. Infusion-associated reactions are manageable with mandatory prophylaxis, close monitoring, and supportive care.

When isatuximab is combined with lenalidomide and low-dose dexamethasone or pomalidomide and low-dose dexamethasone, results appear promising. The overall safety profile of isatuximab in combination with lenalidomide does not appear to add morbidity to the clinical course of patients with RRMM, and is comparable with AEs observed with other established regimens. In the ongoing Phase 1b study TCD14079 (isatuximab, pomalidomide and dexamethasone), despite the high incidence of Grade 3 to 4 neutropenia (85.7%) reported as a laboratory abnormality (see Section 4.4.2.2.2), no increase in the incidence of febrile neutropenia or neutropenic infection has been observed compared to the available data on the combination of pomalidomide and dexamethasone (15).

Thus, the collective clinical experience shows a positive balance of benefit over risk and warrants further evaluation of the combination of isatuximab with pomalidomide and low-dose dexamethasone in RRMM as proposed in this clinical trial.

4.5.4 Study design

The study protocol has been designed to demonstrate a progression free survival and an overall survival advantage of isatuximab at the dose of 10 mg/kg weekly during first month, followed by every 2 weeks administrations administered in combination with pomalidomide and dexamethasone compared to pomalidomide and dexamethasone in patients with relapse and refractory multiple myeloma previously treated with at least 2 lines of therapy.

Patients will be randomly assigned in a 1:1 ratio to one of the two arms according 2 stratification factors: age (<75 years versus ≥75 years) and number of previous lines of therapy (two or three versus more than three).

5 STUDY OBJECTIVES

5.1 PRIMARY

To demonstrate the benefit of isatuximab in combination with pomalidomide and low-dose dexamethasone (IPd arm) in the prolongation of PFS as compared to pomalidomide and low-dose dexamethasone (Pd arm) in patients with refractory or relapsed and refractory multiple myeloma.

5.2 SECONDARY

5.2.1 Key secondary objectives

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

5.2.2 Other secondary objectives

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

5.3 EXPLORATORY

- [redacted]
- To explore PK and PDy relationships.
- To explore the MRD rate in both treatment arms.

6 STUDY DESIGN

6.1 DESCRIPTION OF THE STUDY

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

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

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

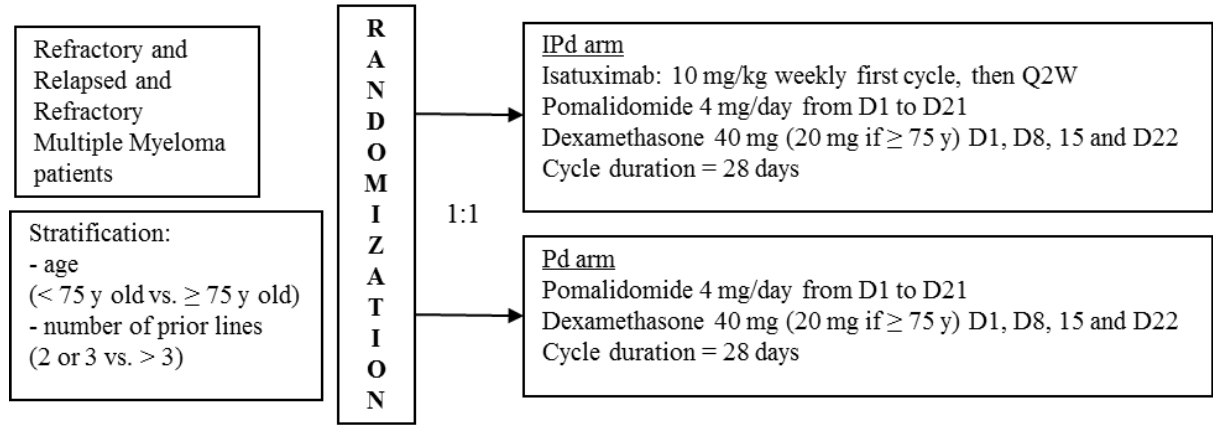
Isatuximab, pomalidomide and dexamethasone are defined in this protocol as “study treatments”.

Randomization will be stratified by age (<75 years versus ≥75 years) and number of previous lines of therapy (2 or 3 versus more than 3). A complete transplant procedure (induction, mobilization, conditioning, transplant, consolidation and maintenance) will be considered as one line. Each other regimen will be considered as one line, whatever the reason of discontinuation (progression, adverse event or patient request).

Patients will continue treatment until disease progression, unacceptable AEs or patient wish, whichever comes first.

Study design is summarized in the graph below:

Figure 4 - Study design



D=study day, y=years, IPd=isatuximab, pomalidomide, dexamethasone, PD=pomalidomide, dexamethasone

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 OS cut-off date, whichever occurs first.

The duration of the study for a patient will include a period for screening of up to 21 days (or up to 28 days for FCBP). A cycle duration is 28 days. Patients will continue study treatment until disease progression, unacceptable AEs, patient wish, or any other reason. All adverse events 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 treatments for end-of-treatment assessments, and 60 days after the last dose of study treatments for assessments including ADA (IPd arm only). If the ADA test at Day 60 is positive or inconclusive, ADA testing will be repeated every 30 days until negative (IPd arm only). If isatuximab is stopped prior to pomalidomide and dexamethasone, ADA will be tested on Day 1 of the 2 next cycles. If the ADA test at the second cycle administered without isatuximab is positive or inconclusive, ADA testing will be repeated every cycle until negative.

The related AEs and all SAEs regardless of relationship to 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, any new related adverse events (regardless of seriousness) will be collected and followed until resolution or stabilization.

During FU, patients who discontinue study treatment due to progressive disease (PD) will be followed every 3 months (12 weeks) for further anti-myeloma therapy, second primary malignancies, and survival until death or OS cut-off date, whichever comes first. Patients who discontinue the study treatment prior to documentation of PD will be followed-up monthly until confirmation of PD (even for patients who would initiate further anti-myeloma therapy without PD), and then every 3 months (12 weeks) for further anti-myeloma therapy, second primary malignancies, and survival, until death or OS cut-off date, whichever comes first.

If a patient is still on treatment at the time of the cut-off date for OS and is benefitting from the study treatment, the patient can continue the study treatment until disease progression, unacceptable AEs, patient wish, or any other reason. For cycles completed after the cut-off date for OS, study treatment administration, pregnancy tests for FCBP, all related AEs, all serious AEs (regardless of relationship to study treatment), laboratory abnormalities if applicable, and reason of end of treatment (EOT) will continue to be collected. For patients in the IPd arm, 1 ADA sample should be drawn 60 ±5 days after last study treatment administration. If ADA is positive or inconclusive at 60 days, the repeat samples will be taken every 30±7 days until the results become negative (see Section 1.3).

6.2.2 Determination of end of clinical trial (all patients)

PFS analysis (primary endpoint analysis) is event driven and the cut-off date for PFS analysis will be when 162 PFS events (progression or death, whichever comes first) have occurred (around 18 months from first patient being randomized).

The OS analysis is event driven and the final cut-off date will be when 220 deaths have occurred (around 51 months from first patient being randomized).

6.3 INTERIM ANALYSIS

No interim analysis of PFS is planned. An interim analysis of OS will be performed at time of the primary analysis of PFS. The procedure and criteria for undertaking an interim analysis are described in Section 11.5.

6.4 STUDY COMMITTEES

The **Steering Committee (SC)** will include a Chairman, investigators and Sponsor's representatives. The SC 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 **Data Monitoring Committee (DMC)**, consisting of 5 external independent members (4 physicians with multiple myeloma 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).

The first meeting will be set up to review early safety results (eg, after approximately 30 patients have completed at least 2 cycles), 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 SC and the Sponsor's representatives regarding the continued safety of treating ongoing and future study patients, as well as the course of action regarding the conduct of the trial.

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 **Independent Response Committee (IRC)** will determine disease response and progression according to efficacy MM laboratory data (central laboratory results), bone marrow, and imaging as per IMWG criteria and in line with the IRC charter up to primary analysis on PFS; no IRC review will be performed after the cut-off for the primary analysis.

Specific to Japan, please refer to Appendix N for IRC review after the global cut-off date.

7 SELECTION OF PATIENTS

7.1 INCLUSION CRITERIA

Eligible 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 [or 28 days for FCBP]):

I 01. Age ≥18 years or country's legal age of majority if the legal age is >18 years old.

I 02. Patients must have a documented diagnosis of multiple myeloma with evidence of 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. Patients must have received at least 2 prior lines of anti-myeloma therapy, which must include at least 2 consecutives cycles of lenalidomide and a proteasome inhibitor (bortezomib, carfilzomib or ixazomib) given alone or in combination.

Note: An induction treatment followed by ASCT and consolidation/maintenance is considered as one line of treatment.

I 04. Patients must have failed treatment with lenalidomide and a proteasome inhibitor (bortezomib, carfilzomib or ixazomib) alone or in combination, defined by any of the following (failure to lenalidomide and a proteasome inhibitor can have occurred at any line of therapy):

- Progression has occurred while on or within 60 days from end of the treatment with lenalidomide and/or a proteasome inhibitor.
- In case of previous response ≥PR to lenalidomide and/or a proteasome inhibitor, patient must have progressed within 6 months after discontinuation of the treatment.
- Patients who have developed intolerable toxicity after a minimum of 2 consecutive cycles of a regimen containing lenalidomide and a proteasome inhibitor (bortezomib, carfilzomib or ixazomib) alone or in combination. Intolerance is defined as below:
  - For proteasome inhibitor containing regimens: any toxicity leading to discontinuation of a proteasome inhibitor, like ≥G2 peripheral neuropathy or ≥G2 neuropathic pain. Peripheral neuropathy must be ≤G1 before study entry (according to National Cancer Institute Common Terminology for Adverse Event (NCI-CTCAE)v4.03),

- For lenalidomide containing regimens: any toxicity leading to discontinuation of lenalidomide, like G3 rash. Rash must not have been G4 and other non-hematologic toxicities should not have been G4. All non-hematologic toxicities must be ≤G1 before study entry.

I 05. Patients must have progressed on or within 60 days after end of the previous therapy before study entry, ie, refractory to the last line of treatment. This patient population includes the following two categories:

- Refractory disease: patients who were refractory to all previous lines of treatment but should have achieved at least a MR in one previous line.
- Relapsed and refractory disease: patients who were relapsed from at least one previous line of treatment and refractory to the last line of treatment. Patients can be refractory to other previous line/lines of treatment.

Note: Patients must have achieved a MR or better to at least one of the previous lines of treatment (ie, primary refractory disease is not eligible).

I 06. Patient has given voluntary written informed consent before performance of any study related procedures not part of normal medical care, with the understanding that consent may be withdrawn by the patient at any time without prejudice to his/her 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. Primary refractory multiple myeloma defined as: patients who have never achieved at least a MR with any treatment during the disease course.

E 02. Free Light Chain measurable disease only.

E 03. Patient with prior anti-CD38 monoclonal antibody treatment with progression on or within 60 days after end of anti-CD38 monoclonal antibody treatment or failure to achieve at least MR to treatment (ie, refractory to anti-CD38).

E 04. Prior therapy with pomalidomide.

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

E 06. Prior allogenic HSC transplant with active graft versus host disease (GvHD) (GvHD any grade and/or being under immunosuppressive treatment within the last 2 months).

E 07. Any major procedure within 14 days before the initiation of the study treatment: plasmapheresis, major surgery (kyphoplasty is not considered a major procedure), radiotherapy.

E 08. Patient who has received any other investigational drugs or prohibited therapy for this study within 28 days or 5 half-lives from randomization, whichever is longer.

E 09. ECOG status >2 (Appendix B).

E 10. Platelets <75 000 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 three days before the screening hematological test.

E 11. ANC <1000 µ/L (1 x 10^9/L). The use of G-CSF is not allowed to reach this level.

E 12. Creatinine clearance <30 mL/min (MDRD Formula, see Appendix A).

E 13. Total bilirubin >2 x ULN.

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

E 15. AST and/or ALT >3 x ULN.

E 16. Ongoing toxicity (excluding alopecia and those listed in eligibility criteria) from any prior anti-myeloma therapy >G1 (NCI-CTCAE v4.03).

E 17. Hypersensitivity to IMiDs (thalidomide or lenalidomide) defined as any hypersensitivity reaction leading to stop IMiDs within the 2 first cycles or reaction, which does meet intolerance definition (see I 04).

E 18. Hypersensitivity to dexamethasone, sucrose histidine (as base and hydrochloride salt) and polysorbate 80 or any of the components of study therapy that are not amenable to premedication with steroids, or H2 blockers that would prohibit further treatment with these agents.

E 19. Significant cardiac dysfunction; myocardial infarction within 12 months; unstable, poorly controlled angina pectoris.

E 20. Diagnosed or treated for another malignancy within 3 years prior to randomization with the exception of complete resection of basal cell carcinoma or squamous cell carcinoma of the skin, an in situ malignancy, or low risk prostate cancer after curative therapy.

E 21. Known to be HIV+ or to have hepatitis A, B or C active infection.

E 22. Malabsorption syndrome or any condition that can significantly impact the absorption of pomalidomide.

E 23. Active primary amyloid-light (AL) amyloidosis (evidence of end organ damage or receiving treatment for amyloidosis).

E 24. Concomitant plasma cell leukemia.

E 25. Unable or unwilling to undergo to thromboprophylaxis.

E 26. Daily requirement for corticosteroids (equivalent to ≥10 mg/day of prednisone) for more than 7 days (except for inhalation corticosteroids).

E 27. Pregnant or breastfeeding female or female who intends to become pregnant during the participation in the study. Females of childbearing potential (FCBP) unwilling to prevent pregnancy by the use of 2 reliable methods of contraception for ≥4 weeks before the start of study treatment, during treatment (including dose interruptions), and up to 3 or 5 months following the last dose of study treatment for Pd and IPd respectively, and/or who are unwilling or unable to be tested for pregnancy before study treatment initiation (2 negative tests), weekly during 1st month of treatment and then prior each treatment cycle administration or every 2 weeks in case or irregular menstrual cycles up to 3 or 5 months following the last dose of study treatment for Pd and IPd respectively.

E 28. Male participants who disagree to practice true abstinence or disagree to use a condom during sexual contact with a pregnant female or a FCBP while participating in the study, during dose interruptions and at least 3 or 5 months following study treatment discontinuation for Pd and IPd respectively, even if has undergone a successful vasectomy.

Note 1: a FCBP is a female who: 1) has achieved menarche at some time point, 2) has not undergone a hysterectomy or bilateral oophorectomy or 3) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (ie, has had menses at any time in the preceding 24 consecutive months).

Note 2: True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

E 29. All patients who disagree to refrain from donating blood while on study treatment and for 4 weeks after discontinuation from this study treatment.

E 30. All patients who do not agree to keep study treatment for their personal use only.

E 31. Any country-related specific regulation that would prevent the patient from entering the study.

E 32. 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 study results (eg, systemic infection unless specific anti-infective therapy is employed) or patient unable to comply with the study procedures.

8 STUDY TREATMENTS

8.1 INVESTIGATIONAL MEDICINAL PRODUCT(S)

8.1.1 Isatuximab

8.1.1.1 Pharmaceutical form

The [redacted] drug product is presented as a concentrate for solution for infusion in vials [redacted]

[redacted]

For administration to patients, the appropriate volume of isatuximab will be diluted in an infusion bag of 0.9% sodium chloride solution. The final infusion volume corresponding to the dose of isatuximab will be administered for a period of time that will depend on dose administered and will be based on protein amount given per hour.

8.1.1.2 Dilution method

Isatuximab concentrate for solution for infusion will be diluted in an infusion bag with 0.9% sodium chloride 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, decision to use central line is left to investigator 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 patient’s weight should be measured prior to each cycle to allow calculation of the isatuximab dose.

For IV infusion, an IV tubing administration set with a 0.20-µm in-line filter will be used for infusion; if an in-line filter is unavailable, a 0.20-µm filter unit may be attached to the administration set before administration. Further details are provided in the Pharmacy Manual.

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

8.1.2 Pomalidomide

Pomalidomide 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.

When commercial supplies will be used:

- Please refer to package insert for further details as regards to formulation, storage and handling procedures.
- When applicable the Pomalidomide Pregnancy Prevention Plan (Appendix L) or the country specific risk management plan (in countries where pomalidomide is not supplied by the Sponsor) has to be followed to ensure adherence of the pregnancy risk mitigation plan already in place in addition to the protocol requirements.

8.1.3 Dexamethasone PO/IV

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 Good Manufacturing Practice (GMP) guidelines before supplies are provided to the study sites.

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

The patient's weight should be measured prior to each cycle to allow calculation of the isatuximab dose.

Dose adjustment (dose delay, dose omission, and for pomalidomide 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 8.2.5).

8.2.1 Study treatments (IMP)

Study treatment is defined as isatuximab/pomalidomide/dexamethasone in IPd experimental arm and pomalidomide/dexamethasone in Pd control arm.

Patients allocated to IPd arm should routinely receive pre-medications prior to isatuximab infusion to reduce the risk and severity of infusion associated reactions (IARs) commonly observed with monoclonal antibodies. 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.

Pomalidomide may be taken with water and should be swallowed whole. Patients are not permitted to break, chew or open the capsules. Pomalidomide should be taken with or without food, preferably at the same time every day. Patients will be asked to maintain a diary to record the doses of pomalidomide (except those administered by the study nurse/doctor).

If a dose of pomalidomide is missed, it should be taken as soon as possible on the same day. If it is missed for the entire day, the dose should not be made up and will be considered omitted (and will not be replaced). The next scheduled dose should be taken at the next scheduled time point.

If a dose of dexamethasone is missed, it should be taken as soon as possible within the next 2 days. The dose per cycle must not exceed 160 mg (80 mg if the patient is ≥75 years old). Patients will be asked to maintain a diary to record the doses of dexamethasone taken orally (except those administered by the study nurse/doctor).

IPd arm (experimental arm)

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

- Dexamethasone 40 mg (or 20 mg if the patient is ≥75 years old), PO (the preferred route) or IV (if PO route cannot be used whatever the reason) on Days 1, 8, 15 and 22, between 15-30 minutes (but no longer than 60 minutes) prior to isatuximab. Dexamethasone will be administered at the beginning or at the end of the isatuximab premedications depending on the route PO or IV (see Section 8.2.2).
- Isatuximab 10 mg/kg on Days 1, 8, 15, and 22 at Cycle 1, and then 10 mg/kg on Days 1 and 15 for subsequent cycles. The rate of infusion for isatuximab should be initiated at 175 mg/hour.
  - First infusion: initiate infusion at 175 mg/hour. In the absence of IARs after 1 hour of infusion, increase infusion rate by 50 mg/hour increments every 30 minutes, to a maximum of 400 mg/hour,
  - Subsequent infusions: initiate infusion at 175 mg/hour. In the absence of IAR after 1 hour of infusion, increase rate by 100 mg/hour increments every 30 minutes, to a maximum of 400 mg/hour,
  - Guidelines for patients who develop IARs are provided in Section 10.6.1.
- Pomalidomide will be given 4 mg on Days 1 to 21 in a 28-day cycle. On Day 1 of each cycle, pomalidomide should be taken 1h to 30 min prior to isatuximab. The other infusion days of isatuximab (Day 8 and Day 15 of Cycle 1 and Day 15 of subsequent cycles), pomalidomide will be taken at the time which is the most convenient for the patient after isatuximab infusion, preferably at the same time of the previous dose.

Pd arm (control arm):

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

- Dexamethasone 40 mg (or 20 mg if the patient is ≥75 years old), PO or IV on Days 1, 8, 15 and 22.
- Pomalidomide will be given 4 mg on Days 1 to 21 in a 28-day cycle.

8.2.2 Premedication (NIMP) - Prevention of Infusion Associated Reactions (IARs)

Patients allocated to IPd arm should routinely receive premedication prior to isatuximab infusion to reduce the risk and severity of IARs commonly observed with monoclonal antibodies. The recommended premedication agents are: diphenhydramine 25-50 mg IV (or equivalent: eg, cetirizine, promethazine, dexchlorpheniramine, according to local approval and availability. Intravenous route is preferred for at least the first 4 infusions), dexamethasone IV/PO (dose defined below), ranitidine 50 mg IV (or equivalent: other approved H2 antagonists [eg, cimetidine], oral proton pump inhibitors [eg, omeprazole, esomeprazole]) and acetaminophen (paracetamol) 650-1000 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.

On the day of isatuximab infusion, a total of 40 mg of dexamethasone (regular dose of dexamethasone when used in combination with pomalidomide), or 20 mg in patients ≥75years, will be administered as part of the premedication and study treatment before isatuximab and pomalidomide. For patients who cannot tolerate dexamethasone during study treatment, methylprednisolone 100 mg IV can be administered as premedication only. However, both drugs cannot be used at the same time for premedication purposes.

Patients who do not experience an IAR upon their first 4 administrations of isatuximab may have their need for subsequent premedication reconsidered, at the Investigator's discretion.

When dexamethasone is administered PO, the following order is recommended:

- Dexamethasone 40 mg PO (or 20 mg PO for patients ≥75 years of age).
- Acetaminophen (paracetamol) 650 mg to 1000 mg PO.
- Ranitidine 50 mg IV (or equivalent).
- Diphenhydramine 25 mg to 50 mg IV (or equivalent).

When dexamethasone is administered IV, the following order is recommended:

- Acetaminophen (paracetamol) 650 mg to 1000 mg PO.
- Ranitidine 50 mg IV (or equivalent).
- Diphenhydramine 25 mg to 50 mg IV (or equivalent).
- Dexamethasone 40 mg IV (or 20 mg IV for patients ≥75 years of age).

Whatever the route of administration (IV or PO), dexamethasone will be administered **only** once (the single administration is used for both premedication and study treatment).

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 will be used for this study. Please refer to package insert for further details as regards to formulation, storage and handling purposes.

8.2.2.2 Diphenhydramine or equivalent

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

8.2.2.3 Acetaminophen (paracetamol)

Commercial supplies of acetaminophen (paracetamol) 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 Dose modifications

8.2.3.1 General rules

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

Dose reduction for pomalidomide and low-dose dexamethasone and/or cycle delay (ie, delay of all study treatments) are permitted in case of toxicity. Patient may have dose omitted (isatuximab and/or pomalidomide and/or dexamethasone) within a cycle if toxicity occurs and the patient does not recover by the day of planned 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 pomalidomide or dexamethasone has been decreased, intra-patient re-escalation back to the previous dose level is not permitted.

Administration of the study treatment (isatuximab and/or pomalidomide 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 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 $\geq$1000/ mm^3.
- Platelet count $\geq$50,000/ mm^3. For patients with plasma cells $\geq$50% of bone marrow nucleated cells at baseline, to initiate cycle 2, platelet counts should be $\geq$30 000/mm^3 regardless response status at end of cycle 1. During cycles 2-4, 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 2-4, D1 next cycle can be administered only if platelet counts ≥50 000/mm^3. For D1 administration beyond cycle 4, platelet counts should be ≥50 000/mm^3.

Any other pomalidomide, dexamethasone or isatuximab related AE that may have occurred in the previous cycle has recovered to ≤G1 or baseline severity (or according to the dose modifications shown in Section 8.2.3.3 and Section 8.2.3.4.

If these criteria are not met on the scheduled Day 1, patients should be re-evaluated weekly. 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, and the investigator must discuss the rationale 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 pomalidomide dosing was halted during the previous cycle and was restarted with a one-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 pomalidomide or dexamethasone has been reduced, intra-patient re-escalation back to the previous dose level is not permitted.
- Patients may have isatuximab dose omission within a cycle if toxicity occurs and does not recover on the day of planned infusion or within the following 3 days. Within a cycle, a delay of up to 3 days in cases of unresolved toxicity at the time of planned re-administration is permitted, otherwise infusion is omitted. Patients will receive the next isatuximab infusion after recovery of the toxicity as described in Section 8.2.3.2 No dose reduction of isatuximab is permitted.

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

8.2.3.2 Modification of isatuximab /pomalidomide/ dexamethasone dose levels in case of dose reduction

No dose reduction of isatuximab is permitted.

Dose reduction steps for pomalidomide are shown in Table 1. One or several doses of pomalidomide can be omitted.

Table 1 - Dose levels for pomalidomide dose reduction

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

PO = per os

Dose reduction steps for dexamethasone are shown in Table 2. One or several doses of dexamethasone can be omitted or dose of dexamethasone can be decreased to every other week.

Table 2 - Dose levels for dexamethasone dose reduction

Starting dose (PO or IV)	Dose level -1	Dose level -2	Dose level -3	Dose level -4
40 mg	20 mg	12 mg	8 mg	4 mg
20 mg (patients ≥75 years old[a])	12 mg	8 mg	4 mg	-

PO = per os; IV = intravenous

a all patients ≥75 years old will start dexamethasone treatment at the dose of 20 mg.

8.2.3.3 Dose adjustments in IPd arm

Dose adjustments for patients treated with isatuximab, pomalidomide and dexamethasone combination in the case of hematological toxicity are shown in Table 3.

Table 3 - Guidelines for dose adjustments for hematologic toxicities - isatuximab/pomalidomide/dexamethasone combination

Adverse event	Recommended action		
	Isatuximab[a]	Dexamethasone[a]	Pomalidomide
Platelets			
Thrombocytopenia Grade 3	Day 1 of cycle: delay until improvement ≥50 x 10^9/L[b] and administer at same dose level[c] Within cycle: maintain full dose of study treatment as planned		
Thrombocytopenia Grade 4 with or without bleeding	Day 1 of cycle: delay Day 1 administration until improvement ≥50 x 10^9/L[b] and administer at the same dose level[c] Within cycle: delay isatuximab until bleeding is controlled and platelet recover ≥50 x 10^9/L and then administer full dose. If delay is >3 days omit isatuximab and dexamethasone until next planned administration Further episodes: same recommendations		Day 1 of cycle: delay Day 1 administration until recovery and pomalidomide decreased by one dose level[c] Within cycle: hold pomalidomide until bleeding is controlled and platelet recover ≥50 x 10^9/L, and then re-start with 1 dose level decrease up to planned Day 21. Next cycle will be re-started with this one dose level decrease second episode: same recommendation with decrease of pomalidomide by a second dose level third episode: discontinue pomalidomide

Adverse event	Recommended action		
	Isatuximab[a]	Dexamethasone[a]	Pomalidomide
Neutropenia			
Neutropenia Grade 3 (≥0.5 and <1.0 x 109/L)	Day 1 of cycle: delay until recovery ≥1.0 x 10^9/L and administer at same dose level[a] Within cycle: maintain full dose as planned		
Neutropenia Grade 4[d](<0.5 x 109/)	Day 1 of cycle: delay until recovery ≥1.0 x 10^9/L and administer at the same dose level[c] Within cycle: Maintain same dose as planned Further episodes: same recommendations		Day 1 of cycle: delay Day 1 administration until recovery and restart pomalidomide decreased by one dose level or consider G-CSF use and keep same dose level[c] Within cycle: hold pomalidomide until neutrophil counts recover ≥0.5 x 10^9/L and then: - re-start with 1 dose level decrease up to planned Day 21. Next cycle will be re-started with this one dose level decrease - or consider G-CSF use and keep same dose level Second episode: same recommendations with decrease of pomalidomide by a second dose level third episode, discontinue pomalidomide
Febrile neutropenia and/or neutropenic infection	Day 1 of cycle: delay Day 1 administration until fever and infection recover and add G-CSF until ANC>1 x 10^9/L[c] Then administer Day 1 next cycle with isatuximab and dexamethasone at the same dose level and pomalidomide with dose recommendations below. Within cycle: omit isatuximab and dexamethasone, hold pomalidomide dose and add G-CSF until fever and infection have recovered and ANC>1 x 10^9/L. Then administer isatuximab and dexamethasone at the planned days at the same dose level and re-start pomalidomide up planned Day 21 with dose recommendations below: • first episode, resume same dose pomalidomide with G-CSF or re-start with 1 dose level decrease • second episode, resume with action not done at first episode (same dose with G-CSF or 1 dose decrement pomalidomide) • third episode, resume with one dose decrement of pomalidomide • fourth episode, stop pomalidomide		

a Patients may have isatuximab dose omission within a cycle if certain toxicities do not recover within 3 days following the day of planned infusion (see Section 8.2.3)

b For patients with plasma cells >50% of bone marrow 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 2-4, 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 2-4, D1 next cycle can be administered only if platelet counts ≥50 000/mm^3. For D1 administration beyond cycle 4, platelet counts should be ≥50 000/mm^3

c 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 8.2.3)

d If G4 neutropenia, assess ANC every 2-3 days until ANC ≥0.5 x 10^9/L and at least weekly thereafter until ANC ≥1.0 x 10^9/L

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

Table 4 - Guidelines for dose adjustments for non-hematologic toxicities - isatuximab/pomalidomide/dexamethasone combination

Adverse event	Recommended action		
	Isatuximab[c]	Dexamethasone[c]	Pomalidomide
DVT/PE			
Grade 3	Day 1 of cycle: initiate appropriate anticoagulation therapy and when efficient anticoagulation administer cycle at full dose isatuximab and the same dose level of dexamethasone and pomalidomide[a] Within cycle: maintain full dose isatuximab and the same dose level of dexamethasone as planned. For pomalidomide: • first episode: hold pomalidomide, initiate appropriate anticoagulation therapy and restart same dose pomalidomide when efficient anticoagulation • second episode: despite appropriate anticoagulation pomalidomide permanently discontinued		
Grade 4	Day 1 of cycle: delay Day 1 administration until controlled and administer the full dose of isatuximab and the same dose level of dexamethasone[a] Within cycle: delay isatuximab and dexamethasone until stabilization and resume without dose reduction at the next planned dates. If delay is >3 days omit isatuximab and dexamethasone until next planned administration		Pomalidomide permanently discontinued.
Edema Grade ≥3 (limiting function and unresponsive to therapy or anasarca), excluding infusion associated reaction	Day 1 of cycle or within cycle: maintain full dose isatuximab 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	Day 1 of cycle or within cycle: maintain full dose pomalidomide as planned
Allergic reaction/hypersensitivity (excluding infusion associated reaction)			
Grade 2	Hold study treatment until <Grade 2, and patient clinically stable; then, resume study treatment at the same dose level [a] **For infusion** reaction related to isatuximab, refer to Section 10.6.1 For allergic reaction related to pomalidomide, refer to site local protocol		
Grade ≥3	Permanent discontinuation of the drug responsible of the allergic reaction.		
Infection without concomitant neutropenia	Hold study treatment until systemic treatment of infection complete. Resume all at the same dose level		
Herpes zoster	Hold study treatment until lesions are dry, then resume all at the same dose level		

Adverse event	Recommended action		
	Isatuximab[c]	**Dexamethasone**[c]	**Pomalidomide**
Neuropathy			
Grade 2 with pain or Grade 3	Full dose isatuximab and same dose level of dexamethasone		Hold pomalidomide until neuropathy improves to Grade≤ 2 without pain. First episode: resume pomalidomide with a decrease of pomalidomide by 1 dose level Second episode: resume pomalidomide with a decrease by a second dose level Third episode: pomalidomide permanently discontinued
Grade 4	Full dose isatuximab and same dose level of dexamethasone		Pomalidomide permanently discontinued
Confusion or mood alteration Grade ≥2 (interfering with function +/- daily activities)	Day 1 of cycle or within cycle: maintain full dose isatuximab as planned	Hold dexamethasone until symptoms resolve. Restart with 1 dose level reduction. If symptoms persist despite above measures, dexamethasone permanently discontinued	Day 1 of cycle or within cycle: maintain same dose level of pomalidomide as planned
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	Treat with H2 blockers, sucralfate, or omeprazole. If symptoms persist despite above measures, decrease dexamethasone dose by 1 dose level	Day 1 of cycle or within cycle: maintain same dose level of pomalidomide as planned
>Grade 3 (requiring hospitalization or surgery)	Hold study treatment until symptoms adequately controlled. Then, restart full dose isatuximab and same dose level of pomalidomide, and decrease dexamethasone by one dose level of current dose along with concurrent therapy with H2 blockers, sucralfate, or omeprazole. If symptoms persist despite above measures, dexamethasone permanently discontinued		
Acute pancreatitis	Dexamethasone permanently discontinued Day 1 of cycle: delay Day 1 until recovery[a] and re-start full dose isatuximab and same dose level of pomalidomide Within cycle: hold all study treatment until recovery and re-start full dose isatuximab and same dose level of pomalidomide.		

Adverse event	Recommended action		
	Isatuximab[c]	**Dexamethasone**[c]	**Pomalidomide**
Hyperglycemia ≥Grade 3	Day 1 of cycle or within cycle: maintain full dose isatuximab as planned	Treatment with insulin or oral hypoglycemic agents as needed. If uncontrolled despite above measures, decrease dose by one dose level until levels are satisfactory	Day 1 of cycle or within cycle: maintain same dose level of pomalidomide as planned
Muscle weakness ≥Grade 2 (symptomatic and interfering with function +/- daily activities)	Day 1 of cycle or within cycle: maintain full dose isatuximab as planned	Decrease dexamethasone by one dose level. If weakness persists despite above measures decrease dose by one level. if symptoms persist dexamethasone permanently discontinued	Day 1 of cycle or within cycle: maintain same dose level of pomalidomide as planned
Renal dysfunction			
CrCl <30 mL/min (MDRD formula)	Day 1 of cycle: delay Day 1 administration until CrCl returns to ≥30 mL/min[a] Within cycle: hold study treatment until improvement to ≥30 mL/min. Then re-start full dose isatuximab, same dose level of dexamethasone and pomalidomide up to planned Day 21. If delay is >3 days, omit isatuximab and dexamethasone.		
Any other drug related non-hematologic Grade 3-4 AE	Day 1 of cycle: delay Day 1 administration until recovery and apply same rules of dose modification than the rules below[a] 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 pomalidomide 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, pomalidomide discontinuation		

a 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 8.2.3)

b See Section 10.6.1 for IAR management

c Patients may have isatuximab 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 8.2.3)

8.2.3.4 Dose adjustments in Pd arm

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

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

Adverse event	Recommended action	
	Dexamethasone[a]	**Pomalidomide**
Platelets		
Thrombocytopenia Grade 3 without bleeding	Day 1 of cycle: delay until improvement ≥50 x 10^9/L[b] and administer at same dose level[c] Within cycle: maintain full dose of study treatment as planned	
Thrombocytopenia Grade 4 with or without bleeding	Day 1 of cycle: delay Day1 administration until improvement ≥50 x 10^9/L[b] and administer at the same dose level[c] Within cycle: maintain full dose of study treatment as planned Further episodes: same recommendations	Day 1 of cycle: delay Day 1 administration until recovery and decrease pomalidomide by one dose level[c] Within cycle: hold pomalidomide until bleeding is controlled and platelet recover ≥50 x 10^9/L, and then re-start with1 dose level decrease up to planned Day 21. Next cycle will be re-started with this one dose level decrease Second episode: same recommendation with decrease of pomalidomide by a second dose level Third episode: discontinue pomalidomide
Neutropenia		
Neutropenia Grade 3 (≥0.5 and <1.0 x 10^9/L)	Day 1 of cycle: delay until recovery ≥1.0 x 10^9/L and administer at same dose level[a] Within cycle: maintain the same dose level as planned	
Neutropenia Grade 4[d] (<0.5 x 10^9/)	Day 1 of cycle: delay until recovery ≥1.0 x 10^9/L and administer at the same dose level[c] Within cycle: maintain the same dose level as planned Further episodes: same recommendations	Day 1 of cycle: delay Day 1 administration until recovery and restart pomalidomide decreased by one dose level or consider G-CSF use and keep same dose level[c] Within cycle: hold pomalidomide until neutrophil counts recover ≥0.5 x 10^9/L and then: - re-start with1 dose level decrease up to planned Day 21. Next cycle will be re-started with this one dose level decrease - or consider G-CSF use and keep same dose level Second episode: same recommendations with decrease of pomalidomide by a second dose level Third episode, discontinue pomalidomide

Adverse event	Recommended action	
	Dexamethasone[a]	Pomalidomide
Febrile neutropenia and/or neutropenic infection	Day 1 of cycle: delay Day 1 administration until fever and infection recover and add G-CSF until ANC>1 x 10^9/L[c] Then administer D1 next cycle with dexamethasone at the same dose level and pomalidomide with dose recommendations below. Within cycle: omit dexamethasone, hold pomalidomide dose and add G-CSF until fever and infection have recovered and ANC>1 x 10^9/L. Then administer dexamethasone on the planned days at the same dose level and restart pomalidomide as planned on Day 21 with the dose modifications below: When fever/infection is resolved dexamethasone re-start at same dose. For pomalidomide: • First episode, resume same dose pomalidomide with G-CSF or re-start with 1 dose level decrease • Second episode, resume with action not done at first episode (same dose with G-CSF or 1 dose decrement pomalidomide) • Third episode, resume with one dose decrement of pomalidomide • Fourth episode, stop pomalidomide	

a Patients may have dexamethasone dose omission within a cycle if certain toxicities do not recover within 3 days following the day of planned infusion (see Section 8.2.3)

b For patients with plasma cells >50% of bone marrow 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 2-4, 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 2-4, D1 next cycle can be administered only if platelet counts ≥50 000/mm^3. For D1 administration beyond cycle 4, platelet counts should be ≥50 000/mm^3

c 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 8.2.3)

d If G4 neutropenia, assess ANC every 2-3 days until ANC ≥ 0.5 x 10^9/L and at least weekly thereafter until ANC ≥1.0 x 10^9/L

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

Table 6 - Guidelines for dose adjustments for non-hematologic toxicities - pomalidomide/dexamethasone combination

Adverse event	Recommended action	
	Dexamethasone[b]	Pomalidomide
DVT/PE		
Grade 3	Day 1 of cycle: initiate appropriate anticoagulation therapy and when efficient anticoagulation, administer cycle at the same dose level of dexamethasone and pomalidomide[a] Within cycle: Maintain same dose level of dexamethasone as planned. For pomalidomide: • First episode: hold pomalidomide, initiate appropriate anticoagulation therapy and restart same dose pomalidomide when efficient anticoagulation • Second episode: despite appropriate anticoagulation pomalidomide permanently discontinued	

Adverse event	Recommended action	
	Dexamethasone[b]	Pomalidomide
Grade 4	Day 1 of cycle: delay Day 1 administration until stabilization and administer at the same dose level[a] Within cycle: delay dexamethasone until stabilization and resume without dose reduction at the next planned dates. If delay is >3 days omit dexamethasone until next planned administration	Pomalidomide permanently discontinued.
Edema Grade ≥3 (limiting function and unresponsive to therapy or anasarca), excluding infusion associated reaction	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	Day 1 of cycle or within cycle: maintain same dose level of pomalidomide as planned
Allergic reaction/hypersensitivity (excluding infusion associated reaction)		
Grade 2	Hold study treatment until <Grade 2, and patient clinically stable; then, resume study treatment at full dose[a] For allergic reaction related to pomalidomide, refer to site local protocol	
Grade ≥3	Permanent discontinuation of the drug responsible for the allergic reaction.	
Infection without concomitant neutropenia	Hold study treatment until systemic treatment of infection complete. Resume all at the same dose level	
Herpes zoster	Hold study treatment until lesions are dry, then resume all at the same dose level	
Neuropathy		
Grade 2 with pain or Grade 3	Same dose level of dexamethasone	Hold pomalidomide until neuropathy improves to Grade ≤ 2 without pain. First episode: resume pomalidomide with a decrease of pomalidomide by 1 dose level Second episode: resume pomalidomide with a decrease by a second dose level Third episode: pomalidomide permanently discontinued
Grade 4	Same dose level of dexamethasone	Pomalidomide permanently discontinued
Confusion or mood alteration Grade ≥2 (interfering with function +/- daily activities)	Hold dexamethasone until symptoms resolve. Restart with 1 dose level reduction. If symptoms persist despite above measures, dexamethasone permanently discontinued	Day 1 of cycle or within cycle: maintain same dose level of pomalidomide as planned

Adverse event	Recommended action	
	Dexamethasone[b]	Pomalidomide
Gastrointestinal dyspepsia, gastric or duodenal ulcer, gastritis		
Grade 1-2 (requiring medical management)	Treat with H2 blockers, sucralfate, or omeprazole. If symptoms persist despite above measures, decrease dexamethasone dose by 1 dose level	Day 1 of cycle or within cycle: maintain full dose pomalidomide as planned
≥Grade 3 (requiring hospitalization or surgery)	Hold study treatment until symptoms adequately controlled. Then, restart the same dose level of pomalidomide, and decrease dexamethasone by one dose level of current dose along with concurrent therapy with H2 blockers, sucralfate, or omeprazole. If symptoms persist despite above measures, dexamethasone permanently discontinued	
Acute pancreatitis	Dexamethasone permanently discontinued Day 1 of cycle: delay Day 1 until recovery[a] and re-start the same dose level of pomalidomide Within cycle: hold all study treatment until recovery and re-start the same dose level of pomalidomide.	
Hyperglycemia ≥Grade 3	Treatment with insulin or oral hypoglycemics as needed. If uncontrolled despite above measures, decrease dose by one dose level until levels are satisfactory	Day 1 of cycle or within cycle: maintain the same dose level of pomalidomide as planned
Muscle weakness ≥Grade 2 (symptomatic and interfering with function +/- daily activities)	Decrease dexamethasone by one dose level. If weakness persists despite above measures decrease dose by one level. if symptoms persist dexamethasone permanently discontinued	Day 1 of cycle or within cycle: maintain same dose level of pomalidomide as planned
Renal dysfunction		
CrCl <30 mL/min	Day 1 of cycle: delay Day 1 administration until CrCl returns to ≥30 mL/min[a] Within cycle: hold study treatment until improvement to ≥30 mL/min. Then re-start the same dose level of dexamethasone and pomalidomide up to planned Day 21. If delay is >3 days omit dexamethasone.	
Any other drug related non-hematologic Grade 3-4 AE	Day 1 of cycle: delay Day 1 administration until recovery and apply same rules of dose modification than the rules below[a] 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 pomalidomide 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, pomalidomide discontinuation	

a 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 8.2.3)

b Patients may have dexamethasone dose omission within a cycle if certain toxicities do not recover within 3 days following the day of planned infusion (see Section 8.2.3)

8.2.4 Infusion reactions

Patients should routinely receive premedications prior to isatuximab infusion as detailed in Section 8.2.2 to reduce the risk and severity of IARs commonly observed with mAbs. Infusion associated reactions (for example, NCI-CTCAE version 4.03 terms 'infusion related reaction', 'allergic reaction', or 'cytokine release syndrome') are defined as AEs related to isatuximab with onset typically within 24 hours from the start of the infusion.

Patients who experience Grade 2 IAR(s) may resume isatuximab after recovery, at half of the initial infusion rate under close monitoring and supportive care as needed. Additional medication can be provided for symptom treatment as per Investigator judgment including diphenhydramine 25 mg IV (or equivalent) and methylprednisolone 100 mg IV. These patients must be informed of the potential risk of recurrent infusion associated reactions. The infusion must be completed within the time specified in the pharmacy manual.

Further treatment (subsequent isatuximab infusions) is to be started at the 175 mg/h initial infusion rate and follow the same rule in case of IAR.

Once a Grade 2 IAR leading to interruption has improved to Grade≤1, the infusion may be restarted at half (87.5 mg/h) the initial infusion rate. If symptoms do not recur after 30 minutes, the infusion rate may be increased in 50 mg/hour increments every 30 minutes, to a maximum of 400 mg/hour.

Patients with a Grade 3 or 4 isatuximab IAR must have isatuximab permanently discontinued and appropriate supportive therapy should be administered. Should an isatuximab IAR of Grade ≥2 occur, additional blood sampling during the AE is required for analysis of cytokine levels (TNFα, IL-1β, IL-6, IL-4 and IFNγ), markers of complement activation (C3a, C4 and CH50) and serum tryptase, the IAR and the therapy administered must be documented in the eCRF.

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

Table 7 - Management of infusion associated reaction

NCI-CTCAE version 4.03 criteria definition	Intervention recommendation
Mild (Grade 1) Infusion interruption or intervention not indicated	Continuation of isatuximab infusion per the judgment of the Investigator following close direct monitoring of the patient's clinical status. Isatuximab 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 infusion. Give additional medication with IV diphenhydramine 25 mg IV (or equivalent, see Section 8.2.2.2) and/ or IV methylprednisolone 100 mg (or equivalent) as needed. Isatuximab may be resumed only after patient recovery, with slower infusion rate and with close monitoring. Blood samples for additional safety labs will be collected. Important: additional blood sampling during the AE is required for analysis of cytokine levels (TNF-α, IL-4, IL-6, IL-1β, and IFN-γ), markers of complement activation (C3a, C4, CH50), serum tryptase
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 infusion. Give additional medication with diphenhydramine 25 mg IV (or equivalent, see Section 8.2.2.2) and/ or IV methylprednisolone 100 mg (or equivalent) and/or epinephrine as needed. Blood samples for additional safety labs will be collected. Definitive treatment discontinuation. Important: additional blood sampling during the AE is required for analysis of cytokine levels (TNF-α, IL-4, IL-6, IL-1β, and IFN-γ), markers of complement activation (C3a, C4, CH50), serum tryptase

Note: The infusion should be completed within the time specified in the pharmacy manual.

AE: adverse event; IAR: infusion associated reaction; IFN: interferon; IL: interleukin; IV: intravenous; NCI-CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events; NSAIDs: nonsteroidal anti-inflammatory drugs; TNF: tumor necrosis factor

8.2.5 Other toxicities

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

8.3 TUMOR LYSIS SYNDROME MANAGEMENT

Management of tumor lysis syndrome is detailed in Section 10.6.2.

8.4 BLINDING PROCEDURES

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

A centralized randomization system (IRT) will be used to prevent the investigators from knowing in advance the treatment assignment, as the randomization is the best method to avoid bias.

Despite the open-label administration of isatuximab, assessment of outcomes will be based on objectively collected data, which are radiological and laboratory assessments for tumor response by IRC blinded to study treatment groups.

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

8.5 METHOD OF ASSIGNING PATIENTS TO TREATMENT GROUP

All eligible patients will be randomly assigned to a treatment group (either IPd arm or Pd arm) in a 1:1 ratio using an IRT. Patient assignment to a treatment group will be performed according to a stratified randomization list according to age (<75 versus ≥75) and number of previous lines (2 or 3 versus more than 3).

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 central laboratory (or local, only if central results are not available) evaluations (serum or urine M-protein), the study site will contact the IRT. The site will enter the following information regarding the clinical site and study patient:

- Personal identifier number.
- Patient's date of birth (in line with country specific regulations).
- Number of previous lines of anti-MM treatment.
- Serum or urine M-protein laboratory value.

The information above will be used by IRT to assign the patients to the IPd or Pd arm according to the predefined randomization schedule.

Details of the IRT procedure will be provided in the IRT Site Manual.

All efforts should be made to start treatment within 3 working days even if a maximum up to 5 working days can be allowed.

8.6 PACKAGING AND LABELING

8.6.1 Isatuximab

Isatuximab (SAR650984) is packaged in 30 mL [redacted] glass vials fitted with elastomeric closure.

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

8.6.2 Dexamethasone IV/PO

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

For local commercial supplies, please refer to package insert for further details for formulation and handling purposes.

8.6.3 Pomalidomide

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

For local commercial supplies, please refer to package insert for further details for formulation and handling purposes.

8.7 STORAGE CONDITIONS AND SHELF LIFE

8.7.1 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.

8.7.2 Dexamethasone IV/PO

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

For local commercial supplies, please refer to package insert for further details for storage conditions.

8.7.3 Pomalidomide

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

For local commercial supplies, please refer to package insert for further details for storage conditions.

8.8 RESPONSIBILITIES

The Investigator, the Hospital Pharmacist, or other personnel allowed to store and dispense IMP will be responsible for ensuring that the IMP used in the clinical trial is securely maintained as specified by Sanofi and in accordance with the applicable regulatory requirements.

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

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

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

Under no circumstances will the Investigator supply the IMP to a third party, allow the IMPs to be used other than as directed by this Clinical Trial Protocol, or dispose of the IMPs in any other manner.

8.8.1 Treatment accountability and compliance

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

The person responsible for drug dispensing 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 pomalidomide and dexamethasone PO, a patient diary will be used to document all oral pomalidomide and dexamethasone drug administrations (except those administered by the study nurse/doctor).

8.8.2 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 IMP unless Sanofi provides written authorization.

8.9 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 CRF.

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).

8.9.1 Antithrombotic therapy

Pomalidomide increases the risk of venous thromboembolism. Anticoagulation prophylaxis is required after an assessment of each patient’s underlying risk factors. Unless there is an excess risk of bleeding, all patients should receive prophylactic antithrombotic treatment. If aspirin is contraindicated, patients will receive another form of antithrombotic therapy according to hospital guidelines or physician preference.

Aspirin prophylaxis is recommended for patients with standard risk and low-molecular weight heparin for patients with at least one risk factor (ie, history of prior venous thromboembolism, immobilization, concomitant use of an erythropoiesis-stimulating agent).

8.9.2 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 (ASCO) guidelines (2006) during the first 3 treatment cycles in order to decrease the risk of neutropenia specially in patients with baseline extensive bone marrow involvement and/or low neutrophil count (16).

8.9.3 Prohibited concomitant therapy

- Concurrent treatment with any other anti-myeloma therapy not specified in the protocol, including immunotherapy, hormonal therapy, targeted therapy or biological therapies, or 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 bone marrow 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 (or inhaled glucocorticosteroids whenever indicated), antihistamines, and analgesics, for the management of IARs are permitted.
- 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 haemophilus influenza.
- Avoid co-administration of strong inhibitors of CYP1A2:
  - Cinafloxacin
  - Ciprofloxacin
  - Enoxacin
  - Fluvoxamine
  - Oltipraz
  - Rofecoxib
  - Zafirlukast

8.9.4 Contraceptive measures and pregnancy counseling

Pomalidomide is structurally related to thalidomide. Pomalidomide was found to be teratogenic in both rats and rabbits when administered during the period of major organogenesis. If pomalidomide is taken during pregnancy, a teratogenic effect of pomalidomide in humans is expected. Therefore, a risk minimization plan to prevent pregnancy must be observed. All study participants must comply with the requirements of Pomalidomide Pregnancy Prevention Plan recommendations (Appendix L) or the country specific risk management plan in countries where pomalidomide is not supplied by the Sponsor.

Criteria for Females of Childbearing Potential

This protocol defines a FCBP as a sexually mature female who:
1) has not undergone a hysterectomy or bilateral oophorectomy or 2) has not been naturally postmenopausal for at least 24 consecutive months (ie, has had menses at any time in the preceding 24 consecutive months).

The investigator must ensure that:

- Females of childbearing potential comply with the conditions for pregnancy risk minimization, including confirmation that she has an adequate level of understanding.
- Females NOT of childbearing potential acknowledge that they understand the hazards and necessary precautions associated with the use of pomalidomide.

- Male patients taking pomalidomide acknowledge that they understand that traces of pomalidomide have been found in semen, that they understand the potential teratogenic risk if engaged in sexual activity with a FCBP or pregnant female, and that they understand the need for the use of a condom even if they have had a vasectomy.

Contraception

Females of childbearing potential enrolled in this protocol must agree to use two reliable forms of contraception simultaneously or to practice complete abstinence from heterosexual intercourse during the following time periods related to this study: 1) for at least 28 days before starting pomalidomide; 2) throughout the entire duration of pomalidomide treatment; 3) during dose interruptions; and 4) for at least 3 or 5 months after study treatment discontinuation for Pd and IPd respectively.

The two methods of reliable contraception must include one highly effective method and one additional effective (barrier) method. A FCBP must be referred to a qualified provider of contraceptive methods if needed. The following are examples of highly effective and additional effective methods of contraception:

- Highly effective methods:
  - Intrauterine device (IUD)
  - Hormonal (birth control pills, injections, implants)
  - Tubal ligation
  - Partner's vasectomy
- Additional effective methods:
  - Male condom
  - Diaphragm
  - Cervical Cap

Because of the increased risk of venous thromboembolism in patients with multiple myeloma taking pomalidomide and dexamethasone, combined oral contraceptive pills are not recommended. If a patient is currently using combined oral contraception the patient should switch to one of the effective method listed above. The risk of venous thromboembolism continues for 4 to 6 weeks after discontinuing combined oral contraception. The efficacy of contraceptive steroids may be reduced during co-treatment with dexamethasone.

Implants and levonorgestrel-releasing intrauterine systems are associated with an increased risk of infection at the time of insertion and irregular vaginal bleeding. Prophylactic antibiotics should be considered particularly in patients with neutropenia.

Pregnancy testing

Medically supervised pregnancy tests with a minimum sensitivity of 25 mIU/mL must be performed for FCBP, including FCBP who commit to complete abstinence, as outlined below.

Before starting pomalidomide

Female Patients:

Females of childbearing potential must have two negative pregnancy tests (sensitivity of at least 25 mIU/mL) prior to prescribing pomalidomide. The first pregnancy test must be performed within 10 to 14 days prior initiation of pomalidomide and the second pregnancy test must be performed within 24 hours prior pomalidomide administration. The patient may not receive pomalidomide until the Investigator has verified that the results of these pregnancy tests are negative.

Male Patients:

Must agree to practice complete abstinence or agree to use a condom during sexual contact with pregnant females or FCBP throughout the entire duration of pomalidomide treatment, during dose interruptions and for at least 3 or 5 months following study treatment discontinuation for Pd and IPd respectively, even if he has undergone a successful vasectomy.

During study participation and up to 3 or 5 months following study treatment discontinuation

Female Patients:

- Females of childbearing potential with regular or no menstrual cycles must agree to have pregnancy tests weekly for the first 28 days of pomalidomide treatment, including dose interruptions and then every 28 days throughout the remaining duration of pomalidomide treatment, including dose interruptions, at pomalidomide discontinuation, and monthly up to 3 or 5 months following study treatment discontinuation for Pd and IPd respectively. If menstrual cycles are irregular, the pregnancy testing must occur weekly for the first 28 days of pomalidomide treatment, including dose interruptions, and then every 14 days throughout the remaining duration of pomalidomide treatment, including dose interruptions, at pomalidomide discontinuation, and at Days 14 and monthly up to 3 or 5 months following study treatment discontinuation for Pd and IPd respectively.
- At each visit, the Investigator must confirm with the FCBP that she is continuing to use two reliable methods of birth control at each visit during the time that birth control is required.
- If pregnancy or a positive pregnancy test does occur in a study patient, pomalidomide must be immediately discontinued.
- Pregnancy testing and counseling must be performed if a patient misses her period or if her pregnancy test or her menstrual bleeding is abnormal. Pomalidomide treatment must be temporarily discontinued during this evaluation.
- Females must agree to abstain from breastfeeding during study participation and for at least 3 or 5 months after study treatment discontinuation for Pd and IPd respectively.

Male Patients:

- Must practice complete abstinence or use a condom during sexual contact with pregnant females or FCBP throughout the entire duration of pomalidomide treatment, during dose interruptions and for at least 3 or 5 months following study treatment discontinuation for Pd and IPd respectively, even if he has undergone a successful vasectomy.
- If pregnancy or a positive pregnancy test does occur in the partner of a male study patient during study participation, the investigator must be notified immediately.
- Male patients should not donate semen or sperm during therapy or for at least 3 or 5 months following discontinuation of study treatment for Pd and IPd respectively.

Additional precautions

- Female caregivers of childbearing potential should not touch the pomalidomide capsules or bottles unless they are wearing gloves.
- Patients should be instructed never to give pomalidomide to another person.
- Patients should not donate blood during therapy and for at least 3 or 5 months following discontinuation of study treatment for Pd and IPd respectively.
- Only enough pomalidomide for one cycle of therapy may be prescribed with each cycle of therapy.
- Any unused pomalidomide must be returned as instructed in the Pomalidomide Pregnancy Prevention Plan (Appendix L) or the country specific risk management plan in countries where pomalidomide is not supplied by the Sponsor.

9 ASSESSMENT OF INVESTIGATIONAL MEDICINAL PRODUCT

9.1 PRIMARY ENDPOINT

The primary endpoint is Progression Free Survival (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.

The following disease assessment procedures will be performed at screening (for eligibility) and **again** prior to (within 24 hours) the start of study treatment administration at Cycle 1 Day 1 (baseline for response assessment) and then Day 1 of every cycle during treatment up to progression and for patients who discontinue study treatment for reasons other than progression, every 4 weeks during follow-up until PD:

- M-protein quantification (serum and 24-hour urine, protein immunoelectrophoresis and immunofixation) (local and central laboratory). After C1D1, immunofixation will be done in case of undetectable M protein (serum and urine)
- Free light chains quantification (local and central laboratory).
- Quantitative immunoglobulins (local and central laboratory)
- Other examinations for disease assessment will be done as below:
- Bone marrow aspiration (or biopsy as clinically indicated) at baseline, and then to confirm response (local laboratory, and in case of CR central laboratory will be done to assess MRD)
- Bone disease assessment:
  - Skeletal survey (including skull, spine, all long bones, pelvis and chest) or low-dose whole-body 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 or documented extramedullary disease (plasmacytoma) at baseline, CT scan or MRI is to be done at baseline and to be repeated every 12 weeks (±1 week), 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 assessment or extramedullary disease, the same modality (skeletal survey or low-dose whole-body CT; CT or MRI) should be used throughout the study for each individual patient.

    All imaging to be sent for central review.

Efficacy assessments leading to treatment continuation will be performed according to local laboratory results and based on the Investigator assessment. Efficacy assessments for the primary and secondary endpoints will be performed on the basis of central laboratory findings on Day 1 of every cycle. Response/progression will be determined according to IMWG criteria (Appendix D). Response/progression based on paraprotein will be confirmed based on 2 consecutive assessments. A blinded IRC will evaluate disease assessments at each cycle and determine the progression and response status of each patient per IMWG (Appendix D) and as described in the IRC Charter. 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.

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

- Increase of ≥25% in Serum M-component from nadir (the absolute increase must be ≥0.5 g/dL) in 2 consecutive assessments; 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 h) in 2 consecutive assessments 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 will not be considered progression in the primary analysis of PFS and 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 D for assessment of progression and overall response.

9.2 KEY SECONDARY EFFICACY ENDPOINTS

Two key secondary efficacy endpoints are considered:

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

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

Overall survival (OS): is defined as the time from the date of randomization to date of death from any cause.

9.3 OTHER SECONDARY ENDPOINTS

9.3.1 Other secondary efficacy endpoints

Other secondary efficacy endpoints will be evaluated as follows:

Time to Progression (TTP): is defined as the time from the date of randomization to the date of first documentation of PD (as determined by IRC). The same definition of progression as for the PFS endpoint will be used.

PFS in the high risk cytogenetic population: is defined as PFS as defined in Section 9.1 in the subgroup of patients carrying high risk cytogenetic changes including del(17p), t(4;14) or t(14;16) assessed by FISH.

Duration of response (DOR): is defined as the time from the date of the first IRC determined response to the date of first IRC PD or death, whichever happens first. Duration of response is determined only for patients who have achieved a response of ≥PR.

9.3.2 Safety endpoints

Safety in terms of treatment-emergent adverse events/serious adverse events (TEAE/SAE), laboratory parameters, vital signs (blood pressure, heart rate and temperature), weight, ECOG performance status, and physical examination will be assessed throughout the study and will be reported in the eCRF.

Adverse event data will be collected by reporting at specified intervals throughout the study. TEAEs are defined as AEs that develop, worsen (according to the Investigator opinion), or become serious during the TEAE period. The TEAE period is defined as the time from first dose of study treatments up to 30 days after last dose of study treatments. Adverse events and laboratory parameters will be graded using NCI-CTC v4.03 (Appendix C).

Specific safety laboratory tests are planned in case of infusion reaction (see study flow chart in Section 1.2 and Section 10.6.1).

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

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

Patient-reported outcome measures to be included are the European Organisation 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.

Timing of Assessments

All three questionnaires have been designed for self-completion.

Cycle 1 Day 1 (prior to study treatment administration) will serve as the baseline assessment for all patients. All the electronic patient-reported outcomes (ePROs) are to be completed by the patient using the tablet provided via the study, before other clinician assessments are conducted, and before his/her clinical condition, treatment plan, AEs, etc are discussed. The latter is to ensure the objectivity of the patient responses free from their emotional reactions to prevent bias. The patient is to complete ePRO questionnaires on his or her own.

There will be a minimum of 20 minutes time allocated to train patients on ePRO technology at Cycle 1 Day 1 visit. Training assistance will be provided for subsequent cycles, EOT, and follow-up if the patient requests a refresher.

While on treatment, ePROs are to be administered prior to treatment on Day 1 of every cycle, at the EOT visit and at 60 (±5 days) days after last study treatment administration. The time estimated to complete the EORTC QLQ-C30 and the EORTC QLQ-MY20 is approximately 10-15 minutes. The time estimated to complete the EQ-5D-5L is approximately 5 to 10 minutes.

In order to optimize compliance of the patient, and to ensure the completeness of the ePRO data, it is recommended that a key person (eg, research nurse) is assigned and responsible at each center for ePRO data collection.

A statistical analysis plan for the three ePROs will be detailed in the SAP.

9.3.3.1 EORTC QLQ-C30

The EORTC QLQ-C30 is a cancer-specific instrument that contains 30 items and provides a multi-dimensional 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, impact of symptoms and of toxicities). 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 both multi-item scales and single-item measures. These include five functional scales (physical, role, emotional, cognitive, and social functioning), three symptom scales (fatigue, nausea and vomiting, and pain), a Global Health Status (GHS)/ quality of life scale, and 6 single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). 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 functioning/HRQL, where a higher score for symptoms/ items represents a higher level of symptomatology/problems. The recall period for this instrument is 1 week.

9.3.3.2 EORTC QLQ-MY20

The EORTC QLC-MY20 will be administered in conjunction with the EORTC QLQ-C30 to assess disease- and treatment-specific symptoms and side effects in patients with multiple myeloma (21, 22).

The MY20 contains 20 items, 4 independent subscales covering 2 functional domains (Future Perspective and Body Image) and 2 symptom scales (Disease Symptoms and Side Effects of Treatment). 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 two instruments together (50 items) take approximately 15 minutes on average to administer. The instruments have been validated and used in many countries.

9.3.3.3 EQ-5D-5L

The EQ-5D-5L is a standardized measure of health status that provides a general assessment of health and wellbeing. For this study, the updated 2011 version will be used.

The instrument is composed of a descriptive section that includes the 5 dimensions and a VAS. The EQ-5D descriptive system comprises 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has a 5-level response: no problems, slight problems, moderate problems, severe problems, and extreme problems. The EQ VAS records the respondent's self-rated health on a 20 cm vertical, visual analogue scale with endpoints labelled 'the best health you can imagine' and 'the worst health you can imagine'. This information provides a quantitative measure of health as judged by the individual respondents.

Response options are measured with a 5-point Likert scale (for the 5L version). Global scores are available while higher scores indicate better HRQL.

9.3.4 Pharmacokinetics

Pharmacokinetics samples will be collected for isatuximab, and therefore will be done only in IPd arm.

9.3.4.1 Sampling time

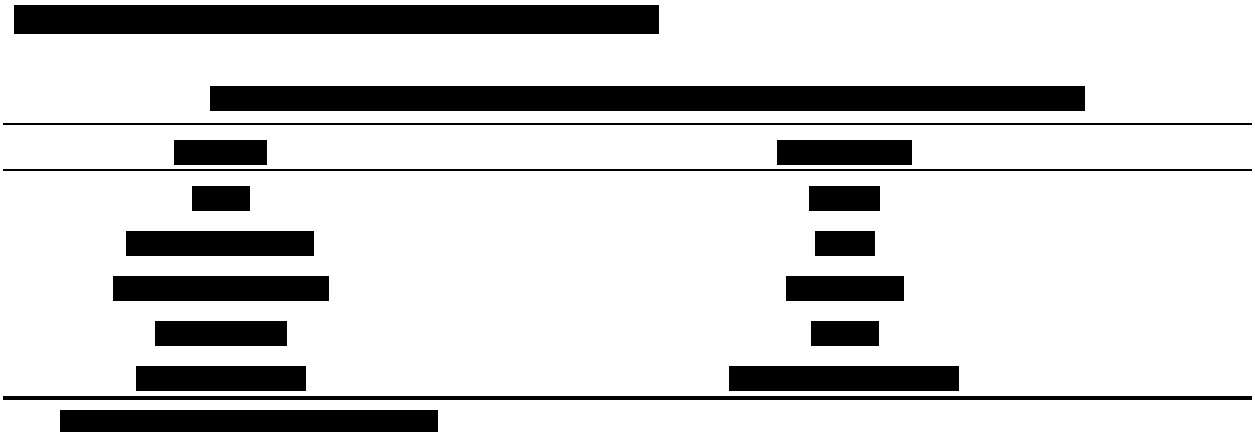
It is of utmost importance to collect all blood samples at the specified times and according to the specifications.

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

9.3.4.2 Pharmacokinetics handling procedure

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

9.3.4.3 Bioanalytical method



9.3.4.4 Pharmacokinetics parameters

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 pharmacokinetic parameters estimates and the assessments of pathophysiologic covariate effects on CL and possibly on volume if warranted. Empirical Bayesian estimation of individual parameters and of individual exposure (AUCs) will also be performed. The PK estimates will then be investigated as prognostic factors for clinical outcome including safety and efficacy endpoints, if possible.

9.3.5 Immunogenicity

9.3.5.1 Anti-drug antibodies

Human anti-drug antibodies (ADA) to isatuximab will be assessed throughout the study for the IPd arm only. Blood samples will be collected for ADA detection according to the Flow Charts (see Section 1.2 and Section 1.3). The sampling times for ADA detection can be modified based on the updated knowledge of isatuximab on immunogenicity.

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.

In case of positivity or inconclusive sample at 60 days post last isatuximab administration, additional assessment of ADA will be performed at 90 days and then every 30 days until the sample is negative. If isatuximab is stopped prior to pomalidomide and dexamethasone, ADA will be tested on D1 of the 2 next cycles. If ADA test at the second cycle administered without isatuximab is positive or inconclusive, ADA testing will be repeated every cycle until negative.

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

Transient ADA response:

- Treatment-induced ADA detected only at one 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 two 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 two 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 of 16 weeks or longer or,
- Treatment-induced ADA incidence only in the last sampling time point of the treatment study period or at a sampling time point with less than 16 weeks before an ADA-negative last sample.

9.4 EXPLORATORY ENDPOINTS

9.4.1 Pharmacogenetic assessment

[redacted]

9.4.3 Minimal residual disease

Minimal residual disease (MRD) will be assessed by next-generation sequencing in bone marrow samples from patients who achieve CR, to determine the depth of response at the molecular level. Bone marrow aspirates will be collected at baseline/screening and the time of CR confirmation. If the patient presents with CR but is determined MRD positive, another bone marrow 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 bone marrow samples are to be obtained.

9.5 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, metabolism or related to MM.

These other research analyses will help to understand either disease subtypes or drug response, or to develop and/or validate a bioassay method, 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 five years after completion of the final study report. After that period, any samples remaining will be destroyed.

9.6 APPROPRIATENESS OF MEASUREMENTS

Each of the efficacy and safety assessments chosen for use in this study are 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 (or 28 days for FCBP), 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.

The following procedures are to be performed/assessed:

- Signed informed consent.
- Contraception counselling for FCBP and partner (28 days prior to randomization).
- Demography (age, gender, ethnicity, and race) and medical/surgical history (other than multiple myeloma; including smoking status).
- Myeloma history and prior anti-myeloma treatment (including date of initial diagnosis of symptomatic multiple myeloma, stage and type of disease at diagnosis and study entry, heavy and light chain component, previous anti-myeloma therapy - including drug name, transplant dates, intent, date of progression, best response and reason for discontinuation).
- Physical examination to be performed at screening to include examination of main body systems including neurological, digestive exam, respiratory (signs and symptoms, respiratory rate), hepatic and spleen span, lymph node examination, weight and height (height at baseline only).
- Vital signs including blood pressure, heart rate and body temperature.
- Prior medication use within 21 days prior randomization.
- 12-lead ECG.
- ECOG PS.
- All AEs/SAEs occurring after signed informed consent for all patients.

Local laboratory assessments

- Pregnancy test (urine or serum; with a minimum sensitivity of 25 mIU/mL) to be performed within 10 to 14 days prior first study treatment administration for FCBP.

- Blood chemistry: to be done at screening: SGOT (AST), SGPT (ALT), bilirubin (total and direct), alkaline phosphatase, lactate dehydrogenase (LDH), sodium, potassium, chloride, bicarbonate/carbon dioxide, 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 (including ANC), and platelet count.
- Coagulation: prothrombin time, international normalized ratio, and activated partial thromboplastin time.
- Quantitative urinalysis: red blood cells, leukocytes, protein, glucose, ketone, pH, bilirubin.
- Thyroid function tests: TSH, T3 and T4.
- Serum β2-microglobulin.

Disease assessment:

- Laboratory disease assessment (local and central laboratory): measurable disease for eligibility will be assessed on central laboratory results.
  - Serum M-protein (immunoelectrophoresis and immunofixation),
  - Urine M-protein (immunoelectrophoresis and immunofixation),
  - Serum free light chains (sFLC, quantification and ratio),
  - Immunoglobulins: IgG, IgA, IgM, IgD and IgE (IgD or IgE only if the heavy chain component of the disease is known to be IgE or IgD).
- Bone marrow aspirate (or biopsy as clinically indicated):
  - Bone marrow aspirate (BMA) for FISH including but may not be limited to (t(4;14), t(14;16), del(17q) to determine risk status (central laboratory). If local FISH assessment is done using purified CD138+ plasma cells or by cIg FISH, the most recent local FISH report will be collected in patients who fail central FISH testing, for a central review,
  - BMA for MRD assessment (central laboratory),
  - Bone marrow plasma cell infiltration (local laboratory).
- Bone disease assessment:
  - Skeletal survey (including skull, spine, all long bones, pelvis and chest) or low-dose whole-body 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 or documented extramedullary disease (plasmacytoma) at baseline, CT scan or MRI is to be done at baseline and to be repeated every 12 weeks (±1 week), to confirm CR, and if clinically indicated.

Note: for bone lesion assessment or extramedullary disease, the same modality (skeletal survey or low-dose whole-body CT; CT or MRI) should be used throughout the study for each individual patient.

All imaging to be sent for central review.

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.

Results for central serum and urine M-protein must be available before the patient may be randomized. In the absence of central lab results, sites may use local laboratory results for eligibility. Central laboratory results may not be available due to (but not limited to) the following reasons: samples were not able to be analyzed by central lab (for various reasons) or lab-dependent decisions needed for patient treatment had to be made before the availability of central lab results.

All eligible patients must be randomized by contacting the IRT (see Section 8.4).

The results of the screening examinations will be recorded in each patient's CRF. Source documentation to support the screening results must be maintained in the patient's medical record. All efforts should be made to start treatment within 3 working days even if a maximum up to 5 working days can be allowed.

10.1.3 Treatment period

10.1.3.1 Cycle 1 (Day 1, Day 8, Day 15 and Day 22 all ±1 day)

The following procedures are to be performed/assessed/completed **within 24 hours prior to the start of study treatment on Day 1 in both arms unless specified otherwise**:

- Physical examination to be performed within 24 hours prior to study treatment administration: main diagnoses to be reported in the eCRF as AEs and newly occurring laboratory abnormalities to be recorded in laboratory pages.
- Vital signs including blood pressure, heart rate and body temperature on D1, D8, D15, and D22. In addition in IPd arm, prior to start of each isatuximab infusion, 1 hour after start of each infusion and at the end of each infusion.
- ECOG PS on D1, D8, D15, and D22.
- Study treatment administration.
- ePROs (EORTC QLQ-C30, MY20 and EQ-5D-5L).
- All AEs/SAEs throughout the cycle.
- Concomitant medications from randomization and used throughout the cycle.
- Second primary malignancies.

- Patient diaries for oral study treatment (dexamethasone when taken orally and pomalidomide; except for study treatment doses administered by the study nurse/doctor).
- Contraception and counselling for FCBP and partner (Day 1).
- Thromboprophylaxis as described in Section 8.9.1.

Local laboratory assessments

- Pregnancy test (urine or serum; with a minimum sensitivity of 25 mIU/mL) to be performed and results available on Day 1 within 24 hours prior to study treatment start and then weekly (independently of treatment delay/hold) for FCBP.
- Blood chemistry to be assessed within 24 hours prior to study treatment administration on Day 1, Day 8, Day 15, and Day 22: SGOT (AST), SGPT (ALT), bilirubin (total and direct), alkaline phosphatase, lactate dehydrogenase (LDH), sodium, potassium, chloride, bicarbonate/carbon dioxide, 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, to be assessed weekly within 24 hours prior to study treatment administration on Day 1, Day 8, Day 15, and Day 22: hemoglobin, hematocrit, RBC, WBC with differential (including ANC), and platelet count. If G4 neutropenia, assess ANC every 2-3 days until ANC ≥0.5 x 109/L and at least weekly thereafter until ANC ≥1.0 x 109/L.

Central and local laboratory disease assessment

Value of the tests performed/completed prior to study treatment administration on Cycle 1 Day 1 will be the reference value to assess response during study treatment. The following are to be performed within 24 hours prior to study treatment administration on Day 1:

- Serum M-protein (immunoelectrophoresis and immunofixation).
- Urine M-protein (immunoelectrophoresis and immunofixation).
- Serum free light chains (sFLC, quantification and ratio).
- Immunoglobulins: IgG, IgA, IgM, IgD and IgE (IgD or IgE only if the heavy chain component of the disease is known to be IgE or IgD).

Central laboratory assessments

[redacted]

IPd arm only

- IAR laboratory tests on Day 1 prior to first isatuximab administration: (TNF- α, IL-1-β, IL-4, IL-6, and IFN-γ). If a isatuximab infusion associated reaction of Grade ≥2 occurs during the cycle, additional blood sampling during the AE is required for analysis of cytokine release (TNF-α, IL-1-β, IL-4, IL-6, and IFN-γ), markers of complement activation (C3a, C4, CH50), serum tryptase (central laboratory).

- Blood sample collection for PK/PDy and ADA evaluation (see Section 1.3) (central laboratory).
- Antibody screening test **before the first isatuximab dose**: Blood typing and complete blood phenotyping (C,c; E,e; Kell. Kidd; Duffy; S,s is recommended, if not available follow site's standard) if not already done, and antibody screening (Indirect Coombs Test/Indirect Antiglobulin Test [IAT]). Blood type card will be kept by the patient with the study card and the blood bank needs to be informed that the patient is receiving a treatment with an anti-CD38 and a potential interference with the Indirect Coombs test is possible (Appendix K).
- One additional blood sample will be collected for testing potential interference of isatuximab with the M protein assessment. The sample will be collected at the same time as for serum M protein sample above (central laboratory).

If clinically indicated only:

- Coagulation at any time during the cycle.
- Qualitative urinalysis: blood, leukocytes, protein, glucose, ketone, pH, bilirubin at any time during the cycle.
- Thyroid function tests (TSH, T3 and T4) at any time during the cycle.
- Markers for TLS (uric acid, creatinine, potassium, phosphate, calcium and corrected calcium) at any time during the cycle.
- Any other exams clinically indicated.
- Disease assessment (BM, radiological, laboratory). The same method of assessment as at baseline is to be used throughout the study.

10.1.3.2 Subsequent cycles (Day 1 and 15)

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

- Physical examination to be performed within 24 hours prior to study treatment administration: main diagnoses to be reported in the eCRF as AEs and newly occurring laboratory abnormalities to be recorded in laboratory pages.
- Vital signs including blood pressure, heart rate and body temperature. In addition in IPd arm, prior to start of each isatuximab infusion, 1 hour after start of each infusion and at the end of each infusion on D1 and on D15 up to and including Cycle 4 and as clinically indicated.
- 12-lead ECG at C2D1 pre-dose.
- ECOG PS.
- Study treatment administration.
- ePROs (EORTC QLQ-C30, MY20 and EQ-5D-5L).

- All AEs/SAEs throughout the cycles.
- Concomitant medications used throughout the cycle.
- Second primary malignancies.
- Patient diaries for oral study treatment (dexamethasone when taken orally and pomalidomide; except for study treatment doses administered by the study nurse/doctor).
- Contraception and counselling for FCBP and partner (Day 1).
- Thromboprophylaxis as described in Section 8.9.1.

Local laboratory assessments

- Pregnancy test (urine or serum; with a minimum sensitivity of 25 mIU/mL) for FCBP every 4 weeks with results available prior to study treatment administration on Day 1 if regular menstruation and every 2 weeks if irregular menstruation even in case of treatment delay/hold.
- Blood chemistry to be assessed within 24 hours prior to study treatment administration on Day 1: SGOT (AST), SGPT (ALT), bilirubin (total and direct), alkaline phosphatase, lactate dehydrogenase (LDH), sodium, potassium, chloride, bicarbonate/carbon dioxide, 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, to be assessed within 24 hours prior to study treatment administration on Day 1 and Day 15 at Cycle 2 and Cycle 3 and then within 24 hours prior to study treatment administration on Day 1 and as clinically indicated: hemoglobin, hematocrit, RBC, WBC with differential (including ANC), and platelet count. If G4 neutropenia, assess ANC every 2-3 days until ANC $\geq 0.5 \times 10^9$/L and at least weekly thereafter until ANC $\geq 1.0 \times 10^9$/L.
- Thyroid function tests (TSH, T3 and T4) once a year and at any time during the cycle if clinically indicated.
- IAT on Cycle 2 Day 1 (IPd arm only); if the test is not performed at this visit, it can be done at the next blood sampling. Additional IAT data will be collected whenever a blood transfusion is needed.

Disease assessment

Investigator decision to continue study treatment or not will be done on local laboratory efficacy data (except in selected country[ies] where central laboratory results are available on an ongoing basis [in which case, one sample will be collected at each timepoint]) plus radiological and bone marrow assessments when planned by the protocol or if indicated according to IMWG criteria.

- Local and Central laboratories to be assessed within 24 hours prior to study treatment administration on Day 1 of each cycle (reference value to assess response will be value from the lab taken on Cycle 1 Day 1):

- Serum M-protein: immunoelectrophoresis and if M protein undetectable, immunofixation will be performed?
- Urine M-protein: immunoelectrophoresis and if M protein undetectable, immunofixation will be performed. If urine M-protein is negative (negative immunofixation) at screening and Cycle 1 Day 1, this assessment is to be repeated every 3 cycles only (Cycle 4, Cycle 7, Cycle 10, etc.) and to confirm CR,
- A sample for FLC assay is to be obtained on Day 1 of every cycle; samples to be centrally analyzed only in case of CR (M-protein undetectable in SPEP/UPEP and negative immunofixation),
- Immunoglobulins: IgG, IgA, IgM, IgD and IgE (IgD or IgE only if the heavy chain component of the disease is known to be IgE or IgD).

- Bone marrow aspirate (or biopsy as clinically indicated):
  - Bone marrow plasma cell infiltration (local laboratory) to confirm CR, or if suspicion of disease progression in the absence of biochemical progression and as clinically indicated,
  - BMA for MRD assessment in case of CR (central laboratory). In case of MRD positive, another bone marrow 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 bone marrow samples are to be obtained.
- Bone disease assessments:
  - Skeletal survey or low-dose whole-body CT scan once a year and anytime during the study if clinically indicated.
- Extramedullary disease (plasmacytoma) assessment (including bone plasmacytoma):
  - If known extramedullary disease, CT scan or MRI is to be repeated every 12 weeks (±1 week), to confirm CR, 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 assessment or extramedullary disease, the same modality (skeletal survey or low-dose whole-body CT; CT or MRI) should be used throughout the study for each individual patient.

    All imaging to be sent for central review.

IPd arm only

- If a isatuximab infusion associated reaction of Grade ≥2 occurs during the cycle, additional blood sampling during the AE is required for analysis of cytokine release (TNF-α, IL-1-β, IL-4, IL-6, and IFN-γ), markers of complement activation (C3a, C4, CH50), serum tryptase (central laboratory).

- Blood sample collection for PK/PDy and ADA evaluation (see Section 1.3) (central laboratory).
- One additional blood sample will be collected for testing potential interference of isatuximab with the M protein assessment. The sample will be collected at the same time as for serum M protein sample above (central laboratory).

If clinically indicated only:

- Coagulation at any time during the cycle.
- Qualitative urinalysis: blood, leukocytes, protein, glucose, ketone, pH, bilirubin at any time during the cycle.
- Markers for TLS (uric acid, creatinine, potassium, phosphate, calcium and corrected calcium) at any time during the cycle.
- Any other exams clinically indicated.

10.1.4 End of treatment

The EOT visit will occur 30 days after last study treatment administration or prior to start of further anti-myeloma therapy, whichever comes first

The following procedures are to be performed at the EOT visit:

- Physical examination.
- Vital signs.
- 12-lead ECG.
- ECOG PS.
- ePROs (EORTC QLQ-C30, 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.
- Second primary malignancies.

Local laboratory tests

- Pregnancy test (urine or serum; with a minimum sensitivity of 25 mIU/mL) for FCBP.
- Blood chemistry: SGOT (AST), SGPT (ALT), bilirubin (total and direct), alkaline phosphatase, lactate dehydrogenase (LDH), sodium, potassium, chloride, bicarbonate/carbon dioxide, 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 (including ANC), and platelet count. If G4 neutropenia, assess ANC every 2-3 days until ANC ≥0.5 x 10^9/L and at least weekly thereafter until ANC ≥1.0 x 10^9/L.
- Thyroid function tests (TSH, T3 and T4).

Disease assessment

Investigator decision to discontinue study treatment due to PD will be done on local laboratory efficacy data plus radiological and bone marrow assessments when planned by the protocol or if indicated according to IMWG criteria.

- Local and Central laboratories
  - Serum M-protein: immunoelectrophoresis and if M protein undetectable, immunofixation will be performed
  - Urine M-protein: immunoelectrophoresis and if M protein undetectable, immunofixation will be performed,
  - Serum free light chains (sFLC, quantification and ratio),
  - Immunoglobulins: IgG, IgA, IgM, IgD and IgE (IgD or IgE only if the heavy chain component of the disease is known to be IgE or IgD),
  - Bone marrow aspirate (or biopsy as clinically indicated):
    - Bone marrow plasma cell infiltration (local laboratory) to confirm CR, or if suspicion of disease progression in the absence of biochemical progression and as clinically indicated,
    - MRD assessment in case of CR if indicated (central laboratory).
- Radiological disease assessments if needed for bone disease assessment or extramedullary disease assessment.

IPd arm only

- Blood sample collection for PK/PDy and ADA evaluation (see Section 1.3).
- One additional blood sample will be collected for testing potential interference of isatuximab with the M protein assessment. The sample will be collected at the same time as for serum M protein sample above (central laboratory).

10.1.5 Post treatment follow up

10.1.5.1 60 days visit

The following procedures are to be performed 60±5 days after the last study treatment:

- AE assessment: related AEs and all serious AEs (regardless of relationship to study treatment) ongoing at the time of study treatment discontinuation will be followed until resolution or stabilization. All (serious or non-serious) new AEs related to study treatment will be collected and followed until resolution or stabilization.

- Further anti-myeloma therapy.
- Second primary malignancies.
- Survival status.
- ePROs (EORTC QLQ-C30, MY20 and EQ-5D-5L).
- ECOG PS.
- Pregnancy test (urine or serum; with a minimum sensitivity of 25 mIU/mL) for FCBP will be done monthly up to 3 or 5 months after last study treatment (local laboratory) for Pd and IPd respectively.

IPd arm only:

- One ADA sample should be drawn 60 ±5 days after the last study treatment administration (see Section 1.3).

Disease assessment (only for patients without confirmed disease progression at the Day 60 visit, including patients who would have initiated further anti-myeloma therapy without PD)

- Central and local laboratory tests
  - Serum M-protein: immunoelectrophoresis and if M-protein undetectable, immunofixation will be performed,
  - Urine M-protein: immunoelectrophoresis and if M-protein undetectable, immunofixation will be performed,
  - Serum free light chains in case of CR (sFLC, quantification and ratio),
  - Immunoglobulins: IgG, IgA, IgM, IgD and IgE (IgD or IgE only if the heavy chain component of the disease is known to be IgE or IgD),
  - One additional blood sample will be collected for testing potential interference of isatuximab with the M protein assessment for patient treated in IP arm. The sample will be collected at the same time as for serum M protein sample above (central laboratory only).
- If needed BMA (or biopsy as clinically indicated):
  - Bone marrow plasma cell infiltration (local laboratory) to confirm CR, or if suspicion of disease progression in the absence of biochemical progression and as clinically indicated,
  - BMA for MRD assessment in case of CR (central laboratory).
- Bone disease assessments (skeletal survey or low-dose whole-body CT scan) if applicable.
- Extramedullary disease (plasmacytoma) assessment (CT scan or MRI, including bone plasmacytoma) if applicable.

  Note: for bone lesion assessment or extramedullary disease, the same modality (skeletal survey or low-dose whole-body CT; CT or MRI) should be used throughout the study for each individual patient.

  All imaging to be sent for central review.

10.1.5.2 Further follow-up visits (Day 90±7 days after last study treatment administration and then every 3 months [±7 days])

Pregnancy tests (urine or serum; with a minimum sensitivity of 25 mIU/mL) for FCBP will be done monthly up to 3 or 5 months after last study treatment (local laboratory) for Pd and IPd respectively.

IPd arm only, if ADA is positive or inconclusive at 60 days, repeat samples will be taken every 30 ±7 days until the results become negative (see Section 1.3)

For patients with confirmed disease progression (at EOT or during follow-up): the post-treatment follow-up period includes visits every 3 months (±7 days) after administration of the last study treatment.

The following procedures are to be performed during the post-treatment follow up period:

- AE assessment: related AEs and all serious AEs (regardless of relationship to 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 will be collected and followed until resolution or stabilization.
- Further anti-myeloma therapy.
- Survival status.
- Second primary malignancies.

For patients discontinued without disease progression (including patients who would have initiated further anti-myeloma therapy without PD): the post-treatment follow-up period includes visits every month after last study treatment administration. The following procedures are to be performed up to PD (after PD, FU visit will be done every 3 months [±7 days] as described above):

Disease assessment

- Central and local laboratory tests
  - Serum M-protein: immunoelectrophoresis and if M protein undetectable, immunofixation will be performed,
  - Urine M-protein: immunoelectrophoresis and if M protein undetectable, immunofixation will be performed,
  - Serum free light chains in case of CR (sFLC, quantification and ratio),
  - Immunoglobulins: IgG, IgA, IgM, IgD and IgE (IgD or IgE only if the heavy chain component of the disease is known to be IgE or IgD).
- Bone marrow aspirate (or biopsy as clinically indicated):
  - Bone marrow plasma cell infiltration (local laboratory) to confirm CR, as clinically indicated,

  - BMA for MRD assessment in case of CR (central laboratory).
- Bone disease assessments if applicable:
  - Skeletal survey or low-dose whole-body CT scan once a year and anytime during the study if clinically indicated.
- Extramedullary disease (plasmacytoma) assessment (including bone plasmacytoma) if applicable:
  - If known extramedullary disease, CT scan or MRI is to be repeated every 12 weeks (±1 week), to confirm CR, 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 assessment or extramedullary disease, the same modality (skeletal survey or low-dose whole-body CT; CT or MRI) should be used throughout the study for each individual patient.

    All imaging to be sent for central review.
- AE assessment: related AEs and all serious AEs (regardless of relationship to 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 new related AEs (regardless of seriousness) will be collected and followed until resolution or stabilization.
- Further anti-myeloma therapy.
- Survival status.
- Second primary malignancies.

10.1.6 Post PFS study cut-off date

For Japan only, please refer to Appendix N for data collection after the primary PFS analysis cut-off date.

Patients still on treatment at the PFS cut-off date will continue study treatment until at least 1 treatment discontinuation criterion as defined in Section 10.3.2 is met. The following information will be collected during the study treatment administration:

- Study treatment administration.
- Physical examination: main diagnoses to be reported in the eCRF as AEs and newly occurring laboratory abnormalities to be recorded in laboratory pages.
- Vital signs including blood pressure, heart rate and body temperature. In addition in IPd arm, prior to start of each isatuximab infusion, 1 hour after start of each infusion and at the end of each infusion on Day 1 and on Day 15 up to and including cycle 4 and as clinically indicated.
- ECOG PS.
- Concomitant medications used throughout the cycle.
- Second primary malignancies.

- Patient diaries for oral study treatment (dexamethasone when taken orally and pomalidomide; except for study treatment doses administered by the study nurse/doctor).
- AE assessment: all related AEs and all serious AEs (regardless of relationship to study treatment) ongoing at the time of cut-off will be followed until resolution or stabilization. All new related AEs (regardless of seriousness) will be collected and followed until resolution or stabilization.

Disease assessment

- Only overall response according to assessment per Investigator and based on local laboratories and local reading of radiological assessment will be collected.
- Bone marrow aspirate (or biopsy as clinically indicated):
  - Bone marrow plasma cell infiltration (local laboratory) to confirm CR, and as clinically indicated,
  - BMA for MRD assessment in case of CR (central laboratory).

Local laboratory assessments

- Pregnancy test (urine or serum; with a minimum sensitivity of 25 mIU/mL) to be performed for FCBP on Cycle 1 Day 1, Day 8, Day 15, and Day 22 and then on Day 1 of subsequent cycles (independently of treatment delay/hold), within 24 hours prior to study treatment administration. Females with irregular menstruation must have pregnancy testing on Cycle 1 Day 1, Day 8, Day 15, and Day 22 and then every 14 days while on study treatment(independently of treatment delay/hold).
- Blood chemistry within 24 hours prior to study treatment administration on Cycle 1 Day 1, Day 8, Day 15, and Day 22 and within 24 hours prior to study treatment administration on Day 1 of every subsequent cycle: SGOT (AST), SGPT (ALT), bilirubin (total and direct), alkaline phosphatase, lactate dehydrogenase (LDH), sodium, potassium, chloride, bicarbonate/carbon dioxide, 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, to be done within 24 hours prior to study treatment administration on Cycle 1 Day 1, Day 8, Day 15, and Day 22, within 24 hours prior to study treatment administration on Days 1 and 15 of Cycles 2 and 3, and then within 24 hours prior to study treatment on Day 1 of ever subsequent cycle: hemoglobin, hematocrit, RBC, WBC with differential (including ANC), and platelet count.

IPd arm only

- If an isatuximab IAR of Grade ≥2 occurs during the cycle, additional blood sampling during the AE is required for analysis of cytokine release (TNF-α, IL-1-β, IL-4, IL-6, and IFN-γ), markers of complement activation (C3a, C4, CH50), serum tryptase (central laboratory).
- One additional blood sample will be collected for testing potential interference of isatuximab with the M protein assessment. The sample will be collected at the same time as for serum M protein sample above (central laboratory).

If clinically indicated only:

- Coagulation at any time during the cycle.
- Qualitative urinalysis: blood, leukocytes, protein, glucose, ketone, pH, bilirubin at any time during the cycle.
- Markers for TLS (uric acid, creatinine, potassium, phosphate, calcium and corrected calcium) at any time during the cycle.
- Any other exams clinically indicated.

10.1.7 Post OS study 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 and patients will be managed according to local clinical practice. The following information will be collected during the study treatment administration:

- Study treatment administration.
- Pregnancy tests for FCBP.
- AE assessment: all related AEs and all serious AEs (regardless of relationship to study treatment) ongoing at the time of cut-off will be followed until resolution or stabilization. All new related AEs (regardless of seriousness) will be collected and followed until resolution or stabilization.
- Laboratory abnormalities will continued to be collected as AEs if the results have an impact on the study treatment or meet seriousness criteria.
- End of treatment reason.
- For patients in the IPd arm, 1 ADA sample should be drawn 60 ±5 days after last study treatment administration. If ADA is positive or inconclusive at 60 days, the repeat samples will be taken every 30±7 days until the results become negative (see Section 1.3).

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 adverse events considered as related to study treatment still ongoing or occurring after the end of study treatment, which will be followed until resolution/stabilization

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. Study treatment discontinuation should be a last resort. Any study treatment discontinuation should be fully documented in the CRF. In any case, the patient should remain in the study as long as possible.

Patients are free to withdraw their participation at any time during this study. The Investigator has the right to remove any patient from study treatment or participation in the study.

Any study treatment discontinuation should be fully documented in the eCRF.

Pregnancy in patients 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 or the patient not to re-expose the patient to the study treatment at any time.

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 and/or pomalidomide and/or dexamethasone can be discontinued prematurely. 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 complete the evaluations scheduled for the EOT and follow-up visits as detailed in the Study Flow Chart (Section 1.2).

All treatment discontinuation should be recorded by the Investigator in the appropriate eCRF pages 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. 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.

If possible, the patients are assessed using the procedure normally planned for the EOT visit ADA and PK assessments. If ADA test is positive or inconclusive, ADA testing should be repeated every 30 days until negative.

Patients who withdraw should be explicitly asked about the contribution of possible AEs to their decision to withdraw consent, and any AE information elicited should be documented. Preferably the patient should withdraw consent in writing and, if the patient or the patient's representative refuses or is physically unavailable, the site should document and sign the reason for the patient's failure to withdraw consent in writing.

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

For patients who fail to return to the site, unless the patient withdraws consent for follow-up, the Investigator should make every effort to re-contact 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 statistical analysis plan will specify how these patients lost to follow-up for their primary endpoints 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 **adverse event** (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 the treatment.

10.4.1.2 Serious adverse event

A 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
- 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 conditions are to be considered a medically important events. The list is not intended to be exhaustive:

- Intensive treatment in an emergency room or at home for:
  - Allergic bronchospasm
  - Blood dyscrasias (ie, agranulocytosis, aplastic anemia, bone marrow aplasia, myelodysplasia, pancytopenia, etc),
  - 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
- Cancers diagnosed during the study or aggravated during the study, if judged unusual/significant by the Investigator.

10.4.1.3 Adverse event of special interest

An AE of special interest (AESI) is an AE (serious or nonserious) of scientific and medical concern specific to the Sponsor's product or program, 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:

Acute infusion associated reactions Grade 3 or 4 (IARs; Appendix G for diagnosis and symptoms typical of an IAR). An IAR is a related adverse event typically with onset within 24 hours from the start of isatuximab 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 a study with IMP (see Section 10.4.1.4):

- Pregnancy occurring in a female patient entered in the clinical trial or in a female partner of a male patient entered in the clinical trial will be qualified as an SAE only if it fulfills one of the seriousness criteria (see Section 10.4.1.2).
- In the event of pregnancy in a female participant, IMP should be discontinued.
- Follow-up of the pregnancy in a female participant or in a female partner of a male participant is mandatory until the outcome has been determined and for up to 1 year after the delivery of a newborn.

Symptomatic overdose (serious or nonserious) with IMP (isatuximab or pomalidomide or dexamethasone) or NIMP (see Section 10.4.1.5):

- An overdose (accidental or intentional) with the IMP or NIMP is an event suspected by the Investigator or spontaneously notified by the patient (not based on systematic pills count) and defined as:
- For IMP, an increase of at least 30% of the dose to be administered in the specified duration
- For NIMP (acetaminophen [paracetamol], ranitidine or equivalent, diphenhydramine or equivalent), an increase of at least twice the intended dose within the intended therapeutic interval

Of note, asymptomatic overdose has to be reported as a standard AE.

Second primary malignancies are to be reported using the AE report form and must be considered AESIs; these AEs must also be documented in the appropriate page(s) of the eCRF and patient's source documents. Diagnosis and tests completed as per standard clinical practice of the second primary malignancy must be provided at the time of reporting (eg, any confirmatory histology or cytology results, X-rays, CT scans, etc.).

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.

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 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.

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 (30 days after the last dose of study treatment), are to be recorded on the corresponding page(s) or screen(s) of the eCRF for included patients. For screen failed patients, recording in the eCRF is only performed in case of SAE occurring during the screening period or in case of AE when some screening procedures expose the patient to safety risks (eg, any substance administered as premedication, invasive tests performed or chronic treatment interrupted).

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.

All study treatment-related AEs and all SAEs (regardless of their causal relationship to study treatment) ongoing at the time of study treatment discontinuation need to be followed until resolution or stabilization. Any AE or SAE assessed as study treatment-related that are new during the follow-up period are to be reported and followed until resolution or stabilization.

When treatment is discontinued, observations will continue for that patient as defined by the protocol.

Vital signs or ECG abnormalities are to be recorded as AEs only if they are symptomatic and/or require corrective treatment and/or lead to treatment discontinuation and/or modification of dosing and/or fulfilling a serious criterion and/or are defined as an AESI.

Laboratory abnormalities are to be recorded as AEs only if they lead to treatment discontinuation and/or modification of dosing and/or fulfill a serious criterion and/or are defined as an AESI. Laboratory values will be reported in the appropriate pages of eCRF.

Instructions for AE reporting are summarized in Table 10.

Table 10 - 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

Event category	Reporting timeframe	Specific events in this category	Case Report Form completion		
			AE form	Safety Complementary Form	Other specific forms
		Pregnancy	Yes	Yes	Yes
		Second primary malignancies	Yes	Yes	No
		Symptomatic overdose	Yes	Yes	No

AESI=adverse event of special interest; SAE=serious adverse event

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.
- SEND (preferably by fax or e-mail) a photocopy of all examinations carried out and the dates on which these examinations were performed, to the representative of the monitoring team whose name, fax number, and email address appear on the clinical trial protocol. Care should be taken to ensure that the patient's identity is protected and the patient's identifiers in the clinical trial are properly mentioned on any copy of a source document provided to the Sponsor. For laboratory results, include the laboratory normal ranges.
- All further data updates should be recorded in the eCRF as appropriate, and further documentation as well as additional information (for laboratory data, concomitant medications, patient status, etc) should be sent (by fax or e-mail) to the monitoring team 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 1-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 IMP with a reasonable possibility, should be reported to the monitoring team.

Instructions for SAE reporting are summarized in Table 10.

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 pages of the CRF (to be sent) or screens in the eCRF.

Instructions for AESI reporting are summarized in Table 10.

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 IMP (suspected unexpected serious adverse reaction), to the regulatory authorities, independent ethics committees (IECs)/institutional review boards (IRBs) as appropriate and to the Investigators.
- All SAEs that are expected and at least reasonably related to the IMPs 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 are specified in the reference safety information within the Investigator's Brochure, Section 8 (see the Table entitled "Expected adverse drug reactions for isatuximab in combination with pomalidomide and dexamethasone").

Sanofi will report all safety observations made during the conduct of the study 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 isatuximab 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 8.2.4.

10.6.2 Guidelines for the management of tumor lysis syndrome

Tumor lysis syndrome may occur. 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.

General guidelines for the management of TLS are provided in Table 11.

Table 11 - Management of tumor lysis syndrome

TLS diagnosis	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.
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	Ensure normal hydration, correct laboratory abnormalities, fluid overload, electrolyte or acid-base deviation. Monitor TLS complications including renal functions. Reinstitute study treatment at full dose after resolution.

TLS: tumor lysis syndrome

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)

10.7 ADVERSE EVENTS MONITORING

All AEs 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 Statistical Analysis Plan (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:

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

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

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

- OS has an exponential distribution in both treatment groups.
- Pd arm has a median OS of 13.0 months.
- IPd will have 31.5% risk reduction in hazard rate in comparison to Pd arm. The targeted hazard ratio is 0.685 and this is expected to correspond to a difference of 6 months in median OS between the control arm and the experimental arm.
- A log-rank test at a one-sided 2.5% significance level.
- An interim analysis for efficacy assessment on OS is planned at the time of primary analysis on PFS which is estimated to occur when about 36% of the OS events will be observed. An O'Brien and Fleming α-spending function will be used to obtain the nominal significance levels for the interim and final analyses of survival (see Section 11.5).

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

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

Assuming a uniform accrual rate of 15 patients per month, cut-off dates for primary analyses of PFS and OS will be approximately 18 and 51 months after first patient in (FPI) respectively.

PFS, ORR and OS will be tested according to a closed test procedure according this order. Please refer to Section 11.4.2.3 for further details on the closed test procedure.

11.2 DISPOSITION OF PATIENTS

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

Randomized patients will consist of all patients 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.

Reasons for treatment discontinuation will be summarized using the safety population.

11.3 ANALYSIS POPULATIONS

11.3.1 Efficacy populations

11.3.1.1 Intent-to-treat population

The Intent-to-treat (ITT) population will include all patients who have given their informed consent and for whom there is confirmation of successful allocation of a randomization number by the IRT. Patients will be included in a treatment arm as randomized, regardless of whether patients receive any study treatment or receive a different study treatment from which they were randomized.

This population is the primary population for all efficacy parameters.

11.3.2 Safety population

The safety population will include ITT patients who receive at least one dose or a part of a dose of the study treatments.

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

11.3.3 Pharmacokinetic population

The PK population will include patients from the safety population who receive at least 1 dose of Isatuximab, even if incomplete, with data for at least 1 PK parameter available.

11.3.4 ADA population

The ADA population will include patients with at least one sample taken post-baseline after drug administration during the treatment or follow-up observation period that is appropriate for ADA testing with a reportable result.

11.3.5 Patient reported outcome population

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

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 observation, mean, standard deviation, median, minimum, and maximum. Categorical and ordinal data will be summarized using number and percentage of patients.

The analysis cut-off date for the primary analysis of PFS is the date when the 162 events have been observed. This is estimated to be approximately 18 months after FPI.

The analysis cut-off date for the analysis of OS is the date when the 220 events have been observed. This is estimated to be approximately 51 months after FPI.

11.4.1 Extent of study treatment exposure and compliance

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

- Overall number of cycles started.
- Overall duration of exposure in weeks defined as [(Last day of last cycle - first day of first cycle)/7].

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

IPd arm:

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

Pd arm:

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

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

In addition, the following variables will be summarized with descriptive statistics for each IMP (ie, isatuximab, pomalidomide and dexamethasone):

- Number of cycles started with each drug.
- Duration of exposure of each drug 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 pomalidomide: [Min(date of last dose of pomalidomide + 8 days, date of death) - first dose of pomalidomide]/7,
  - For dexamethasone: [date of last dose of dexamethasone + 7 days - first dose of dexamethasone]/7.
- Isatuximab: number of infusions.
- Cumulative dose (in mg) for each compound: The cumulative dose at is the sum of all doses administered from first to last dose.
- Actual dose intensity (ADI): 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.
- Dose reduction of pomalidomide or dexamethasone:
  - Reduction of the administered dose for cycle number n+1, Day 1, compared to cycle n, Day 1,
  - A dose is deemed to have been reduced if the dose level a patient receives differs from the previous actual dose level.
- Cycle delays: A cycle is deemed to have been delayed if the start date is >3 days beyond the scheduled Day 1.
- Isatuximab infusion delays (within cycle): a dose is deemed to have been delayed if the study treatment is ≥2 days beyond the theoretical day of treatment for weekly dose, and ≥3 days beyond the theoretical day of treatment for Q2W schedule of administration.
- Isatuximab infusion interruption: administration of isatuximab treatment was temporarily stopped during the infusion. Dose interruptions are not applicable for dexamethasone when given orally or pomalidomide since they are orally administered.
- Dose omission (isatuximab infusion or pomalidomide dose or dexamethasone dose). Partially administered cycle: Cycle with at least one isatuximab/pomalidomide dexamethasone dose omitted.

11.4.2 Analyses of efficacy endpoints

11.4.2.1 Analysis of primary efficacy endpoint(s)

The primary analysis of PFS will be based on the following censoring rules: If progression and death are not observed before the analysis cut-off date, PFS will be censored at the earliest of the date of the last valid disease assessment not showing disease progression performed prior to initiation of a further anti myeloma treatment (if any) or the analysis cut-off date, whichever comes first.

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

This analysis will be performed on the ITT population.

Response will be determined according to IMWG criteria (1). The date of disease progression is the date of the first documented (and further confirmed) progression according to IMWG criteria as assessed by IRC. For patients without measurable M protein on Cycle 1 D1 efficacy laboratory results, progression and date of progression will be assessed by IRC according to criteria defined in Appendix D.

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 analysis of PFS is expected to be the date when the 162nd event (first occurrence of either disease progression or death due to any cause) has been observed.

The estimates of the hazard ratio and corresponding 95% confidence interval will be provided using a Cox proportional hazard model stratified by the same stratification factors as those used for the log-rank test described above. The survival curves will be estimated using Kaplan-Meier estimates. At the time of PFS final analysis, critical value for the logrank test on PFS hazard rate would be 0.734.

Sensitivity analyses of PFS will be performed (eg, different censoring rules and PFS assessed by the Investigator).

11.4.2.2 Analyses of secondary efficacy endpoints

11.4.2.2.1 Analysis of key secondary efficacy endpoints

The key secondary efficacy endpoints are ORR and OS.

Best overall response, ORR and clinical benefit rate will be summarized using the ITT population with descriptive statistics at the time of the primary analysis on PFS (based on data collected up to the PFS analysis cut-off date). Confidence intervals will be computed using the Clopper-Pearson method. ORR will be compared between treatment groups using Cochran Mantel Haenszel stratified method.

The analysis on key secondary endpoint will also consist of OS comparison between the IPd group versus the Pd group through a 1-sided log-rank test procedure. Patients without death prior to the analysis cut-off date will be censored at the last date the patient was known to be alive or the cut-off date, whichever is earlier. This analysis will be performed on the ITT population, both at the time of the primary analysis on PFS (at about 36% information fraction), and at the end of the study (final analysis on OS). An O'Brien and Fleming α-spending function will be used to obtain the nominal significance levels for the interim and final analyses of survival. The nominal significance (one-sided) level for the final survival comparisons would be of 0.0249 for 220 death events (corresponding to a HR of 0.767).

If death is not observed before the analysis data cut-off date, data on OS will be censored at the date patient is known to be alive or at the cut-off date, whichever comes first.

11.4.2.2.2 Analysis of other secondary efficacy endpoints

Other secondary efficacy endpoints include: TTP, PFS in the high risk cytogenetic population, and DOR. These time-to-event endpoints will be analyzed at the time of the primary analysis on PFS using Kaplan-Meier methods. Among patients who achieve a CR, the number of patients without MRD will be provided.

Similarly to the primary analysis of PFS, if progression and deaths (excluding TTP) are not observed before the analysis data cut-off date, TTP, PFS in the high risk cytogenetic population, and DOR will be censored at the date of the last valid disease assessment not showing disease progression performed prior to initiation of further anti-myeloma treatment (if any) or the data cut-off date, whichever comes first. The DOR will not be calculated for patients that do not achieve a response.

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

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 not further testing will be performed unless the significance level had been reached on PFS. The hierarchical procedure will be then carried out at the one-sided 2.5% significance level in the following order:

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

11.4.3 Analyses of safety data

The summary of safety results will be presented by actual treatment group. Analysis of TEAEs and laboratory data, vital signs will be descriptive and conducted on the safety population. Summary of safety data will also be performed by patient. 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.

11.4.3.1 Adverse events

Adverse events will be collected from informed consent is signed until the EOT (at least 30 days after last dose of study treatment).

Adverse events will be graded according NCI-CTCAE v4.03 (Appendix C) and classified by system organ class (SOC) / preferred term (PT) according the last available version of the MedDRA dictionary.

The observation period will be divided into 3 segments: screening, TEAE and post-treatment:

- The screening period is defined as the time informed consent is signed until the first dose of study treatments administration.
- The TEAE observation period is defined as the time from the first dose of study treatments up to 30 days after last dose of study treatments.
- The post-treatment period is defined as the time starting 31 days after the last dose of study treatments to study closure or death, whichever comes first.

Pre-treatment AEs are defined as any AE during the screening period.

Treatment-emergent AEs are defined as AEs that develop, worsen (according to the Investigator opinion), or become serious during the TEAE period.

Post-treatment AEs are defined as AEs that occur during the post-treatment period.

The severity grade will be taken into account in the summary. For patients with multiple occurrences of the same PT, the maximum grade will be used.

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

Similar analysis will be presented for SAEs and AEs that cause dose modification (reduction and/or delay, interruption) and treatment discontinuation.

11.4.3.2 Treatment-emergent adverse events

An overall summary of TEAEs will be provided. The number and percentage of patients who experience any of the following will be provided:

- TEAEs
- TEAEs of ≥Grade 3
- Grade 5 TEAE (any TEAE with a fatal outcome during the treatment period)
- Serious TEAEs
- Serious treatment-related TEAEs
- TEAE leading to permanent (full study treatment) discontinuation/premature (partial study treatment) discontinuation

- AESIs: IARs of ≥Grade 3, pregnancy, overdose reports, and second primary malignancies
- IARs of all severity grade and by grade
- 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 (screening, TEAE and post-treatment). For that purpose, the table of all TEAEs will be presented by SOC and PT sorted by internationally agreed order unless otherwise specified.

11.4.3.3 Deaths

The following death summaries will be generated:

- Number (%) of patients who died by study period (TEAE and post-treatment) and reasons for death summarized on the safety population by treatment received.
- Deaths in non-randomized patients or, randomized and not treated patients.
- TEAEs with fatal outcome (on the AE eCRF page as reported by the Investigator), and related TEAEs with fatal outcome summarized by primary SOC and PT.
- TEAE with fatal outcome summarized by primary system organ class (SOC), high level general term (HLGT), high level term (HLT) and preferred term (PT) sorted by internationally agreed order of SOC and alphabetic order of HLGT, HLT, and PT.

11.4.3.4 Other safety evaluations

Laboratory data

Clinical laboratory values will be analyzed after conversion into standard international units. International units will be used in all listings and tables. Complete blood count and serum chemistry results will be graded according to NCI-CTCAE Version 4.03, when applicable. For patients with multiple occurrences of the same laboratory variable during the TEAE period, the maximum grade (worst) per patient will be used. The denominator used for percentage calculation is the number of patients with at least 1 evaluation of the laboratory test during the considered observation period.

The number and proportion of patients with abnormal laboratory tests at baseline (ie, last assessment before the first dose of study treatments administration) will be presented for ≥Grade 3, all grades together and Grade 3 and Grade 4 separately. Similar tables showing abnormalities during the TEAE period will be provided.

When the NCI-CTCAE V4.03 scale is not applicable, the number of patients with a laboratory abnormality out-of-normal laboratory range value will be displayed.

Vital signs

Potentially clinically significant abnormality (PCSA) values are defined as abnormal values considered medically important by the Sponsor according to predefined criteria/thresholds based on literature review. The incidence of PCSAs prior to study treatment administration at any cycle during the TEAE period (on-treatment PCSAs) will be summarized by treatment group whatever the baseline level and/or according to the following baseline categories:

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

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

Other evaluations

Cytokines (TNF-α, IL-1-β, IL-4, IL-6, IFN-γ), markers of complement activation (C3a, C4, CH50), serum tryptase will be summarized with descriptive statistics.

Number (%) of patients with second primary malignancies will be summarized.

11.4.4 Analyses of pharmacokinetic and pharmacodynamic variables

11.4.4.1 Analysis of pharmacokinetic variables

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

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

11.4.5 Analyses of immunogenicity

The immunogenicity for isatuximab will be assessed by summarizing the number of evaluable patients, the percentage of ADA positive patients (either treatment induced, or those with increased titers during treatment), and the percentage of ADA negative patients.

ADA prevalence (proportion of patients tested positive at any point in time) and ADA incidence (proportion of patients seroconverted - treatment induced ADAs - or having increased titers during the study) will be calculated.

In addition, ADA titers will be summarized by descriptive statistics and time of measurement.

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

11.4.6 Analyses of patient reported outcomes (HRQL/health economics) variables

Change from baseline for the following variables from EORTC QLQ-C30: global HRQL, five functional scales (physical, emotional, cognitive, role and social) and nine symptom domains (fatigue, nausea/vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties); for the MY-20: future perspective, body image, disease symptoms and side effects of treatment; and for the EQ-5D-5L: [redacted]. Descriptive statistics including number of patients, mean and standard error will be provided. [redacted]

[redacted]

Each of the following criteria will be assessed via a comparison of change scores from baseline to EOT and 60 days after last study treatment administration between treatment arms:

A) Disease-specific HRQL (EORTC QLQ-C30)

B) Disease- and treatment-related symptoms (EORTC QLQ-C30 and MY20)

C) Health state utility (EQ-5D-5L)

D) Health status (EQ-5D-5L visual analogue scale).

[redacted]

11.5 INTERIM ANALYSIS

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

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

If an improvement in median PFS is demonstrated (according to the PFS final analysis presented in Section 11.4.2), the analysis on ORR and interim analysis on OS will be performed. The ORR will be tested, at the one sided 2.5%-level. Then, if the improvement in ORR is also significant, OS will be tested as a formal comparison that would allow for early stopping for overwhelming efficacy. The stopping boundaries will be derived based on the O'Brien and Fleming α -spending functions.

The stopping boundaries for efficacy on OS endpoint will depend on the actual number of deaths observed at the time of the interim analysis. However, in case where exactly 80 deaths are observed, the Sponsor could stop the study for overwhelming efficacy if the p-value is ≤0.000184 (corresponding to a HR of 0.448). Under current accrual assumptions of 15 patients per month, the 162 PFS events milestone (and interim analysis on OS) is estimated to occur at about 18 months after FPI.

The final analysis of survival, provided that the survival portion of the study is not stopped early, will take place after at least 220 deaths have been observed, which is projected to occur approximately 51 months after the first patient is randomized. The nominal significance level for the final survival comparisons will be determined by an O'Brien and Fleming alpha spending function. It would be of 0.0249 for 220 events (corresponding to a HR of 0.767).

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 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.

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.

Prior to collection of blood for pharmacogenetics, the optional pharmacogenetic informed consent form (written) 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 optional informed consent form will be provided to the patient.

The informed consent form and the optional pharmacogenetic 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.

Participants who can read the consent form will do so before writing their name and dating or signing and dating the form.

Participants who can write but cannot read will have the assent form read to them before writing their name on the form.

Participants who can understand but who can neither write nor read will have the assent form read to them in presence of an impartial witness, who will sign and date the assent form to confirm that assent was given.

The informed consent form and the assent 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.

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, package insert) Investigator's curriculum vitae, etc) and the date of the review should be clearly stated on the written (IRB/IEC) approval/favorable opinion.

The IMP 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 or labeling information, will be sent to the IRB/IEC and to health authorities (competent regulatory authority), as required by local regulation.

A progress report is sent to the IRB/IEC at least annually and a summary of the clinical trial's outcome at the end of the clinical trial.

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 CRF, 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, IMP allocation, patient compliance with the IMP regimen, IMP accountability, concomitant therapy use and quality of data 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 CRF. 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 CRFs (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).

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

It is the responsibility of the Investigator to maintain adequate and accurate CRFs (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 CRFs 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.

13.4 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 and Investigator study files.

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 the confidentiality of all study documentation, and take measures to prevent accidental or premature destruction of these documents.

The Investigator should retain the study documents for 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 IMP 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). Data may be further processed if they have been anonymized.

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, it being understood that these personnel are 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 the 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 for 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 IMP, 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 thirty (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 (see Appendix M).

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 twelve (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.

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17 APPENDICES

Appendix A Modification of Diet in Renal Disease (MDRD) equation

GFR (mL/min/1.73 m2) =

$175 \times (Scr)^{-1.154} \times (Age)^{-0.203} \times (0.742 \text{ if Female}) \times (1.212 \text{ if African-American})$

Appendix B 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, Robert L. Comis, MD, Group Chair (23)

Appendix C 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:

http://ctep.cancer.gov/reporting/ctc.html

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 D IMWG Response Criteria

Disease response will be assessed using the updated International Myeloma Working Group Response Criteria (IMWG) (1). A confirmation assessment for disease response within 4 weeks is required in this protocol (either MR 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 serum FLC increase only, even in patients for whom serum and urine M-protein become below level of eligibility on efficacy laboratory performed on Cycle 1 Day 1 (see below the table for assessment of overall response and progression diagnosis of these patients).

Adapted from updated International Myeloma Working Group Response Criteria

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

VGPR	• Serum and urine M-protein detectable by immunofixation but not on electrophoresis or • ≥90% reduction in serum M-protein plus urine M-protein level <100 mg/24 h or • ≥90% decrease in the sum 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/soft tissue lesions if radiographic studies were performed**
PR	• ≥50% reduction of serum M-protein and reduction in 24 hours urinary M-protein by ≥90% or to <200 mg/24 h • In addition to the above listed criteria, if present at baseline, a ≥50% reduction in the size (SPD) of soft tissue plasmacytomas is also required **Two consecutive assessments are needed. No known evidence of progressive disease or new bone/soft tissue lesions if radiographic studies were performed**
MR	≥25% but ≤ 49% reduction in serum M-protein and reduction in 24h urine M-protein by 50-89%, which still exceed 200 mg/24h. In addition to the above listed criteria, if present at baseline, ≥50% reduction in size (SPD) of soft tissue plasmacytomas is also required **No known evidence of progressive disease or new bone/soft tissue lesions if radiographic studies were performed**
Stable Disease	• Not meeting criteria for CR, VGPR, PR, MR or progressive disease **Two consecutive assessments are needed. No known evidence of progressive disease or new bone/soft tissue lesions if radiographic studies were performed**
Progressive disease	Any one or more of the following criteria: Increase of ≥25% from lowest confirmed value in any one of the following criteria: • Serum M-protein (the absolute increase must be ≥0.5 g/dL) • Serum M-protein increase ≥1 g/dL if the lowest M component was ≥5 g/dL • Urine M-component (the absolute increase must be ≥200 mg/24 h) Appearance of new lesion(s), ≥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.**

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

Patients with disease only measurable by FLC are not allowed.

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

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

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

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

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 IFX positive] and <0.5 g/dL):

- Patients with M-protein (urine and/or serum) below the level of measurability (M-protein value >0 [or IFX positive] and <0.5 g/dL) can have CR, non-PD or PD responses only according to the increase or decrease of M protein or extramedullary disease if applicable, following the IMWG criteria.

- Patients with FLC measurable disease only only (M-protein =0 and IFX negative), can have either non-PD or PD responses (PD will be an absolute increase of >10 mg/dL in the difference between involved and uninvolved FLC).
- Patients with serum M-protein value >0 g/dL (or serum IFX positive) and <0.5 g/dL, independently of FLC can only be qualified as: CR, non-PD, or PD

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

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

Appendix E 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, 3-6 cycles of initial therapy with bortezomib-dexamethasone followed by stem cell transplantation consolidation, and lenalidomide maintenance is considered 1 line).

New line of Therapy

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

1. **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.

2. **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.

3. **Stem cell transplantation (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 recommend 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. Guidelines for the determination of the number of prior lines of therapy in multiple myeloma Blood 2015;126[7]:921-922) (24).

Appendix F Definition of Relapsed and Refractory Myeloma

Refractory Myeloma:

Refractory myeloma is defined as disease that is non-responsive (failure to achieve minimal response 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: Relapsed and refractory myeloma is defined as disease that is non-responsive while on salvage therapy or progresses within 60 days of last therapy in patients who have achieved minimal response or better at some point previously to then progressing in their disease course.
- Primary refractory myeloma: refractory myeloma is defined as disease that is non-responsive in patients who have never achieved minimal response 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 VS, Harousseau J-Let al Consensus recommendations for the uniform reporting of clinical trials: report of the International Myeloma Workshop Consensus Panel 1. Blood 2011; 117(18):4691-95) (25).

Appendix G Infusion Associated Reactions Observed with Isatuximab

Main types of infusion associated reactions

- Anaphylactic reaction
- Cytokine release syndrome
- Drug hypersensitivity
- Infusion related reaction

Symptoms typically associated with infusion reactions

- Abdominal pain
- Apnea
- Bronchospasm
- Chest discomfort
- Chest tightness
- Chills
- Cough
- Dizziness
- Dysgeusia
- Dyspnea
- Feeling hot
- Flushing
- Headache
- Head discomfort
- Hoarseness
- Hot flush
- Hypertensive crisis
- Hypoxia
- Influenza like illness
- Injection site pain
- Lacrimation increased
- Laryngospasm
- Myalgia
- Nasal congestion
- Nausea
- Pruritus
- Pyrexia
- Respiratory distress
- Rhinitis
- Rhinorrhea
- Stridor
- Tachycardia
- Throat irritation
- Tracheal stenosis
- Tremor
- Urticaria
- Vision blurred
- Vomiting
- Wheezing

Appendix H EORTC-QLQ-C30 scales, items and CIDs

ENGLISH

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials:
Your birthdate (Day, Month, Year):
Today's date (Day, Month, Year): 31

		Not at All	A Little	Quite a Bit	Very Much
1.	Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2.	Do you have any trouble taking a long walk?	1	2	3	4
3.	Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4.	Do you need to stay in bed or a chair during the day?	1	2	3	4
5.	Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:		Not at All	A Little	Quite a Bit	Very Much
6.	Were you limited in doing either your work or other daily activities?	1	2	3	4
7.	Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8.	Were you short of breath?	1	2	3	4
9.	Have you had pain?	1	2	3	4
10.	Did you need to rest?	1	2	3	4
11.	Have you had trouble sleeping?	1	2	3	4
12.	Have you felt weak?	1	2	3	4
13.	Have you lacked appetite?	1	2	3	4
14.	Have you felt nauseated?	1	2	3	4
15.	Have you vomited?	1	2	3	4
16.	Have you been constipated?	1	2	3	4

Please go on to the next page

ENGLISH

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

[redacted]

[redacted]

Appendix I MY20 scales, items and CIDs

ENGLISH

EORTC QLQ – MY20

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:		Not at All	A Little	Quite a Bit	Very Much
31.	Have you had bone aches or pain?	1	2	3	4
32.	Have you had pain in your back?	1	2	3	4
33.	Have you had pain in your hip?	1	2	3	4
34.	Have you had pain in your arm or shoulder?	1	2	3	4
35.	Have you had pain in your chest?	1	2	3	4
36.	If you had pain did it increase with activity?	1	2	3	4
37.	Did you feel drowsy?	1	2	3	4
38.	Did you feel thirsty?	1	2	3	4
39.	Have you felt ill?	1	2	3	4
40.	Have you had a dry mouth?	1	2	3	4
41.	Have you lost any hair?	1	2	3	4
42.	Answer this question only if you lost any hair: Were you upset by the loss of your hair?	1	2	3	4
43.	Did you have tingling hands or feet?	1	2	3	4
44.	Did you feel restless or agitated?	1	2	3	4
45.	Have you had acid indigestion or heartburn?	1	2	3	4
46.	Have you had burning or sore eyes?	1	2	3	4

Please turn to next page

ENGLISH

During the past week:	Not at All	A Little	Quite a Bit	Very Much
47. Have you felt physically less attractive as a result of your disease or treatment?	1	2	3	4
48. Have you been thinking about your illness?	1	2	3	4
49. Have you been worried about dying?	1	2	3	4
50. Have you worried about your health in the future?	1	2	3	4

Appendix J EQ-5D-5L scales, items and CIDs

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

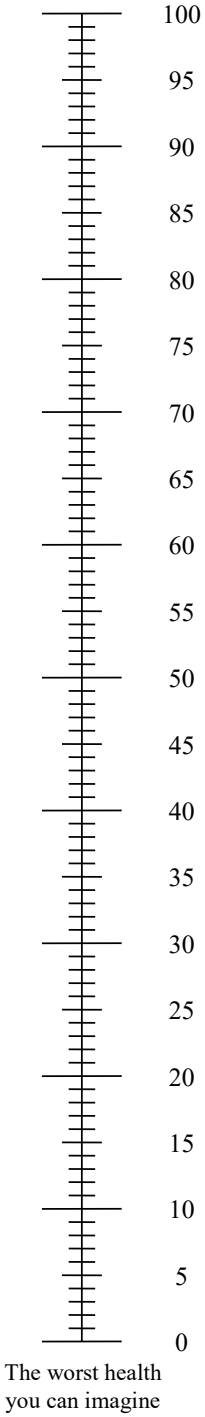
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



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Appendix K CD38 blood test interference guideline AABB2016

Advancing Transfusion and Cellular Therapies Worldwide

Association Bulletin #16-02

Date: January 15, 2016
To: AABB Members
From: Donna M. Regan, MT(ASCP)SBB—President
Miriam A. Markowitz—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]

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Appendix L Global Pomalidomide Pregnancy Prevention Plan

1. POMALIDOMIDE PREGNANCY PREVENTION PLAN FOR SUBJECTS IN CLINICAL TRIALS

The Pregnancy Prevention Plan (PPP) applies to all subjects receiving pomalidomide within a clinical trial. The following PPP documents are included:

1. The Pomalidomide Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods document (Section 2) provides the following information:
   - Potential risks to the fetus associated with pomalidomide exposure
   - Definition of female of childbearing potential (FCBP)/female not of childbearing potential (FNCBP)
   - Requirements for counseling of all subjects receiving pomalidomide about pregnancy precautions and the potential risks of fetal exposure to pomalidomide
   - Acceptable birth control methods for both female subjects of childbearing potential and male subjects receiving pomalidomide in the study
   - Pregnancy testing requirements for subjects receiving pomalidomide who are FCBP
2. The Pomalidomide Education and Counseling Guidance Document for each gender (female and male; Section 3 and Section 4 respectively) must be completed and signed by a trained counselor at the participating clinical center prior to each dispensing of pomalidomide. A copy of this document must be maintained in the subject's records for each dispense.
3. The Pomalidomide Information Sheet (Section 5) will be given to each subject receiving pomalidomide. The subject must read this document prior to starting pomalidomide and each time the subject receives a new supply of pomalidomide.

2. POMALIDOMIDE RISKS OF FETAL EXPOSURE, PREGNANCY TESTING GUIDELINES AND ACCEPTABLE BIRTH CONTROL METHODS

2.1. Risks Associated with Pregnancy

Pomalidomide was teratogenic in both rats and rabbits when administered during the period of organogenesis. Pomalidomide is an analogue of thalidomide. Thalidomide is a known human teratogen that causes severe life-threatening human birth defects. If pomalidomide is taken during pregnancy, it can cause birth defects or death to an unborn baby.

The teratogenic effect of pomalidomide in humans cannot be ruled out. Therefore, a pregnancy prevention program must be followed.

2.1.1. Definition of Females of Childbearing Potential

A FCBP is a female who: 1) has achieved menarche at some point, 2) has not undergone a hysterectomy or bilateral oophorectomy or 3) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (ie, has had menses at any time in the preceding 24 consecutive months).

2.1.2. Definition of Females Not of Childbearing Potential

Females who do not meet the above definition of FCBP should be classified as FNCBP.

2.2. Counseling

2.2.1. Females of Childbearing Potential

For a FCBP, pomalidomide is contraindicated unless all of the following are met (ie, all FCBP must be counseled concerning the following risks and requirements prior to the start of pomalidomide):

- She understands the potential teratogenic risk to the unborn child
- She understands the need for effective contraception, without interruption, 28 days before starting pomalidomide, throughout the entire duration of pomalidomide, during dose interruptions and for at least 28 days after the last dose of pomalidomide
- She understands and agrees to inform the Investigator if a change or stop of method of contraception is needed
- She must be capable of complying with effective contraceptive measures
- She is informed and understands the potential consequences of pregnancy and the need to notify her study doctor immediately if there is a risk of pregnancy
- She understands the need to commence pomalidomide as soon as it is dispensed following a negative pregnancy test

- She understands and accepts the need to undergo pregnancy testing based on the frequency outlined in this plan (Section 2.4) and in the Informed Consent
- She acknowledges that she understands the hazards pomalidomide can cause to an unborn fetus and the necessary precautions associated with the use of pomalidomide.

The Investigator must ensure that a FCBP:

- Complies with the conditions of the pregnancy prevention plan, including confirmation that she has an adequate level of understanding
- Acknowledges the aforementioned requirements.

2.2.2. Females Not of Childbearing Potential

For a FNCBP, pomalidomide is contraindicated unless all of the following are met (ie, all FNCBP must be counseled concerning the following risks and requirements prior to the start of pomalidomide):

- She acknowledges she understands the hazards pomalidomide can cause to an unborn fetus and the necessary precautions associated with the use of pomalidomide.

2.2.3. Males

The effect of pomalidomide on sperm development is not known and has not been studied. The risk to an unborn baby in females of child bearing potential whose male partner is receiving pomalidomide is unknown at this time. Therefore, male subjects taking pomalidomide must meet the following conditions (ie, all males must be counseled concerning the following risks and requirements prior to the start of pomalidomide):

- Understand the potential teratogenic risk if engaged in sexual activity with a pregnant female or a FCBP
- Understand the need for the use of a condom even if he has had a vasectomy, if engaged in sexual activity with a pregnant female or a FCBP
- Understand the potential teratogenic risk if the subject donates semen or sperm.

2.3. Contraception

2.3.1. Female Subjects of Childbearing Potential

Females of childbearing potential enrolled in this protocol must agree to use two reliable forms of contraception simultaneously or to practice complete abstinence (True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence [eg calendar, ovulation, symptothermal or post-ovulation methods] and withdrawal are not acceptable methods of contraception.) from heterosexual contact during the following time periods related to this study: 1) for at least 28 days before starting pomalidomide; 2) while taking pomalidomide; 3) during dose interruptions; and 4) for at least 28 days after the last dose of pomalidomide.

The two methods of reliable contraception must include one highly effective method and one additional effective (barrier) method. If the below contraception methods are not appropriate for the FCBP, she must be referred to a qualified provider of contraception methods to determine the medically effective contraception method appropriate to the subject. The following are examples of highly effective and additional effective methods of contraception:

- Examples of highly effective methods:
  - Intrauterine device (IUD)
  - Hormonal (birth control pills, injections, implants, levonorgestrel-releasing intrauterine system [IUS], medroxyprogesterone acetate depot injections, ovulation inhibitory progesterone-only pills [e.g. desogestrel])
  - Tubal ligation
  - Partner's vasectomy
- Examples of additional effective methods:
  - Male condom
  - Diaphragm
  - Cervical Cap

Because of the increased risk of venous thromboembolism in subjects with multiple myeloma taking pomalidomide and dexamethasone, combined oral contraceptive pills are not recommended. If a subject is currently using combined oral contraception the subject should switch to another one of the highly effective methods listed above. The risk of venous thromboembolism continues for 4 to 6 weeks after discontinuing combined oral contraception. The efficacy of contraceptive steroids may be reduced during co-treatment with dexamethasone.

[Please note, the above highlighted text is applicable for protocols with dexamethasone-containing pomalidomide regimens.]

Implants and levonorgestrel-releasing intrauterine systems are associated with an increased risk of infection at the time of insertion and irregular vaginal bleeding. Prophylactic antibiotics should be considered particularly in subjects with neutropenia.

2.3.2. Male Subjects

Male subjects must practice complete abstinence (True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence [eg calendar, ovulation, symptothermal or post-ovulation methods] and withdrawal are not acceptable methods of contraception.) or agree to use a condom during sexual contact with a pregnant female or a FCBP while taking pomalidomide, during dose interruptions and for at least 28 days after the last dose of pomalidomide, even if he has undergone a successful vasectomy.

2.4. Pregnancy Testing

Medically supervised pregnancy tests with a minimum sensitivity of 25 mIU/mL must be performed for FCBP.

Females of childbearing potential must have two negative pregnancy tests (sensitivity of at least 25 mIU/mL) prior to starting pomalidomide. The first pregnancy test must be performed within 10 to 14 days prior to the start of pomalidomide and the second pregnancy test must be performed within 24 hours prior to the start of pomalidomide. The subject may not receive pomalidomide until the study doctor has verified that the results of these pregnancy tests are negative.

Females of childbearing potential with regular or no menstrual cycles must agree to have pregnancy tests weekly for the first 28 days of study participation and then every 28 days while taking pomalidomide, at study discontinuation, and at Day 28 following the last dose of pomalidomide.

Females of childbearing potential with irregular menstrual cycles must agree to have pregnancy tests weekly for the first 28 days of study participation and then every 14 days while taking pomalidomide, at study discontinuation, and at Days 14 and 28 following the last dose of pomalidomide.

2.5. Pregnancy Precautions for Pomalidomide Use

2.5.1. Before Starting Pomalidomide

2.5.1.1. Female Subjects of Childbearing Potential

Females of childbearing potential must have two negative pregnancy tests (sensitivity of at least 25 mIU/mL) prior to starting pomalidomide. The first pregnancy test must be performed within 10 to 14 days prior to the start of pomalidomide and the second pregnancy test must be performed within 24 hours prior to the start of pomalidomide. The subject may not receive pomalidomide until the study doctor has verified that the results of these pregnancy tests are negative.

Females of childbearing potential must use two reliable forms of contraception simultaneously, or practice complete abstinence (True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence [eg calendar, ovulation, symptothermal or post-ovulation methods] and withdrawal are not acceptable methods of contraception.) from heterosexual contact for at least 28 days before starting pomalidomide.

2.5.1.2. Male Subjects

Male subjects must agree to practice complete abstinence (True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence [eg calendar, ovulation, symptothermal or post-ovulation methods] and withdrawal are not acceptable methods of contraception.) or agree to use a condom during sexual contact with a pregnant female or a FCBP while taking pomalidomide, during dose interruptions and for at least 28 days after the last dose of pomalidomide, even if he has undergone a successful vasectomy.

2.5.2. During and After Study Participation

2.5.2.1. Female Subjects

- Females of childbearing potential with regular or no menstrual cycles must agree to have pregnancy tests weekly for the first 28 days of study participation and then every 28 days while taking pomalidomide, at study discontinuation, and at Day 28 following the last dose of pomalidomide.
- Females of childbearing potential with irregular menstrual cycles must agree to have pregnancy tests weekly for the first 28 days of study participation and then every 14 days while taking pomalidomide, at study discontinuation, and at Days 14 and 28 following the last dose of pomalidomide.
- At each visit, the Investigator must confirm with the FCBP that she is continuing to use two reliable methods of birth control if not committing to complete abstinence, or confirm commitment to complete abstinence.
- If a FCBP considers the need to change or to stop a method of contraception, the Investigator must be notified immediately.
- Counseling about pregnancy precautions and the potential risks of fetal exposure must be conducted at a minimum of every 28 days.
- If pregnancy or a positive pregnancy test does occur in a subject, pomalidomide must be immediately discontinued.
- Pregnancy testing and counseling must be performed if a subject misses her period or if her pregnancy test or her menstrual bleeding is abnormal. Pomalidomide must be discontinued during this evaluation.
- Females must agree to abstain from breastfeeding while taking pomalidomide and for at least 28 days after the last dose of pomalidomide.

2.5.2.2. Male Subjects

- Must practice complete abstinence (True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence [eg calendar, ovulation, symptothermal or post-ovulation methods] and withdrawal are not acceptable methods of contraception.) or use a condom during sexual contact with a pregnant female or a FCBP while receiving pomalidomide, during dose interruptions and for at least 28 days after the last dose of pomalidomide, even if he has undergone a successful vasectomy.
- Must not donate semen or sperm while receiving pomalidomide, during dose interruptions or for at least 28 days after the last dose of pomalidomide.
- Counseling about pregnancy precautions and the potential risks of fetal exposure must be conducted at a minimum of every 28 days.

- If pregnancy or a positive pregnancy test does occur in the partner of a male subject while taking pomalidomide, the Investigator must be notified immediately.

2.5.3. Additional Precautions

- Subjects should be instructed to never give pomalidomide to another person.
- Subjects should be instructed to return any unused capsules to the study doctor.
- Subjects should not donate blood while receiving pomalidomide, during dose interruptions and for at least 28 days after the last dose of pomalidomide.
- No more than a 28-day pomalidomide supply may be dispensed with each cycle of pomalidomide.

3. POMALIDOMIDE EDUCATION AND COUNSELING GUIDANCE DOCUMENT FOR FEMALE SUBJECTS

To be completed prior to each dispensing of pomalidomide.

Protocol Number: _____

Subject Name (Print): _____ DOB: _____/_____/_____ (dd/mmm/yyyy)

Check one risk category:

- ☐ FCBP (Female of childbearing potential): a female who: 1) has achieved menarche (first menstrual cycle) at some point, 2) has not undergone a hysterectomy (the surgical removal of the uterus) or bilateral oophorectomy (the surgical removal of both ovaries) or 3) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (ie, has had menses at any time during the preceding 24 consecutive months)
- ☐ NOT FCBP

3.1. Female of Childbearing Potential:

1. I have verified and counseled the subject regarding the following:
   - ☐ Potential risk of fetal exposure to pomalidomide: A teratogenic potential of pomalidomide in humans cannot be ruled out. If pomalidomide is taken during pregnancy, it may cause birth defects or death to any unborn baby. Females are advised to avoid pregnancy while taking pomalidomide. Females of childbearing potential must agree not to become pregnant while taking pomalidomide.
   - ☐ That the required pregnancy tests performed are negative.
   - ☐ The subject confirmed that she is using TWO reliable methods of birth control at the same time, or complete abstinence (True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence [eg calendar, ovulation, symptothermal or post-ovulation methods] and withdrawal are not acceptable methods of contraception.) from heterosexual contact (at least 28 days prior to receiving pomalidomide, while receiving pomalidomide, during dose interruptions and for at least 28 days after the last dose of pomalidomide).

     One highly effective method and one additional method of birth control must be used AT THE SAME TIME. The following are examples of highly effective and additional effective methods of contraception:

     - Examples of highly effective methods:
       - Intrauterine device (IUD)
       - Hormonal (birth control pills, injections, implants, levonorgestrel-releasing intrauterine system [IUS], medroxyprogesterone acetate depot injections, ovulation inhibitory progesterone-only pills [e.g. desogestrel])

- Tubal ligation
- Partner's vasectomy

– Examples of additional effective methods:
  - Male condom
  - Diaphragm
  - Cervical Cap

☐ The subject confirmed that even if she has amenorrhea she must comply with advice on contraception.

☐ Pregnancy tests before, during administration of pomalidomide and at the last dose of pomalidomide, even if the subject agrees not to have reproductive heterosexual contact.

☐ Frequency of pregnancy tests to be done:

– Two pregnancy tests will be performed prior to receiving pomalidomide, one within 10 to 14 days, and a second within 24 hours of the start of pomalidomide.

– Every week during the first 28 days of this study and a pregnancy test every 28 days while the subject is taking pomalidomide if menstrual cycles are regular.

– Every week during the first 28 days of this study and a pregnancy test every 14 days while the subject is taking pomalidomide if menstrual cycles are irregular.

– If the subject missed a period or has unusual menstrual bleeding.

– When the subject is discontinued from the study and at Day 28 after the last dose of pomalidomide if menstrual cycles are regular. If menstrual cycles are irregular, pregnancy tests will be done at discontinuation from the study and at Days 14 and 28 after the last dose of pomalidomide.

☐ The subject confirmed that she will stop taking pomalidomide immediately in the event of becoming pregnant and to call her study doctor as soon as possible.

☐ The subject confirmed that she has not and will not breastfeed a baby while taking pomalidomide and for at least 28 days after the last dose of pomalidomide.

☐ The subject has not and will never share pomalidomide with anyone else.

☐ The subject has not and will not donate blood while taking pomalidomide, during dose interruptions and for at least 28 days after the last dose of pomalidomide.

☐ The subject has not and will not break, chew, or open pomalidomide capsules at any point.

☐ The subject confirmed that she will return unused pomalidomide capsules to the study doctor.

2. I have provided the Pomalidomide Information Sheet to the subject.

3.2. Female Not of Childbearing Potential (Natural Menopause for at Least 24 Consecutive Months, a Hysterectomy, or Bilateral Oophorectomy):

1. I have verified and counseled the subject regarding the following:
   - ☐ Potential risk of fetal exposure to pomalidomide: A teratogenic potential of pomalidomide in humans cannot be ruled out. If pomalidomide is taken during pregnancy, it may cause birth defects or death to any unborn baby.
   - ☐ The subject has not and will never share pomalidomide with anyone else.
   - ☐ The subject has not and will not donate blood while taking pomalidomide, during dose interruptions and for at least 28 days after the last dose of pomalidomide.
   - ☐ The subject has not and will not break, chew, or open pomalidomide capsules at any point.
   - ☐ The subject confirmed that she will return unused pomalidomide capsules to the study doctor.
2. I have provided the Pomalidomide Information Sheet to the subject.

Do Not Dispense Pomalidomide if:

- **The subject is pregnant.**
- **No pregnancy tests were conducted for a FCBP.**
- **The subject states she did not use TWO reliable methods of birth control (unless practicing complete abstinence from heterosexual contact) at least 28 days prior to receiving pomalidomide, while receiving pomalidomide and during dose interruptions.**
- **The subject stated that she has or does not want to adhere to pregnancy precautions outlined within this PPP.**

Counselor Name (Print): _____

Counselor Signature: _____ Date: _____/_____/_____(dd/mmm/yyyy)

Maintain a copy of the Education and Counseling Guidance Document in the subject's records.

4. POMALIDOMIDE EDUCATION AND COUNSELING GUIDANCE DOCUMENT FOR MALE SUBJECTS

To be completed prior to each dispensing of pomalidomide.

Protocol Number: _____

Subject Name (Print): _____ DOB: _____/_____/_____ (dd/mmm/yyyy)

1. I have verified and counseled the subject regarding the following:
   - ☐ Potential risk of fetal exposure to pomalidomide: A teratogenic potential of pomalidomide in humans cannot be ruled out. If pomalidomide is taken during pregnancy, it may cause birth defects or death to any unborn baby.
   - ☐ The subject confirmed that he has practiced complete abstinence (True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence [eg calendar, ovulation, symptothermal or post-ovulation methods] and withdrawal are not acceptable methods of contraception.) or used a condom when engaging in sexual contact (including those who have had a vasectomy) with a pregnant female or FCBP, while taking pomalidomide, during dose interruptions and for at least 28 days after the last dose of pomalidomide.
   - ☐ The subject confirmed that he has not impregnated his female partner while in the study.
   - ☐ The subject confirmed that he will notify his study doctor if his female partner becomes pregnant and the female partner of a male subject taking pomalidomide confirmed that she will call her healthcare provider immediately if she becomes pregnant.
   - ☐ The subject has not and will never share pomalidomide with anyone else.
   - ☐ The subject confirmed that he has not donated and will not donate semen or sperm while taking pomalidomide or during dose interruptions and that he will not donate semen or sperm for at least 28 days after the last dose of pomalidomide.
   - ☐ The subject has not and will not donate blood while taking pomalidomide, during dose interruptions and for at least 28 days after the last dose of pomalidomide.
   - ☐ The subject has not and will not break, chew, or open pomalidomide capsules at any point.
   - ☐ The subject confirmed that he will return unused pomalidomide capsules to the study doctor.
2. I have provided the Pomalidomide Information Sheet to the subject.

Do Not Dispense Pomalidomide if:

- **The subject stated that he has or does not want to adhere to pregnancy precautions outlined within this PPP.**

Counselor Name (Print): _____

Counselor Signature: _____ Date: _____/_____/_____(dd/mmm/yyyy)

Maintain a copy of the Education and Counseling Guidance Document in the subject's records.

5. POMALIDOMIDE INFORMATION SHEET

For subjects enrolled in clinical research studies

Please read this Pomalidomide Information Sheet before you start taking pomalidomide and each time you get a new supply. This Pomalidomide Information Sheet does not take the place of an informed consent to participate in clinical research or talking to your study doctor or healthcare provider about your medical condition or your treatment.

What is the most important information I should know about pomalidomide?

1. **Pomalidomide may cause birth defects (deformed babies) or death of an unborn baby.** Pomalidomide is similar to the medicine thalidomide. It is known that thalidomide causes life-threatening birth defects. Pomalidomide has not been tested in pregnant women but may also cause birth defects. Pomalidomide was found to cause birth defects when tested in pregnant rats and rabbits.

   If you are a female who is able to become pregnant:

   - **Do not take pomalidomide if you are pregnant or plan to become pregnant**
   - **You must practice complete abstinence from sexual contact with a male or use two reliable, separate forms of effective birth control at the same time:**
     - for 28 days before starting pomalidomide
     - while taking pomalidomide
     - during breaks (dose interruptions) of pomalidomide
     - for at least 28 days after the last dose of pomalidomide
   - **You must have pregnancy testing done at the following times:**
     - within 10 to 14 days prior to the first dose of pomalidomide
     - 24 hours prior to the first dose of pomalidomide
     - weekly for the first 28 days
     - if you have regular menstrual periods: every 28 days after the first month
     - if you have irregular menstrual periods: every 14 days after the first month
     - if you miss your period or have unusual menstrual bleeding
     - 28 days after the last dose of pomalidomide (14 and 28 days after the last dose if menstrual periods are irregular)
   - **Stop taking pomalidomide if you become pregnant while taking pomalidomide**
     - If you suspect you are pregnant at any time during the study, you must stop pomalidomide immediately and immediately inform your study doctor. Your study doctor will report all cases of pregnancy to Celgene Corporation.

- **Do not breastfeed while taking pomalidomide and for at least 28 days after the last dose of pomalidomide**
- The study doctor will be able to advise you where to get additional advice on contraception.

If you are a female not able to become pregnant:

In order to ensure that an unborn baby is not exposed to pomalidomide, your study doctor will confirm that you are not able to become pregnant.

If you are a male:

The effect of pomalidomide on sperm development is not known and has not been studied. The risk to an unborn baby in females whose male partner is receiving pomalidomide is unknown at this time.

- Male subjects (including those who have had a vasectomy) must practice complete abstinence or must use a condom during sexual contact with a pregnant female or a female that can become pregnant:
  - While you are taking pomalidomide
  - During breaks (dose interruptions) of pomalidomide
  - For at least 28 days after the last dose of pomalidomide
- **Male subjects should not donate sperm or semen** while taking pomalidomide, during breaks (dose interruptions) and for at least 28 days after the last dose of pomalidomide.
- **If you suspect that your partner is pregnant any time during the study, you must immediately inform your study doctor. The study doctor will report all cases of pregnancy to Celgene Corporation. Your partner should call their healthcare provider immediately if they become pregnant.**

2. **All subjects:**
   - **Do not share pomalidomide with other people. It must be kept out of the reach of children and should never be given to any other person.**
   - **Do not donate blood** while you take pomalidomide, during breaks (dose interruptions) and for at least 28 days after the last dose of pomalidomide.
   - **Do not break, chew, or open pomalidomide capsules at any point.**
   - You will get no more than a 28-day supply of pomalidomide at one time.
   - Return unused pomalidomide capsules to your study doctor.

   Additional information is provided in the informed consent form and you can ask your study doctor for more information.

Appendix M Guidance for notification of early termination of the trial according to country applicable regulatory requirements

Detailed guidance from the European Commission, CT-1 4.2.2- 163 states that in case of early termination of the trial, the Sponsor must notify the end of the trial to the national competent authority and the Ethics Committee of the Member State concerned immediately, and at the latest within 15 days after the trial is halted. This notification should clearly explain the reasons for termination and describe follow-up measures, if any, taken for safety reasons.

Appendix N Country-specific requirements

For Japan only

Section 6.4: Study Committee

Independent Review Committee

After the global cut-off date for the primary analysis, the IRC review will continue to review efficacy assessments of Japanese patients with same rules than the one applied before the cut-off for the primary analysis until at least 7 PFS events in the Japanese population are reported.

Section 10.1.6: Post PFS study cut-off date

Data collection for Japanese patients post PFS study cut-off date

For Japanese patients who did not progress and who will be still on treatment at the primary PFS analysis cut-off date, data will continue to be collected as per Section 10.1.3.2, Section 10.1.4 and Section 10.1.5 until disease progression is diagnosed or further anti-myeloma therapy is started or until at least 7 PFS events are observed in the Japanese population (cut-off for the Japanese PFS analysis), whichever comes first.

For Japanese patients who did not progress and will have discontinued study treatment at the primary PFS analysis cut-off date, data will continue to be collected as per Section 10.1.5 until disease progression is diagnosed or further anti- myeloma therapy is started or until at least 7 PFS events are observed in the Japanese population (cut-off for the Japanese PFS analysis), whichever comes first.

Japanese patients who have PD already diagnosed at the cut-off of the primary PFS analysis will be followed as per Section 10.1.6 and Section 10.1.7.

After Japanese PFS cut-off date, all Japanese patients will be followed as per Section 10.1.6 and Section 10.1.7.

In case 7 PFS events are observed in the Japanese population at the time of the primary PFS cut-off date, all Japanese patients will be followed as per Section 10.1.6 and Section 10.1.7.

Appendix O Protocol amendment history

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

Amended clinical trial protocol 4 (25-OCT-2018)

This amended protocol (amendment 04) is considered to be nonsubstantial 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 because it neither significantly impacts the safety or physical/mental integrity of participants nor the scientific value of the study.

Overall rationale for the amendment:

Following a request from the French Health Authorities, wording about the precautions of using dexamethasone together with CYP3A inhibitors has been added in to Section 8.9 concomitant medications. Other changes are to address inconsistencies between tables and the protocol body and to allow the collection of minimal residual disease (MRD) data after the primary analysis cut-off date.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Schedule of assessment table Section 1.2	Addition of minimal residual disease (MRD) assessment to be performed in case of complete response (CR) at end of treatment (EOT) ie. 30 days after last study treatment administration and post treatment Follow-up period ie 60±5 days and every 3 months (±7 days) after last study treatment administration	To provide clarity on he MRD assessment to be performed at EOT and post treatment follow-up visits in case of CR.
Schedule of assessment table footnote [c]	Addition of Day 1 time window of ±2 days for any delay ablow these time windows to be reported in electronic case report form (eCRF)	To clarify on the time window of ±2 days for subsequent cycles on day 1 and any delay above these to be reported in eCRF.
Section 8.2.3.3 Dose adjustments in IPd arm Table 3 (footnote) - Guidelines for dose adjustments for hematologic toxicities isatuximab/ pomalidomide/dexamethasone combination and 8.2.3.4 Table 5 (footnote) - Guidelines for dose adjustments for hematologic toxicities - pomalidomide/dexamethasone combination and Section 10.1.3.1 Cycle 1 (Day 1, Day 8, Day 15, and Day 22 all ± 1 day) and Section 10.1.3.2 Subsequent cycles (Day 1 and 15)	The following additional guidance on neutropenia monitoring was added. If G4 neutropenia, assess absolute neutrophil count every 2-3 days until ANC ≥0.5 x 10^9/L and at least weekly thereafter until ANC ≥1.0 x 10^9/L.	To provide additional guidance on monitoring of Grade 4 neutropenia events for dose adjustments.

Section # and Name	Description of Change	Brief Rationale
Section 8.2.3.4 Modification of isatuximab/pomalidomide/dexamethasone dose levels in case of dose reduction Table 5 - Guidelines for dose adjustments for hematologic toxicities - pomalidomide/dexamethasone combination	Clarification to maintain full dose of study treatment as planned within cycle for Grade 4 thrombocytopenia events.	To provide clarity on the dose adjustments to be followed for patients with Grade 4 thrombocytopenia events.
Section 8.9 Concomitant medications	Addition of description about precautions and consideration of risk-benefit ratio while using dexamethasone with CYP3A inhibitors.	To advise that the co-treatment of dexamethasone with CYP3A inhibitors should be avoided unless the benefit outweighs the increased risk.
Section 9.1 Primary endpoint and Section 10.1.1.1 Screening/baseline	Addition of details about various body parts (skull, spine, all long bones, pelvis, and chest) to be assessed during skeletal survey.	To provide clarity on the various body parts to be assessed during skeletal survey.
Section 10.1.3.1 Cycle 1 (Day 1, Day 8, Day 15 and Day 22 and all ±1 day) and Section 10.1.3.2 Subsequent cycles (Day 1 and 15)	Addition of contraception details for females of childbearing potential (FCBP) and partner on Day 1 and thromboprophylaxis.	This addition is to provide clarity on providing contraception councelling for FCBP and partner on Day 1 and thromboprophylaxis (as per Section 8.9)
Section 10.1.3.2 Subsequent cycles (Day 1 and 15)	Addition of details included if urine M-protein shows negative results at Screening and Cycle 1 Day 1 then a repeat assessment should be performed at every 3 cycles (Cycle 4, Cycle 7, Cycle 10, etc.).	To provide clarity on repeat assessment for urine M-protein.
Section 10.1.6 Post PFS study cut-off date	Addition of details of bone marrow aspirate (BMA) or biopsy as a parameter for MRD assessment.	To provide additional details on BMA as disease assessment parameter and to allow collection of minimal residual disease after the primary cut-off date.
Section 10.4.2 General guidelines for reporting of adverse events Table 10 - Summary of adverse event reporting instructions	Addition of second primary malignancies in the adverse event of special interest (AESI) category.	To provide additional details on inclusion of second primary malignancies as AESI.

Amended Clinical Trial Protocol 3: [13-Sep-2018]

This amended protocol (amendment 03) is considered to be nonsubstantial 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 because it neither significantly impacts the safety or physical/mental integrity of participants nor the scientific value of the study.

Rationale for amendment:

At the request of the Japanese regulatory authorities, the Sponsor has to provide progression free survival (PFS) data of the Japanese population enrolled into the study based on the assessment of the Independent Review Committee. This amendment allows the Sponsor to continue collecting and analyzing central laboratory disease assessment of Japanese patients after the global study cut-off date.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Section 6.4 Study Committee	Added text to specify that for Japanese patients, the IRC review will continue after the cut-off for the primary analysis until at least 7 PFS events in the Japanese population are reported	At the request of the Japanese regulatory authorities, to allow the assessment of progression free survival in the Japanese population by the Independent Review Committee after the global cut-off date for the primary analysis
Section 10.1.6 Post PFS study cut-off date	Added text to clarify how data will continue to be collected to evaluate efficacy both as per Investigator and as per IRC	All data should continue to be collected for Japanese patients until PFS event occur to keep homogeneity in PFS events diagnosis.
Appendix N Country Specific Requirements	Added an Appendix with details of country specific requirements for Japan as per the new template requirements	Added this Appendix as per the new template requirements
Appendix O Protocol Amendment History	Added an Appendix with details of past protocol amendment changes as per the new template requirements	Added this Appendix as per the new template requirements

Amended Clinical Trial Protocol 2 based on Protocol Amendment 03: [18-May-2017]

This amendment is considered to be 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.

Table 12 - Rationale for the amendment

Section # and Name	Description of Change	Brief Rationale
Section 1.2 Study flow chart, Section 6.2.1 duration of study participation for each patient, Section 7.1 Inclusion criteria and Section 10.1.1 Screening/baseline	The Screening window was extended to 28 days for female of childbearing potential (FCBP)	In order to comply with contraception requirements outlined in the Global Pomalidomide Pregnancy Prevention Plan, FCBP must use highly effective methods of contraception 28 days before receiving treatment with pomalidomide, therefore the screening window has been extended for FCBP
Tabulated clinical trial summary and Section 7.2 Exclusion criteria	E03 was amended to clarify the ineligibility of a patient previously treated with an anti-CD38 antibody.	An exclusion criterion E32 was added in local Amendment 02 (GB), to exclude patients with severe acute and chronic medical conditions. This criterion is now added to the global protocol for patients from any country.
Section 1.2 Study flow chart	Addition of visit windows to Post treatment Visits	To keep consistency amongst the visits and assessments
Tabulated clinical trial summary, Section 1.2 Study flow chart and Section 10.1 Visit Schedule	Clarification for pregnancy testing requirements	To clarify and keep consistency across the documents and with the Pomalidomide Pregnancy Prevention Plan.

Section # and Name	Description of Change	Brief Rationale
Section 1.2 Study flow chart and Section 10.1.3.2 Subsequent cycles Day 1 and Day 15	Clarification on Investigator decision to continue study treatment based on local laboratory results	In certain countries, the local laboratory is not able to quantify M protein in serum and/or urine, leading to the need to have this analysis performed at the central laboratory.
Section 1.2 Study flow chart and Section 10.1.1 Screening/baseline	Additional assessments regarding antibody screening tests and clarification on blood phenotyping	According to the label of the approved anti CD38 daratumumab, and according to the literature, daratumumab can cause interference with red blood cell antibody screening for blood transfusions. Currently, there is no clinical data with isatuximab, so in order to investigate if the interference is common to isatuximab, an antibody screening test is added after 4 infusions of isatuximab and anytime a red blood cell transfusion is needed.
Section 1.2 Study flow chart and Section 10.1 Visit Schedule	Clarification on timing of Day 1 laboratory assessments and physical examinations	Laboratory assessments and physical examinations can be performed within 24 hours prior to study treatment administration on Day 1 (ie, they may be performed the day before).
Section 1.2 Study flow chart, Section 8.1.2, Pomalidomide, Section 8.9.4 Contraceptive measures and pregnancy counseling, new Appendix L - Global Pomalidomide Pregnancy Prevention Plan	Addition of the Global Pomalidomide Pregnancy Prevention Plan	To update the protocol with the global Pomalidomide Pregnancy Prevention Plan and keep consistency between the requirements of anti-conception counseling and the screening window.
Section 6.4 Study committees	Deletion of description of IRC review of extramedullary disease	The IRC will not confirm presence or absence of extramedullary disease, the IRC will review and assess response only.
Section 4.5.3 Benefit/Risk	Addition of benefit/risk summary	To add the missing benefit/risk assessment in rationale section of the protocol.
Section 8.2 Dosage and schedule	Pre-medication reconsideration for IARs	To add a paragraph explaining that patients who do not experience IARs upon the first 4 administrations of isatuximab are able to have their need for pre-medication reconsidered at the Investigator's discretion, in accordance with recommendations across the isatuximab program. Also, to allow the use of methylprednisolone 100mg IV whenever dexamethasone is not tolerated as premedication.
Section 8.2.3.1 General rules	Clarification regarding dose reductions for pomalidomide	To avoid inconsistencies between the protocol body and Tables 3 and 5.
Section 8.2.4 Infusion reactions	Update information regarding the stability of diluted isatuximab solution (infusion bag)	To clarify that, in case of infusion interruption, re-administration should be done within the time specified in the pharmacy manual.

Section # and Name	Description of Change	Brief Rationale
Section 10.1.7 Post OS study cut-off date	Clarification on the management of patients still receiving treatment at the OS cut off date and addition of pregnancy testing and reporting of laboratory abnormalities	To better define the data to be collected in patients who are still receiving treatment at the OS cut-off date.
Section 10.4.1.3 Adverse events of special interest	Addition of instructions for overdose of Non-Investigational Medicinal Product (NIMP)	To add definition and instructions for the reporting of symptomatic overdose of NIMP during the study
Section 10.5 Obligations of the Sponsor	Inclusion of reference to Investigator Brochure table for expected adverse reactions	Following a request from the UK health authority and subsequent local Amendment 02 (GB), a reference to the table of expected adverse reactions per the Investigator Brochure was added.
Section 11.5 Interim Analysis	Update of the number of OS events observed before interim analysis occurs	Following implementation of Amendment 01, the estimation of PFS analysis had to be adjusted due to a reduction of the enrollment window.
Appendix B ECOG Performance Status Scale	Updates to ECOG performance status scale	To update the ECOG performance scale with the latest version, including a reference.
Appendix D IMWG Response Criteria	Updates to IMWG response criteria	To add clarification and make editorial updates.
Appendix M (new) Guidance for notification of early termination of the trial according to country applicable regulatory requirements	Addition of guidance for notification of early trial termination	To address the request of the Swedish health authority, the corresponding information on trial termination according to the European legislation was added in Appendix M.

Amended Clinical Trial Protocol 01 (GB) based on Protocol Amendment 02 (GB) [24-Feb-2017]

This amendment is not considered to be 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.

Overall Rationale for the Amendment

The protocol was amended following the request of the United Kingdom Medicines and Health Care Products

Table 13 - Rationale for the amendment

Section # and Name	Description of Change	Brief Rationale
Tabulated clinical trial summary and Section 7.2 Exclusion criteria	Addition of exclusion criterion 32	Following the request of the United Kingdom Medicines and Health Care Products Regulatory Agency, an exclusion criterion, E32, is added to prevent the enrolment of patients with serious acute or chronic medical conditions such as systemic infections unless specific anti-infective therapy is employed.
Section 10.5 Obligations of the Sponsor	Clarification regarding the reference safety information in the protocol	Following the request of the United Kingdom Medicines and Health Care Products Regulatory Agency, the specific location of the reference safety information for isatuximab in the Investigator Brochure has been clarified. The number of the table containing the reference safety information has not been referenced as this could potentially change in a subsequent version of the Investigator's Brochure, so the table title has been referenced instead.

Amended Clinical Trial Protocol 01 based on Protocol Amendment: [01-Nov-2016]

This amendment is considered to be 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.

Overall Rationale for the Amendment

Table 14 - Rationale for the amendment

Section # and Name	Description of Change	Brief Rationale
Section 1.2 Study flow chart, Section 1.3 PK/PD Flow chart, Section 10.1.3.2 and Section 10.1.4 End of treatment	Addition of electrocardiogram (ECG) assessments	Isatuximab being a monoclonal antibody, i.e., a large protein, has a low likelihood to inhibit hERG. Available clinical data does not show any evidence of repolarization problems. After interaction with US Federal Drug Administration, the agency agrees with this fact, although they encouraged the Sponsor to add the ECG assessments as a precautionary measure at the end of treatment and once during the study; electrocardiogram assessments were therefore added at Cycle 2 Day 1 (pre-dose) and at end of treatment.
Section 8.2.1 Study treatments (IMP)	Removal of fasting requirements for pomalidomide administration	The requirement for pomalidomide to be taken without food (at 2 hours before or 2 hours after a meal) was removed, this change was made to reflect updates to the pomalidomide prescribing information.

Section # and Name	Description of Change	Brief Rationale
Tabulated clinical trial summary, Section 1.2 Study flow chart, Section 9.1 Primary endpoint, Section 10.1.1 Screening/Baseline Section 10.1.3.2 Subsequent cycles Day 1 and Day 15, Section 10,1.5.1 60 Days visit and Section 10.1.5.2 Further follow-up visits	Clarification of radiographic assessments for bone disease	Updates were made to state there are two options for assessment of bone disease: skeletal survey and low-dose whole-body CT scan. This change was made in order to improve and optimize the way bone disease is assessed at baseline and during the study. The assessment of extramedullary disease was updated in order to clarify that in patients with known extramedullary disease at baseline a CT-scan or MRI is to be done at baseline and every 12 weeks (+/- 1 week) and for those with suspicion of extramedullary involvement (including bone plasmacytoma) a CT scan or MRI is to be performed to confirm or rule-out its presence at baseline. If confirmed, the same approach as known involvement is to be followed.
Section 1.2 Study flow chart and Section 10.1.3.2 Subsequent cycles Day 1 and Day 15	Add clarification regarding the sampling for Free Light Chain assay for the central laboratory	In order to clarify that a sample is to be obtained and to be analyzed only to confirm and document CR in samples obtained for FLC assessment after C1D1
Section 1.2 Study flow chart and Section 10.1.1 Screening/baseline	Add wording allowing to explore cytogenetic abnormalities other than del(17p); t(4:14); t(14:16)	The reason for this change is that even if three alterations defining the high-risk disease are well established there are emerging data showing that some cytogenetic alterations would have additional impact on the prognosis of patients.
Section 9.1 and Appendix D	Update of International Myeloma Working Group (IMWG) criteria for disease assessment	Criteria for assessment of disease status in this study was updated to the most recent IMWG guidance according to Kumar et al, 2016. This is to reflect the most recent best practice in assessment of myeloma.
Section 1.2 Study flow chart and Section 1.3 PK/PD Flow chart	Removal of PK sampling on Day 15 of cycles subsequent to Cycle 4	This change was made to optimize the schedule of PK assessments.
Tabulated clinical trial summary, Section 1.2 Study flow chart, Section 9.3.3, patient-reported outcomes, Section 10.1.2 Randomization, Section 10.1.4 End of treatment and Section 10.1.5 Post treatment follow-up	Patient-reported outcomes assessed at EOT and 60 days after last study treatment	PRO data for those that progress should continue to be collected per EMA recommendation (and 1 to 2 time points post progression should suffice); the data will be collected twice up to Day 60 after the last study treatment administration. The rationale for collecting PRO data for those who do not progress nor discontinue was recommended as useful information to collect for comparison. PRO data collection is not recommended for those who have discontinued treatment without progression, so these assessments will not be collected any more after the End of Treatment visit.
Section 10.4.1.3 Adverse events of special interest	Addition of second primary malignancy as adverse events of special interest	To facilitate accurately and timely report second primary malignancies as potential AEs of IMiDs

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