AMENDED CLINICAL TRIAL PROTOCOL NO. 06

COMPOUND: isatuximab/SAR650984

A Phase 1/2 study to evaluate safety, pharmacokinetics and efficacy of isatuximab in combination with cemiplimab in patients with relapsed/refractory multiple myeloma

STUDY NUMBER: TCD14906

VERSION DATE / STATUS: 21-Mar-2022 / Approved

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PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY

Document	Country/Countries impacted by amendment	Date, version
Amended Protocol 06	All	21-Mar-2022, Version 1 (electronic 6.0)
Amended Protocol 05	All	14-Aug-2020, Version 1 (electronic 5.0)
Amended Protocol 04	All	11-Jun-2019, Version 1 (electronic 4.0)
Amended Protocol 03	All	06-Aug-2018, Version 1 (electronic 3.0)
Protocol Amendment 03	All	06-Aug-2018, Version 1 (electronic 1.0)
Amended Protocol 02	All	17-Nov-2017, Version 1 (electronic 2.0)
Protocol Amendment 02	All	17-Nov-2017, Version 1 (electronic 1.0)
Amended Protocol 01	All	30-May-2017, Version 1 (electronic 1.0)
Protocol Amendment 01	All	30-May-2017, Version 1 (electronic 1.0)
Clinical Trial Protocol	All	12-Apr-2017, Version 1 (electronic 2.0)

Amended protocol 06 (21 March 2022)

This amended protocol (amendment 06) is considered to be non-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 study medication cemiplimab 250 mg, concentrated solution 50 mg/mL in 10 mL vials with 5.0 mL withdrawable is no longer being produced by the manufacturer Regeneron. It is being replaced by cemiplimab 350 mg, concentrated 50 mg/mL in 10 mL vials with 7 mL withdrawable. However, the concentration remained the same (50 mg/mL); only the withdrawable amount is changed to 5.0 mL or 7.0 mL. The patient will continue to receive 5 mL (250 mg).

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Clinical trial summary; Study Treatment(s) – Formulation – Cemiplimab; 8.1.2.1 Pharmaceutical form	The withdrawable amount of cemiplimab was changed to 5.0 mL or 7.0 mL. The 7.0 mL withdrawable was added.	Cemiplimab 250 mg, concentrated solution 50 mg/mL in 10 mL vials with 5.0 mL withdrawable is no longer produced by Regeneron and will be replaced by cemiplimab 350 mg, concentrated solution 50 mg/mL in 10 mL vials with 7.0 mL withdrawable. However, the concentration remains same at 50 mg/mL; and the participant will continue to receive 5.0 mL.

NAMES AND ADDRESSES OF

COORDINATING INVESTIGATOR	Name: Address: Tel: Fax: E-mail:	
MONITORING TEAM'S REPRESENTATIVE	Name: Address: Tel: Fax: E-mail:	
SPONSOR	Company: Address: Tel: Fax:	
OTHER EMERGENCY TELEPHONE NUMBERS		

CLINICAL TRIAL SUMMARY

COMPOUND: isatuximab/ SAR650984	**STUDY No.: TCD14906**
TITLE	A Phase 1/2 study to evaluate safety, pharmacokinetics and efficacy of isatuximab in combination with cemiplimab in patients with relapsed/refractory multiple myeloma
INVESTIGATOR/TRIAL LOCATION	Multiple sites & country
PHASE OF DEVELOPMENT	Phase 1/2
STUDY OBJECTIVE(S)	**Primary objective(s):** • To determine the safety and tolerability of the combination of isatuximab and cemiplimab. • To compare the overall response rate (ORR, defined as complete response [CR]+very good partial response [VGPR]+partial response [PR]) of the combination of Isatuximab and cemiplimab versus isatuximab alone in patients with RRMM based on International Myeloma Working Group (IMWG) criteria (Phase 2 only). **Secondary objective(s):** • To determine the following efficacy measurements (Phase 2 only): - Clinical benefit rate (CBR, CR + VGPR + PR + Minimal response [MR]), - Duration of response (DOR), - Time to response (TTR), - Progression free survival (PFS), - Overall survival (OS). • To determine pharmacokinetic profile of isatuximab and cemiplimab when given in combination. • To assess the immunogenicity of isatuximab and cemiplimab when given in combination. **Exploratory Objectives:** • To explore the minimal residual disease (MRD) in patients achieving a CR. • To assess the relationship between immune phenotypes, immune regulatory marker expression, adaptive immune response and parameters of clinical response. • To explore central/effector memory T cell proliferation.
STUDY DESIGN	This is Phase 1/2 study to evaluate the safety, tolerability, efficacy and pharmacokinetics (PK) of isatuximab in combination with cemiplimab in RRMM. The study will be conducted in 2 parts: • The Phase 1 (lead in) part is to confirm the feasibility of the isatuximab/cemiplimab combination. • The Phase 2 part will further evaluate the safety, efficacy and PK of the combination versus isatuximab monotherapy. Patients will be randomized in 1:1:1 in 3-arms or 1:1 in 2-arms study using an IRT. Isatuximab and cemiplimab are defined in this protocol as “study treatments”.

Phase 1 part:

Given the promising early signs of anti-cancer activity and the acceptable safety profile of each of the two antibodies (no maximum tolerated dose [MTD] has been reached with either one as monotherapy), the starting dose will be 10 mg/kg once weekly (QW) for 4 weeks followed by once every 2 weeks (Q2W) for isatuximab and 250 mg Q2W for cemiplimab. Dose de-escalation will be performed if necessary as defined in the table below:

Dose level (DL)	Isatuximab	Cemiplimab
Dose level 1 (DL1)	10 mg/kg QWx4 >Q2W	250 mg Q2W
Dose level -1 (DL-1)	10 mg/kg QWx4 >Q2W	250 mg Q4W
Dose level -2 (DL-2)	10 mg/kg Q2W	250 mg Q4W

Patients will continue treatment until disease progression, unacceptable adverse events, consent withdrawal, or any other reason.

At dose level 1 (DL1), 3 patients will be enrolled for DLT evaluation (in Cycle 1):

- If 0/3 patient has dose limiting toxicity (DLT), no more patients will be enrolled in Phase 1, and DL1 will be the recommended Phase 2 dose (RP2D).
- If 1/3 patient has DLT at DL1, additional 3 patients will be enrolled at DL1 for DLT assessment:
  - If a total of 1/6 patient treated at DL1 has DLT, DL1 will be the RP2D,
  - If a total of ≥2/6 patients have DLT at DL1, dose will be de-escalated to dose level minus 1 (DL-1).
- If ≥2/3 patients have DLT at DL1, dose will be de-escalated to dose level minus 1 (DL-1).

At DL-1, the same DLT observation rule will be applied for selecting a RP2D and for dose de-escalation.

At DL-2, the same DLT observation rule will be applied for selecting a RP2D, and if ≥2/6 patients have DLT, study committee will analyze all the data collected up to this point and determine whether the study is to be terminated without proceeding to Phase II or if alternative doses and schedules could be further examined in Phase I, or changes in the study design could be made, based on the perceived benefit/risk to patients and on the PK results.

The DLT observation period is 1 cycle (28 days). However, all adverse events (AE) during treatment unless due to disease progression or an obviously unrelated cause will be taken into consideration by the Study Committee for the determination of the MTD and RP2D.

Enrollment of patients within and between cohorts is to be staggered by at least 3 days.

The NCI CTCAE version 4.03 will be used to assess the severity of AEs, causal relationship is to be determined by the investigator. The DLTs will be confirmed by the Study Committee.

Hematologic DLT is defined as any of the followings unless due to disease progression or an obviously unrelated cause:

- Grade 4 neutropenia lasting more than 7 consecutive days.

	• Grade 3 to 4 neutropenia complicated by fever (temperature ≥38.5˚C on more than one occasion) or microbiologically or radiographically documented infection. • Grade 3 to 4 thrombocytopenia associated with clinically significant bleeding requiring clinical intervention. Note: Platelet transfusions in the absence of bleeding will not be considered a DLT because thrombocytopenia is an anticipated complication of multiple myeloma (MM), particularly in a heavily pretreated patient population, and patients can enter the study with pre-existing thrombocytopenia. **Non-hematologic DLT** is defined as any of the followings unless due to disease progression or an obviously unrelated cause: • Grade 4 non-hematologic AE. • Grade ≥2 uveitis. • Grade 3 non-hematological AE lasting >3 days despite optimal supportive care. **except**: - Grade 3 fatigue, - Allergic reaction/hypersensitivity attributed to isatuximab or cemiplimab, - Grade 3 or 4 lab abnormality that is not clinically significant per investigator and study committee. • Delay in initiation of Cycle 2 more than14 days due to treatment related laboratory abnormalities/AE. In addition, any other AE that the investigator / Study Committee deem to be dose limiting, regardless of its grade, may also be considered as DLT. **Phase 2 part:** Phase 2 will have 3 arms (if the MTD or RP2D is at DL1 or DL-1) or 2 arms (if the MTD or RP2D is at DL-2) to assess the treatment response and safety of the combination therapy compared with isatuximab alone. After confirmation of eligibility criteria, patients will be randomly assigned using an interactive response technology (IRT), in a 1:1:1 ratio or 1:1 ratio in 1 of the 3- or 2-arm study, respectively, with 35 patients in each arms. If RP2D is DL1: • Arm 1 (control): isatuximab 10 mg/kg QWx4 followed by Q2W. • Arm 2 (DL1): isatuximab 10 mg/kg QWx4 followed by Q2W + cemiplimab 250 mg Q2W. • Arm 3 (DL-1): isatuximab 10 mg/kg QWx4 followed by Q2W + cemiplimab 250 mg Q4W. If RP2D is DL-1: • Arm 1 (control): isatuximab 10 mg/kg QWx4 followed by Q2W. • Arm 2 (DL-1): isatuximab 10 mg/kg QWx4 followed by Q2W + cemiplimab 250 mg Q4W. • Arm 3 (DL-2): isatuximab 10 mg/kg Q2W + cemiplimab 250 mg Q4W. If RP2D is DL-2: • Arm 1 (control): isatuximab 10 mg/kg QWx4 followed by Q2W. • Arm 2 (DL-2): isatuximab 10 mg/kg Q2W + cemiplimab 250 mg Q4W. Anti-CD38 refractory cohort: Patients who received anti-CD38 mAb within 6 months before study entry and had disease progression while on treatment or within 60 days after the last treatment

	will be enrolled in a separate cohort. A decision will be made to start the cohort after the planned Phase 2 interim analysis suggested a treatment benefit of the combination therapy including pass the futility check. The dose and schedule will be determined based on the efficacy and safety findings in the interim analysis.
STUDY POPULATION **Main selection criteria:**	**Inclusion criteria:** I 01. Age ≥18. I 02. Patients must have a known diagnosis of multiple myeloma with evidence of measurable disease, as defined below: - Serum M-protein ≥1 g/dL (≥0.5 g/dL in case of IgA disease), AND/OR - Urine M-protein ≥200 mg/24 hours, OR - In the absence of measurable M-protein, serum immunoglobulin free light chain ≥10 mg/dL, and abnormal serum immunoglobulin kappa lambda free light chain ratio (<0.26 or >1.65). I 03. Patients must have received prior treatment with an immunomodulatory drug (IMiD) (for ≥2 cycles or ≥2 months of treatment) and a proteasome inhibitor (PI) (for ≥2 cycles or ≥2 months of treatment). I 04. Patients must have received at least 3 prior lines of therapy (Note: Induction therapy and stem cell transplant ± maintenance will be considered as one line). I 05. Patients must have achieved MR or better with any anti-myeloma therapy (ie, primary refractory disease is not eligible). I 06. Patients understand and have signed the Written Informed Consent form and are willing and able to comply with the requirements of the study. I 07. Anti-CD38 refractory cohort only: Patients who received anti-CD38 mAb within 6 months before study entry and had disease progression while on treatment or within 60 days after the last treatment. **Exclusion criteria:** E 01. Has any concurrent hematologic malignancy other than multiple myeloma, including: - Active primary amyloid light-chain (AL) amyloidosis, - Concomitant plasma cell leukemia. E 02. Has prior exposure to: - Isatuximab or participated clinical studies with isatuximab, - Any agent (approved or investigational) that blocks the PD-1/PD-L1 pathway. E 03. Diagnosed or treated for another malignancy within 3 years prior to the study treatment with the exception of resected/ablated basal or squamous cell carcinoma of the skin, or carcinoma in situ of the cervix, or other local tumors considered cured by local treatment, or low risk prostate cancer after curative therapy. E 04. Evidence of other immune related disease /conditions, including: - Ongoing or recent (within 2 years) evidence of significant autoimmune disease that required systemic immunosuppressive treatment (ie, with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc) is not considered a form of systemic treatment,

	- History of moderate immune-mediated acute drug reactions (eg, colitis, hepatitis, etc). E 05. History of non-infectious pneumonitis requiring steroids or current pneumonitis; history of the thoracic radiation. E 06. Has received a live-virus vaccination within 30 days of planned treatment start. Seasonal flu vaccines that do not contain live virus are permitted. E 07. Known to be HIV+, HBV+ or hepatitis A, B, or C active Infection, or active tuberculosis, or severe and active infection requiring systemic antibiotics, antivirals or antifungals within 2 weeks prior to first dose (except when used for chronic prophylaxis). E 08. Has allogenic haemopoietic stem cell (HSC) transplant. E 09. Has prior exposure to treatments, including: - Prior treatment with idelalisib (an PI3K inhibitor), - Any anti-myeloma drug treatment including dexamethasone within 14 days before study entry (90 days if prior anti-CD38 treatment), - Patients who received anti-CD38 mAb within 6 months before study entry and had disease progression while on treatment or within 60 days after the last treatment will be excluded except the anti-CD38 refractory cohort, - Any major procedure within 14 days before the first study treatment: plasmapheresis, major surgery (kyphoplasty is not considered major procedure), radiotherapy (palliative radiotherapy may be given to control pain), - Any investigational drugs within 28 days or 5 half-lives from the first study treatment, whichever is longer. E 10. Congestive heart failure (New York Heart Association class III to IV), myocardial infarction within 6 months or with reduced ejection fraction, symptomatic coronary artery disease, major clinically significant electrocardiogram (ECG) and echocardiogram abnormalities, significant ventricular arrhythmias; E 11. Ongoing Grade ≥2 adverse events (excluding alopecia and those listed in eligibility criteria) from any prior anti-cancer therapy (NCI-CTC v4.03). E 12. Eastern Cooperative Oncology Group (ECOG) performance status (PS) >2. E 13. Inadequate hematological function including: - Platelets <50,000/mm^3. Patient should be platelet transfusion independent for 2 weeks prior to screening lab values), - Absolute neutrophil count (ANC) ≤1000/mm^3 (1 x 10^9/L). (use of colony-stimulating factors to achieve these counts is allowed), - Hemoglobin <8.0 g/dL(patients may receive red blood cell transfusion or receive supportive care such as erythropoietin and darbepoetin in accordance with institutional guidance). E 14. Inadequate liver function including: - Total bilirubin >2 times of the upper limit of the normal range (ULN), - AST and/or ALT >3 x ULN. E 15. Inadequate renal function: estimated glomerular filtration rate (eGFR) <30 mL/min/1.73m^2 (Modified Diet in Renal Disease [MDRD] Formula). E 16. Corrected serum calcium >14 mg/dl (>3.5 mmol/L). E 17. Pregnant or breastfeeding female patients.

	E 18. Women of childbearing potential and male subjects with female partners of childbearing potential who are not willing to avoid pregnancy by using effective contraceptive (prior to initial dose, during the course of study and up to 6 months after the last study treatment. See Appendix J for guidance of the contraceptive and collection of pregnancy information. E 19. Known intolerance or hypersensitivity to any component of isatuximab and/or cemiplimab. E 20. Employees of the clinical study site or any other individuals directly involved in the conduct of the study, or immediate family members of such individuals.
	E 21. Patients who are accommodated in an institution because of regulatory or legal order, or prisoners or subjects who are legally institutionalized, or patients with any severe acute or chronic medical condition, including psychological disorder, which could impair the ability of the patient to participate in the study or interfere with interpretation of study results or patient unable to comply with the study procedures.
Total expected number of patients: **Expected number of sites:**	Approximately 108 to 138 patients Approximately 37
STUDY TREATMENT(s)	
Investigational medicinal product(s) **Formulation:**	Isatuximab Cemiplimab **Isatuximab (also known as SAR650984):** drug product concentrated solution for infusion in vials containing 20 mg/mL (500 mg/25 mL) isatuximab in 20 mM histidine, 10% (w/v) sucrose, 0.02% (w/v) polysorbate 80, pH 6.0. **Cemiplimab (also known as REGN2810):** drug product concentrated solution 50 mg/mL in 10 mL vials with 5.0 mL or 7.0 mL withdrawable, containing 10 mM histidine, 5% (w/v) sucrose, 1.5% (w/v) L-proline, and 0.2% (w/v) polysorbate 80, pH 6.0.
Route(s) of administration: **Dose regimen:**	**Isatuximab:** IV infusion **Cemiplimab**: IV infusion **Isatuximab:** • For isatuximab alone as control, and at DL1 and DL-1: 10 mg/kg QW for 4 weeks followed by Q2W (ie, on Days 1, 8, 15 and 22 in Cycle 1, and on Days 1 and 15 in Cycle 2 and beyond, of a 28-day cycle). • For DL-2: 10 mg/kg Q2W (ie, on Days 1 and 15 every cycle, of a 28-day cycle). **Cemiplimab:** • For DL1: 250 mg Q2W (ie, on Days 1 and 15 in all cycles of a 28-day cycle). • For DL-1 and DL-2: 250 mg Q4W (ie, on Day 1 all cycles of a 28-day cycle) When patients receive combination therapy, cemiplimab will be administered first followed by Isatuximab.

Non investigational medicinal product(s) **Formulation:**	All patients will receive following pre-medications to prevent or reduce infusion associated reactions, 30 to 60 minutes prior to the start of isatuximab infusion. Patients who do not experience an IAR during the first 4 administrations of isatuximab may have the need for subsequent pre-medication reconsidered at the investigator's discretion in consultation with the sponsor. • Acetaminophen 650 to 1000 mg oral route (PO) (or equivalent). • Ranitidine 50 mg IV (or equivalent). • Diphenhydramine 25-50 mg IV (or equivalent). • Methylprednisolone 100 mg IV (or equivalent). (Non-investigational products will be locally sourced and formulations may vary).
Route(s) of administration:	See above
Dose Time: **Dosing sequence:**	Pre-medications will be administered 30 to 60 minutes prior to isatuximab infusion. On Days 1 and 15 of each cycle, the administration sequence is: pre-medications followed by cemiplimab followed by isatuximab. On Days 8 and 22 of Cycle 1, the administration sequence is: pre-medications followed by isatuximab.
ENDPOINT(S)	**Primary endpoint:** Safety evaluation will be performed continuously throughout the study period and will include the following: • DLTs at Cycle 1 (Phase 1 part only). • Vital signs and physical exam. • Adverse event evaluation (throughout study) including immune related AEs. Severity grade will be determined according to the NCI CTCAE v4.03. • Laboratory tests in blood and urine. • Cytokines (TNF-α, IL-1-β, IL-6, IFN-γ), markers of complement (C3a, C4, CH50), LDH, serum tryptase. • Efficacy is the co-primary endpoint (Phase 2 part only) and will be assessed by ORR. • ORR: defined as the proportion of patients with CR (including stringent complete response [sCR]), VGPR, and PR as assessed by investigators using the IMWG response criteria. **Secondary endpoint(s) (efficacy endpoints including CBR, DOR, TTR, PFS and OS apply to Phase 2 part only):** • CBR: defined as the proportion of patients with CR (including sCR), VGPR, PR and minimal response (MR) as assessed by investigators using the IMWG response criteria. • DOR: defined as the time from the date of the first response (≥PR) that is subsequently confirmed to the date of first confirmed disease progression or death, whichever happens first. Disease progression will be determined according to IMWG criteria. Progression determined by M-protein or free light chain will be confirmed based on two consecutive assessments. In the absence of the confirmation of subsequent disease progression or death before the analysis cut-off date or the date of initiation of a further anticancer treatment, the DOR will be censored at the date of the last valid disease assessment not showing disease

	progression performed prior to initiation of a further anticancer treatment and the analysis cut-off date, whichever is earlier. DOR will not be calculated for patients that do not achieve a PR or better. • TTR: defined as time from first study treatment administration (Cycle 1, Day 1) to first response (PR or better) that is subsequently confirmed. • PFS: defined as time from the first study treatment administration to the date of first documentation of disease progression that is subsequently confirmed or the date of death from any cause. Same censoring rules as DOR will be used. • OS: defined as the time from the first study treatment administration to death from any cause. Patients without death prior to the analysis cutoff date will be censored at the last date the patient was known to be alive or the cutoff date whichever comes first. • Immunogenicity of isatuximab and cemiplimab will be assessed before treatment, during treatment and at follow-up visits. • PK evaluation: for both isatuximab and cemiplimab, blood samples will be collected at selected time points in all patients treated in order to assess the PK profile of isatuximab and cemiplimab. Cemiplimab will be measured in serum and isatuximab in plasma. PK parameters for both compounds will be calculated using non-compartmental analysis. **Exploratory endpoints:** • MRD assessment in bone marrow in CR patients, as clinically indicated. • Immunophenotype (such as NK, T, MDSC cells, Treg/CD8 effector ratio) in blood and bone marrow, as well as immune regulatory marker (eg, PD1, PD-L1) expression on immune cell subsets will be analyzed and correlated with clinical response. • Whenever possible, genomic and protein expression of selected markers (including PD-L1) in malignant plasma and immune cells will be determined by IHC and RNA-specific assays in baseline bone marrow biopsy, optional C3 and EOT biopsy samples and correlated with clinical response. • The change in proliferative activity of effector / memory T cell subsets in response to treatment will be assessed by Ki67 flow cytometry assay in blood and any available bone marrow samples. • The T cell receptor sequence clonality in blood and bone marrow at baseline and any available on-treatment samples will be determined by TCR-beta sequencing assay and correlated with clinical response. • Humoral and cellular immune responses to myeloma-related tumor antigens will be analyzed in blood and correlated with clinical response. • Explore exposure-response relationships for efficacy, safety, and biomarkers for the combination.
ASSESSMENT SCHEDULE	Please see Section 1.1 Study Flowchart and Section 1.2 PK/PD.

STATISTICAL CONSIDERATIONS	**Sample size determination:** In Phase 1, the actual sample size is expected to vary depending on DLTs observed and number of dose levels explored. The study will follow a standard 3+3 design and 3 to 18 patients might be enrolled. In Phase 2, assuming ORR = 20% in control arm (isa alone arm) and ORR = 50% in combination arms, using Fisher's exact test to compare the ORR in control vs combination arms, given the 1-sided type I error of 5% for each combination arm), 35 patients per arm is required to achieve 79% power for each combination arm). Therefore a maximum number of 105 patients is required in Phase 2 randomization part. A separate anti-CD38 refractory cohort with 15 patients might be enrolled if a treatment benefit is suggested for the combination therapy at the interim analysis including pass the futility check. Assuming ORR =20% or more in the combination therapy, a size of 15 patients is required to test against a null hypothesis of ORR $\leq$1% (ie, no activity in the Isa alone arm) with a one-sided α of 0.05 and 82% power. Including both Phase 1 and Phase 2 patient, a total of 108 to 138 patients are required. **Main Analysis populations:** Phase 1 and Phase 2 patients will be analyzed separately. For Phase 1, the all-treated (or safety) population will include all screened patients who received at least 1 dose (even incomplete) of study treatments. For Phase 2, the all treated (or safety) population will include all randomized patients who received at least 1 dose (even incomplete) of study treatments. This population is the primary population for the analyses of exposure and safety parameters. For Phase 2 patients only, the intent to treat (ITT, or randomized) population include all patients with a signed informed consent form who have been allocated a randomization number by the IRT, regardless of whether the patient was treated or not. This population is the primary population for the analyses of efficacy parameters. The PK population will include patients from the treated/safety population with at least one drug concentration after study drug administration (whatever the cycle and even if dosing is incomplete). The anti-drug antibody (ADA, immunogenicity) population will include all patients from the all-treated/safety population with at least 1 available ADA result after the study drug administration. **Primary endpoints:** A listing of patients with DLTs will be provided for Phase 1 patients. For Phase 1 and Phase 2 patients separately, number (%) of patients experiencing treatment- emergent AEs (TEAE) by primary system organ class and preferred term will be summarized by CTCAE grade (all grades and Grade ≥3) for the all-treated population. Same table will be prepared for drug related TEAEs, infusion associated reactions, TEAEs leading to treatment discontinuation, serious TEAEs and TEAEs with fatal outcome. For patients with multiple occurrences of the same AE within the TEAE period, the worst grade will be used. In addition, adverse events occurring or worsening during the 'extended safety follow-up period' (defined as the time period from 31days after the last dose of study treatments to 90 days after the last dose of study treatments) will also be summarized. Hematology and biochemistry results will be graded according to the CTCAE version 4.03, 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.

	For Phase 2 patients only, ORR will be summarized with descriptive statistics. Confidence interval will be computed using Clopper-Pearson method. The Fisher's exact test will be performed to compare the ORR in control arm vs each of the combination arm, using a 1-sided significance level of 0.10 with Hochberg adjustment (at time of primary analysis of ORR; ie, cutoff date 6 months after last patient in). **Analysis of secondary endpoints:** For Phase 2 patients only, the analysis of CBR will be similar to that described for ORR. The DOR, PFS and OS will be analyzed using Kaplan-Meier methods. **Pharmacokinetics:** Descriptive statistics on concentrations and PK parameters will be provided for both isatuximab and cemiplimab. **Analysis cutoff:** Cutoff date for primary analysis of ORR will be 6 months after last patient first treatment. The final analysis cutoff date for OS analysis and updated analysis of ORR and other secondary endpoints will be approximately 12 months after last patient first treatment. **Interim analysis:** For Phase 2, an interim analysis of response rate (including confirmed and unconfirmed responses) will be conducted when the first 15 randomized patients in each arm have completed 2 cycles of treatment or permanently discontinue the treatment. A combination arm will be stopped early for futility when the conditional power is less than 30%. In addition, formal safety review by DMC are planned approximately every 3 months to review data relating patient safety and quality of trial conduct.
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. The cycle duration is 28 days. Patients will continue treatment until disease progression, unacceptable adverse events, consent withdrawal, or any other reason. After treatment discontinuation, patients will return to the study site 30 days (+5 days) after the last dose of study treatments for end-of-treatment assessments. The post-treatment follow-up period includes an extended safety follow-up period of 90 days after the last dose of study treatment, and further follow-up beyond 90 days after last treatment until death or final study cut-off date, whichever occurs first. <u>The further follow up schedule beyond 90 days after last treatment is according to the disease progression status:</u> Patients who discontinue study treatment due to disease progression: follow-up visit will be done every 3 months from the date of last study treatment administration until death or final study cut-off date. Patients who discontinue the study treatment without disease progression: will be followed every month for disease assessment until confirmation of disease progression or start treatment with another anti-cancer therapy whichever comes first. After disease progression patient will be followed every 3 months as described just above until death or final study cut-off date.

1 FLOW CHARTS

1.1 STUDY FLOWCHART

Evaluation[a]	Screening/ Baseline	Cycle 1[b]				Subsequent Cycles[b]		End of Treatment (EOT)	Post treatment Follow-up Period[jj]		
	D-21 to D1	D1	D8	D15	D22	D1	D15	30 days after last IMP admin	At 60 days after last IMP admin	At 90 days after last IMP admin	Beyond 90 days after last IMP admin
Informed Consent / Inclusion/Exclusion Criteria	X										
Randomization		X									
Demography, Medical/Surgical and Disease History[c]	X										
Physical Examination[d]	X(within 7 days prior to first dose)	X	X	X	X	X	X	X	X	X	
Weight / Height(at baseline only)[e]	X	X	X	X	X	X	X	X			
Vital Signs[f]	X	X	X	X	X	X	X	X	X	X	
Performance Status (ECOG)	X	X	X	X	X	X	X	X			
12-Lead ECG[g]	X										
Chest X-ray[h]	X										
Laboratory Assessments:											
Pregnancy Test[i]	X (within 7 days prior to first dose)					X		X	X	X	X
Hepatitis B virus (HBV) serology		X[kk]									
Blood Chemistry[j]	X	X[l]	X	X	X	X	X	X	X	X	
Hematology[k]	X	X[l]	X	X	X	X	X	X	X	X	
Coagulation[m]	X	As clinically indicated									
Urinalysis[n]	X	X[l]		X		X	X	X	X	X	
Isatuximab/cemiplimab IAR Labs[o]		Prior C1D1 then if IAR ≥G2									
Markers of potential TLS[p]		As clinically indicated									
Serum β2-microglobulin[q]	X					X		X			
Immunoglobulins: IgG, IgA, IgD, IgE, IgM[q]	X					X		X	X	X	

Evaluation[a]	Screening/ Baseline	Cycle 1[b]				Subsequent Cycles[b]		End of Treatment (EOT)	Post treatment Follow-up Period[jj]		
	D-21 to D1	D1	D8	D15	D22	D1	D15	30 days after last IMP admin	At 60 days after last IMP admin	At 90 days after last IMP admin	Beyond 90 days after last IMP admin
Blood typing interference test[r]	X					C2 only					
PK[s]	See PK/PD Flow-Chart										
ADA[t]	See PK/PD Flow-Chart										
Adaptive immune response (including TCR repertoire) (blood and bone marrow aspirate)[u]	X					C3 (blood only) and in case of CR					
Adaptive immune response (humoral and cellular response) (Blood)[v]		X				C2, C4,C7,C10		X			
Immunophenotyping (Blood and bone marrow aspirate)[w]	X					C3		X (Blood only)			
FISH (bone marrow aspirate)[x]	X										
PD1-PDL1 expression (Bone marrow biopsy [y]	X					C3		X			
MRD assessment (bone marrow aspirate)	X	**In case of CR**									
Disease Assessment[z]											
- Serum M-Protein[aa]	X	X[l]				X		X	X[dd]		
- sFLC[bb]	X	X[l]				X		X	X[dd]		
- Urine M-Protein (24-hr urine)[cc]	X	X[l]				X		X	X[dd]		
- Bone Marrow for disease assessment[ee]	X	to confirm CR and as clinically indicated						X (if clinically indicated)	X (if clinically indicated)[dd]		
- Bone disease assessment (Skeletal survey or low-dose whole body CT)[ff]	X					X (if clinically indicated)		X (if clinically indicated)	X (if clinically indicated)[dd]		
- Plasmacytoma assessment (PET/CT/MRI)[gg]	X					X (if clinically indicated)		X (if clinically indicated)	X (if clinically indicated)[dd]		
Isatuximab Administration[hh]		X	X	X	X	X	X				

Evaluation[a]	Screening/ Baseline	Cycle 1[b]				Subsequent Cycles[b]		End of Treatment (EOT)	Post treatment Follow-up Period[jj]		
	D-21 to D1	D1	D8	D15	D22	D1	D15	30 days after last IMP admin	At 60 days after last IMP admin	At 90 days after last IMP admin	Beyond 90 days after last IMP admin
Cemiplimab Administration		X		X		X	X				
AE/SAE Assessment[ii]	X	Continuously throughout study period							X (ongoing related AE, ongoing SAE, new related AE/SAEs)		
Prior/Concomitant Medication	X (within 21 days prior to first dose)	Continuously throughout study period							X (related to AE/SAEs)		
- New anticancer therapy								X	X		

a **Evaluation:** Assessments to be performed prior to study treatment and prior to premedication administration unless otherwise indicated. Inform consent should be signed before any study specific procedures. In Phase 2 part, **randomization** to 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. All eligible patients must be randomized using Interactive Response Technology (IRT). Every effort should be made to start treatment within 3 working days of randomization.

b **Cycle:** A cycle is 28 days. The treatment window is ±1 day for each of the weekly administrations ±2 day for each of the Q2W administrations and ±4 day for each of the Q4W administrations. A dose is deemed to have been delayed if the treatment is ≥2 days beyond the theoretical day of treatment for weekly dose, ≥3 days beyond the theoretical day of treatment for Q2W dose and ≥5 days beyond the theoretical day of treatment for Q4W dose. The reason for dose delay will be captured. Cycle 1 Day 1 refers to the day the patient receives the first study treatment administration.

c **Demography:** Includes age, gender and race. **Medical/Surgical History:** Includes relevant history of previous/associated pathologies, other than multiple myeloma including respiratory function history, and smoking status. **Disease History:** Includes date of initial diagnosis, subtype, stage and previous anti-MM therapy (type, duration, reason for discontinuation and response to). In addition, results of additional procedures (such as karyotype, FISH, etc) performed as part of standard of care to assess the current disease status may also be collected. If not previously performed, blood type, phenotype or genotype and screen should be done prior to first study treatment administration. The transfusion service should be made aware that the patient is receiving an anti-CD38 treatment (isatuximab). During the study treatment period the transfusion service should follow the recommendations issued in the AABB bulletin in case a blood red cells transfusion is needed. The web link to the AABB bulletin will be indicated on the study patient card (see Appendix I). Patients should keep together their study patient card with their blood type card throughout the duration of the study treatment.

d **Physical Examination:** To be performed at screening (<7 days prior to first dose), prior to study treatment administration on Day 1, Day 8, Day 15 and Day 22 of Cycle 1, Day 1 and Day 15 of each subsequent cycle,at the EOT visit and post treatment follow up visits at 60 and 90 days after last treatment Consists of examination of major body systems, including neurological, digestive exam, respiratory (signs and symptoms, respiratory rate), hepatic and spleen span, lymph node examination. 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.

e **Weight / Height:** Height is required at baseline only. Weight is required at Screening, prior to starting infusion and at the EOT visit.

f **Vital Signs:** Blood pressure, heart rate, temperature, and respiration rate required at Screening, to be taken just before starting infusion, every hour during the infusion, and at the end of infusion on D1, D8, D15 and D22 of Cycle 1； and to be taken just before starting infusion at D1 and D15 of each subsequent cycle and as clinically indicated, at the EOT visit, and at post treatment follow up visits at 60 and 90 days after last treatment.

g **12-Lead ECG:** To be performed at Screening and then as clinically indicated.

h **Chest X-ray**: To be performed at Screening and then as clinically indicated.

i **Pregnancy Test:** Women of child bearing potential must have a negative serum pregnancy test result within 7 days prior to first IMP administration. During the study, test to be done on Day1 of each cycle prior to the study treatment, at the end of treatment, and then every month for 5 months following the last dose of Isatuximab or 6 months following the last dose of cemiplimab, whichever comes last (urine pregnancy test can be performed at home after study treatment discontinuation).

j **Blood Chemistry:** To be done at Screening, then prior to pre-medication and IMP administration on D1, D8, D15 and D22 of Cycle 1 and on D1 and D15 of every subsequent cycle, at the EOT visit, 60 and 90 days after last treatment 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, urea or blood urea nitrogen (BUN), serum creatinine, eGFR(MDRD formula), glucose (fasting), albumin and total protein. Thyroid stimulating hormone (TSH) will be assessed every second cycle, and free T4 if TSH is outside of the normal range.

k **Hematology:** To be done at Screening, then prior to pre-medication and IMP administration on D1, D8, D15 and D22 of Cycle 1 and D1 and D15 of every subsequent cycle, at the EOT visit, 60 and 90 days after last treatment and as clinically indicated. Hematology includes: Hemoglobin, hematocrit, RBC, WBC with differential, and platelet counts. If Grade 4 neutropenia, assess ANC every 2-3 days until ANC $\geq$ 0.5 x 10^9/L and at least weekly thereafter until ANC $\geq$1.0 x 10^9/L. Blood group card to be obtained before study entry.

l **Blood chemistry, hematology, urinalysis and efficacy labs** assessments are not required to be repeated prior to D1 Cycle 1 if the screening labs were performed within 3 days prior to first IMP administration.

m **Coagulation:** To be done at Screening and then as clinically indicated. Coagulation includes: Prothombin time (PT) or international normalized ration (INR) and activated partial thromboplastin time (PTT).

n **Urinalysis:** Quantitative urinalysis (includes Na, K, Ca, Cl, RBC, protein, glucose, pH, ketones, bilirubin, leucocytes, nitrates and specific gravity) to be done at baseline, EOT, 60 and 90 days after last treatment and during the treatment period if hematuria is observed or clinically indicated – Dipstick (qualitative) will be performed on D1 and D15 of each new cycle.

o **Isatuximab/Cemiplimab IAR Labs: include cytokines** (TNF- α, IL-1-β, , IL-6, and IFN-γ), markers of complement activation (C3a, C4, CH50) and serum tryptase, lactate dehydrogenase [LDH]. Baseline sample to be drawn prior to first isatuximab administration at Cycle 1. Then if an isatuximab infusion associated reaction (IAR) of ≥Grade 2 occurs, additional blood sampling during the AE is required for analysis.

p **Markers of potential TLS:** to be done in case of suspicion of TLS (uric acid, BUN/creatinine, potassium, phosphate, calcium and corrected calcium).

q **Serum β2-microglobulin and Immunoglobulins (IgG, IgA, IgM, IgD and IgE):** To be performed at Screening, D1 of each cycle starting from Cycle 2, and at the EOT visit. After EOT, during the follow up visits, Immunoglobulins to be performed only in patients discontinued study without disease progression and have not started new anti-cancer treatment (IgD or E only if the heavy chain component of the disease is known to be E or D).

r **Blood typing interference test:** at screening: blood type (if not already done) and phenotype (according to the site protocol). Recommended phenotype include Rh system (C/c and E/e), Kell system (K/k); Duffy system (Fya/Fyb); kidd system (Jka/Jkb); MNS system (M/N, S/s), and Indirect Antiglobuline Test (IAT, indirect Coombs test). On Cycle 2 Day 1 and before each transfusion: Indirect Antiglobuline Test (IAT, indirect Coombs test or Antibody screen). Blood type card will be kept by the patient with the study card. Blood transfusions are to be recorded in the eCRF. The blood bank needs to be informed that the patient is receiving a treatment with an anti-CD38 and a potential interference with the Coombs test is possible.

s **Pharmacokinetics (PK):** isatuximab and cemiplimab. See PK/PD flow chart.

t **ADA (Anti-Drug Antibodies):** isatuximab and cemiplimab. See PK/PD flow chart.

u **Adaptive immune response (including TCR repertoire assessment) (Blood and bone marrow): To be performed at screening, and D1 of Cycle 3 prior to IP administration (blood only) and in case of CR**.

v Adaptive immune response (humoral and cellular response) (Blood) : To be performed prior to pre-medication and IMP administration on D1 of Cycle 1, Cycle 2, Cycle 4, Cycle 7 and Cycle 10 and in disease progression patients at EOT. Humoral response will be assessed in allsites. Cellular response will be assessed in patients at selected sites.

w **Immunophenotyping (Bone marrow aspirate and blood):** To be performed at screening, D1 of Cycle 3 prior to IP administration and at the EOT visit (blood only).

x **FISH: Bone marrow aspirate:** to be performed at screening.

y **PD1-PDL1 expression (Bone marrow biopsy):** Access to archival bone marrow biopsy material will be requested at screening and if available, retrospective expression analysis will be performed by IHC. For any patients that have bone marrow biopsy available at baseline, there will be optional biopsies performed at pre-dose on Day 1 of Cycle 3 and at the EOT visit.

z **Disease Assessment:** All lab tests include M-protein quantification (serum and 24-hour urine, immunoelectrophoresis, and immunofixation) and serum free light chain levels should be repeated on C1D1 if not performed within 3 days prior to first IMP administration, and all radiologic assessments to be performed within 21 days prior to first IMP administration. Response is assessed on the basis of clinical and laboratory findings on D1 of every cycle (starting C2, prior to IMP administration), whenever disease progression is suspected (eg, symptomatic deterioration) and at the EOT visit. The availability of the results must not prevent the initiation of the next cycle.

aa **Serum M-Protein:** To be performed at Screening, D1 of every cycle prior to IMP administration (not required to be repeated at Cycle 1 if screening labs were performed within 3 days prior to first IMP administration), and at the EOT visit. Immunofixation to be performed at baseline and required after treatment due to disappearance of the M component in the electrophoresis. An additional serum sample will be collected at all time-points to evaluate the potential interference of isatuximab in the M protein assessment (central laboratory).

bb **sFLC:** To be performed at Screening, D1 of every cycle prior to IMP administration (not required to be repeated at Cycle 1 if screening labs were performed within 3 days prior to first IMP administration), and at the EOT visit.

cc **Urine M-Protein (24-hr urine):** 24-hour urine collection for Bence Jones protein with urine electrophoresis at Screening, D1 of every cycle prior to IMP administration (not required to be repeated at Cycle 1 if screening labs were performed within 3 days prior to first IMP administration), and at the EOT visit. Urine immunofixation to be performed in this 24 hours urine at baseline and if required due to disappearance of the M component in the electrophoresis. If negative at baseline, to be repeated every 3 months and to confirm response or PD.

dd **Disease assessments during follow-up period** are only required for patients have discontinued study treatment for reasons other than disease progression and have not yet started treatment with another anti-cancer therapy. Patients will be followed every month for progression during this period. Disease assessments required every month include evaluation of serum M-protein, serum free light chains and urine M-protein. A bone marrow, skeletal survey and PET/CT/MRI are only required if clinically indicated to confirm response or progression according to IMWG criteria. Disease assessments not required once patient starts treatment with another anti-cancer therapy.

ee **Bone marrow (biopsy/aspiration) for disease assessment:** To be performed at Screening, to confirm a sCR, CR and as clinically indicated.

ff **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 study treatment), and during the trial as clinically indicated and to confirm response according to IMWG criteria.

gg **Plasmacytoma assessment (including extramedullary and bone plasmacytoma**): PET/CT/MRI scan too be performed at screening in patients with known or suspected extramedullary disease, and during the trial as clinically indicated and to confirm response according to IMWG criteria. The same modality (PET-CT or MRI) should be used throughout the study for each individual patient.

hh **Cemiplimab/Isatuximab Administration:** At the start of each treatment cycle, the patient's weight will be determined.

ii **AE/SAE assessment**: All AEs, including adverse events 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. After the 30 day all ongoing **related non-serious AEs**, **ongoing SAE** and **new related AE/SAEs** are to be followed to resolution or stabilization. Severity will be graded according to NCI-CTC v4.03.

jj **Follow-up:** The post-treatment follow-up period includes an extended safety follow-up period of 90 days after the last dose of study treatment, and further follow up beyond the 90 days after the last dose of study treatments until death or final study cut-off date, whichever occurs first.

Patients who discontinue study treatment **due to PD**: follow-up visit will be done every 3 months from the date of last study treatment administration until death or final study cut-off date. 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 any effort should be done to schedule follow-up visit at clinical center.

Patients who discontinue the study treatment **without PD**: will be followed every month for disease assessment until confirmation of PD or start treatment with another anti-cancer therapy whichever comes first. After PD patient will be followed every 3 months as described just above.

kk Includes HBsAg, anti-HBsAb, and anti-HBcAb (total and IgM) and HBV DNA in case of positive anti-HBsAg (see Section 6.5.7). Once at any time if HBV status unknown before treatment started and to be repeated if clinically indicated for patient still on treatment at the time of amended protocol 05.

Abbreviations: ADA=anti-drug antibodies; AE=adverse event; ALT=alanine aminotransferase; ANC=absolute neutrophil count; ALP=alkaline phosphatase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; C=Cycle; CR=complete remission; CRF=case report form; D=Day; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; EOT=end-of-treatment visit; FUP=follow-up visit; HBcAb=hepatitis B core antibody; HBsAb=hepatitis B surface antibody; HBsAg=hepatitis B surface antigen; HBV=hepatitis B virus; IgM=immunoglobulin M; IMP=investigational medicinal product; INR=international normalized ratio; LDH=lactate dehydrogenase; MDRD=Modification of Diet in Renal Disease Study; PD=pharmacodynamic or progressive disease; PK=pharmacokinetic; PR=partial remission; PS=performance status; PT=prothrombin time; aPTT=activated partial thromboplastin time; SAE=serious adverse event; sFLC=serum free light chain, SGOT=serum glutamate-oxalate transferase; SGPT=serum glutamate-pyruvate transferase; WBC=white blood cell.

1.2 PK/PD FLOWCHART FOR ISATUXIMAB QW/Q2W + CEMIPILIMAB Q2W

1.2.1 Isatuximab QW/Q2W + cemipilimab Q2W (DL1) - Treatment phase: Cycle 1 (Rich sampling)

Procedure		Treatment Phase									
		C1									
		D1				D4	D8	D15			D22
Cemiplimab	IV infusion	X----------X						X----------X			
	Sample RNT (h)	SOI	EOI	EOI+4h		72h	168h	336h (SOI C1D15)	EOI		
	Sample Time window	[-24h,SOI]	[-5 min,EOI]	±30min		±5h	±24h	[-24h,SOI]	[-5 min,EOI]		
	PK sample ID	S00	S01	S02		S03	S04	S05[c, d]	S06		
	ADA Sample ID[a]	AB00									
Procedure		**C1**									
		D1				**D4**	**D8**	**D15**			**D22**
Isatuximab	IV infusion		X----------X				X---		X----------X		X---
	Sample RNT (h)	SOI		EOI	EOI+4h	72h	168h (SOI C1D8)	SOI		EOI	SOI
	Sample Time window			±10min	±30min	±5h	[-24h,SOI]			±10min	[-24h,SOI]
	PK sample ID[b]	P00[c]		P01	P02	P03	P04[c, d]	P05[c]		P06	P07
	ADA Sample ID[b]	AB00[c]									

a For cemiplimab ADA during treatment phase, samples to be collected every third Cycle from C5 (ie, on D1 of C5, C8, C11, C14, etc) till the last study treatment. In response to AEs of special interest, such as anaphylaxis or hypersensitivity, ADA samples closer to the event may be collected, based on the judgment of the Investigator and/or medical monitor. If isatuximab is stopped and cemiplimab treatment continues, cemiplimab ADA samples should be collected as planned per PK/PD flow-chart

b Isatuximab PK and ADA samples to be collected each cycle till the last study treatment. However, collection can be stopped earlier upon notification from the Sponsor based on the updated knowledge of isatuximab PK and immunogenicity. After FUP 90(±7) days after last IMP administration, no further ADA will be sampled even if the status is positive or inconclusive.

c Isatuximab predose sample (SOI) may be collected at the same time as the predose sample of cemiplimab (SOI) before cemiplimab infusion start.

d Sample (ie, cemiplimab 336h drawn at C1D15 and isatuximab 168h drawn at C1D8) must be collected even if the infusion planned for cemiplimab at C1D15 and for isatuximab at C1D8 is not done or delayed.

Abbreviations: AB=Antibody, ADA= Anti-drug antibody, C= Cycle, D= Day, EOI= End of infusion, EOT= End of Treatment (Post-treatment Safety), FUP= Follow-up period (Post-treatment safety), ID= Identifiant, IMP=investigational medicinal product, IV= Intravenous, P=Plasma, PK= Pharmacokinetic, RNT= relative nominal time, S= Serum, SOI= start of infusion,

1.2.2 Isatuximab QW/Q2W + cemipilimab Q2W (DL1) - Treatment phase: Cycle 2 and beyond (Sparse sampling)

Procedure		Treatment Phase											
		C2~C3					C4						C5 and beyond[d]
		D1			D15		D1				D15		D1
Cemiplimab	IV infusion	X-------X			X--------X		X-------X				X--------X		X---
	Sample RNT (h)	SOI	EOI		SOI	EOI	SOI	EOI			SOI	EOI	SOI
	Sample Time window	[-24h,SOI]	[-5 min,EOI]		[-24h,SOI]	[-5 min,EOI]	[-24h,SOI]	[-5 min,EOI]			[-24h,SOI]	[-5 min,EOI]	[-24h,SOI]
	PK sample ID	S00	S01		S02	S03	S00	S01			S02	S03	S00
	ADA Sample ID[a]	AB00 (C2)											AB00[a]
Procedure		C2~C3					C4						C5 and beyond[d]
		D1			D15		D1				D15		D1
Isatuximab	IV infusion		X-----X			X---		X-----X				X---	X---
	Sample RNT (h)	SOI		EOI	SOI		SOI		EOI	EOI+1h	SOI		SOI
	Sample Time window			±10min					±10min	±10min			
	PK sample ID[b]	P00[c]		P01 (C2)	P02[c]		P00[c]		P01	P02	P03[c]		P00[c]
	ADA Sample ID[b]	AB00[c]					AB00[c]						AB00[c]

a For cemiplimab ADA during treatment phase, samples to be collected every third Cycle from C5 (ie, on D1 of C5, C8, C11, C14, etc) till the last study treatment. In response to AEs of special interest, such as anaphylaxis or hypersensitivity, ADA samples closer to the event may be collected, based on the judgment of the Investigator and/or medical monitor. If isatuximab is stopped and cemiplimab treatment continues, cemiplimab ADA samples should be collected as planned per PK/PD flow-chart

b Isatuximab PK and ADA samples to be collected each cycle till the last study treatment. However, collection can be stopped earlier based on the updated knowledge of isatuximab PK and immunogenicity. After FUP 90(±7) days after last IMP administration, no further ADA will be sampled even if the status is positive or inconclusive.

c Isatuximab predose sample (SOI) may be collected at the same time as the predose sample of cemiplimab (SOI) before cemiplimab infusion start

d Follow-up procedures after the extended safety period of 90 days after last study treatment dose will not be performed anymore for patients still under treatment at the time of amended protocol 05.

Abbreviations: AB=Antibody, ADA= Anti-drug antibody, C= Cycle, D= Day, EOI= End of infusion, EOT= End of Treatment (Post-treatment Safety), FUP= Follow-up period (Post-treatment safety), ID= Identifiant, IMP=investigational medicinal product, IV= Intravenous, P=Plasma, PK= Pharmacokinetic, RNT= relative nominal time, S= Serum, SOI= start of infusion

1.2.3 Isatuximab QW/Q2W + cemipilimab Q2W (DL1) - End of treatment and follow-up periods

Procedure		EOT	FUP	
Cemiplimab	**Sample RNT (h)**	**30 (±7) days after last IMP admin**	**60 (±7) days after last IMP admin**	**90 (±7) days after last IMP admin**
	PK sample ID	SF00	SF01	
	ADA Sample ID	ABF00		ABF01
Procedure		**EOT**	**FUP**	
Isatuximab	**Sample RNT (h)**	**30 (±7) days after last IMP admin**	**60 (±7) days after last IMP admin**	**90 (±7) days after last IMP admin**
	PK sample ID	PF00		
	ADA Sample ID	ABF00		ABF01

NOTE: Follow-up procedures after the extended safety period of 90 days after last study treatment dose will not be performed anymore for patients still under treatment at the time of amended protocol 05. ADA and PK collection was interrupted at cut-off of primary analysis planned 6 months after LPI.

Abbreviations: AB=Antibody, ADA= Anti-drug antibody, C= Cycle, D= Day, EOI= End of infusion, EOT= End of Treatment (Post-treatment Safety), FUP= Follow-up period (Post-treatment safety), ID= Identifiant, IMP=investigational medicinal product, IV= Intravenous, LPI=last patient in, P=Plasma, PK= Pharmacokinetic, RNT= relative nominal time, S= Serum, SOI= start of infusion

1.3 PK/PD FLOWCHART FOR ISATUXIMAB QW/Q2W + CEMIPILIMAB Q4W

1.3.1 Isatuximab QW/Q2W + cemipilimab Q4W (DL-1) - Treatment phase: Cycle 1 (Rich sampling) and Cycle 2

Procedure		Treatment Phase											
		C1								C2			
		D1				D4	D8	D15	D22	D1			D15
Cemiplimab	IV infusion	X----------X								X-----X			
	Sample RNT (h)	SOI	EOI	EOI+4h		72h	168h	336h		SOI (672h at C1D29)	EOI		336h
	Sample Time window	[-24h,SOI]	[-5 min,EOI]	±30min		±5h	±24h			[-24h,SOI]	[-5 min,EOI]		
	PK sample ID	S00	S01	S02		S03	S04	S05[e]		S00[d]	S01		S02[e]
	ADA Sample ID[a]	AB00								AB00			
Procedure		C1								C2			
		D1				D4	D8	D15	D22	D1			D15
Isatuximab	IV infusion		X----------X				X	X----------X	X		X-----X		X
	Sample RNT (h)	SOI		EOI	EOI+4h	72h	168h (SOI D8)	SOI	EOI	SOI	SOI		EOI	SOI
	Sample Time window		-	±10min	±30min	±5h	[-24h,SOI]	[-24h,SOI]	±10min	[-24h,SOI]		-	±10min	[-24h,SOI]
	PK sample ID[b]	P00[c]		P01	P02	P03	P04[d]	P05	P06	P07	P00[c]		P01	P02
	ADA Sample ID[b]	AB00[c]									AB00[c]			

a For cemiplimab ADA during treatment phase, samples to be collected every third Cycle from C5 (ie, on D1 of C5, C8, C11, C14, etc) till the last study treatment. In response to AEs of special interest, such as anaphylaxis or hypersensitivity, ADA samples closer to the event may be collected, based on the judgment of the Investigator and/or medical monitor. If isatuximab is stopped and cemiplimab treatment continues, cemiplimab ADA samples should be collected as planned per PK/PD flow-chart

b Isatuximab PK and ADA samples to be collected each cycle till the last study treatment. However, collection can be stopped earlier upon notification from the sponsor based on the updated knowledge of isatuximab PK and immunogenicity. After FUP 90(±7) days after last IMP administration, no further ADA will be sampled even if the status is positive or inconclusive.

c Isatuximab predose sample (SOI) may be collected at the same time as the predose sample of cemiplimab (SOI) before cemiplimab infusion start.

d Sample (ie, T672h at C1D29 corresponding to C2D1 for cemiplimab and C1D8 T168h for isatuximab) must be collected even if the infusion planned for cemiplimab at C2D1 and/or infusion planned for isatuximab at C1D8 is not done or delayed.

e Cemiplimab predose sample on D15 may be collected on at the same time as the predose sample of isatuximab (SOI) before isatuximab infusion start

Abbreviations: AB=Antibody, ADA= Anti-drug antibody, C= Cycle, D= Day, EOI= End of infusion, EOT= End of Treatment (Post-treatment Safety), FUP= Follow-up period (Post-treatment safety), ID= Identifiant, IMP=investigational medicinal product, IV= Intravenous, P=Plasma, PK= Pharmacokinetic, RNT= relative nominal time, S= Serum, SOI= start of infusion,

1.3.2 Isatuximab QW/Q2W + cemipilimab Q4W (DL-1) - Treatment phase: Cycle 3 and beyond (Sparse sampling)

Procedure		Treatment Phase								
		C3			C4					C5 and beyond[e]
		D1		D15	D1				D15	D1
Cemiplimab	IV infusion	X-------X			X-------X					X
	Sample RNT (h)	SOI	EOI	336h	SOI	EOI			336h	SOI
	Sample Time window	[-24h,SOI]	[-5 min, EOI]		[-24h,SOI]	[-5 min, EOI]				[-24h,SOI]
	PK sample ID	S00	S01	S02[c]	S00	S01			S02[c, d]	S00
	ADA Sample ID[a]									AB00[a]
Procedure		**C3**			**C4**					**C5 and beyond[e]**
		D1		**D15**	**D1**				**D15**	**D1**
Isatuximab	IV infusion		X	X		X-----X			X	X
	Sample RNT (h)	SOI		SOI	SOI		EOI	EOI+1h	SOI	SOI
	Sample Time window			[-24h,SOI]			±10min	±10min	[-24h,SOI]	
	PK sample ID[b]	P00[c]		P02	P00[c]		P01	P02	P03[d]	P00[c]
	ADA Sample ID[b]	AB00[c]			AB00[c]					AB00[c]

a For cemiplimab ADA during treatment phase, samples to be collected every third Cycle from C5 (ie, on D1 of C5, C8, C11, C14, etc) till the last study treatment. In response to AEs of special interest, such as anaphylaxis or hypersensitivity, ADA samples closer to the event may be collected, based on the judgment of the Investigator and/or medical monitor. If isatuximab is stopped and cemiplimab treatment continues, cemiplimab ADA samples should be collected as planned per PK/PD flow-chart

b Isatuximab PK and ADA samples to be collected each cycle till the last study treatment. However, collection can be stopped earlier upon notification from the sponsor based on the updated knowledge of isatuximab PK and immunogenicity. After FUP 90(±7) days after last IMP administration, no further ADA will be sampled even if the status is positive or inconclusive.

c Isatuximab predose sample (SOI) may be collected at the same time as the predose sample of cemiplimab (SOI) before cemiplimab infusion start.

d Cemiplimab predose sample on C4D15 may be collected on at the same time as the predose sample of isatuximab (SOI) before isatuximab infusion start.

e Follow-up procedures after the extended safety period of 90 days after last study treatment dose will not be performed anymore for patients still under treatment at the time of amended protocol 05.

Abbreviations: AB=Antibody, ADA= Anti-drug antibody, C= Cycle, D= Day, EOI= End of infusion, EOT= End of Treatment (Post-treatment Safety), FUP= Follow-up period (Post-treatment safety), ID= Identifiant, IMP=investigational medicinal product, IV= Intravenous, P=Plasma, PK= Pharmacokinetic, RNT= relative nominal time, S= Serum, SOI= start of infusion

1.3.3 Isatuximab QW/Q2W + cemipilimab Q4W (DL-1) - End of treatment and follow-up periods

Procedure		EOT	FUP	
Cemiplimab	**Sample RNT (h)**	**30 (±7) days after last IMP admin**	**60 (±7) days after last IMP admin**	**90 (±7) days after last IMP admin**
	PK sample ID	SF00	SF01	
	ADA Sample ID	ABF00		ABF01
Procedure		**EOT**	**FUP**	
Isatuximab	**Sample RNT (h)**	**30 (±7) days after last IMP admin**	**60 (±7) days after last IMP admin**	**90 (±7) days after last IMP admin**
	PK sample ID	PF00		
	ADA Sample ID	ABF00		ABF01

NOTE: Follow-up procedures after the extended safety period of 90 days after last study treatment dose will not be performed anymore for patients still under treatment at the time of amended protocol 05. ADA and PK collection was interrupted before amended protocol 05.

Abbreviations: AB=Antibody, ADA= Anti-drug antibody, C= Cycle, D= Day, EOI= End of infusion, EOT= End of Treatment (Post-treatment Safety), FUP= Follow-up period (Post-treatment safety), ID= Identifiant, IMP=investigational medicinal product, IV= Intravenous, P=Plasma, PK= Pharmacokinetic, RNT= relative nominal time, S= Serum, SOI= start of infusion

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3 LIST OF ABBREVIATIONS

ADCC: antibody-dependent cellular-mediated cytotoxicity
AE: adverse event
AESI: adverse event of special interest
AL: amyloid light-chain
ALT: alanine aminotransferase
ANC: absolute neutrophil count
AST: aspartate aminotransferase
BMA: bone marrow aspirate
CBR: clinical benefit rate
CR: complete response
DL: dose level
DLT: dose limiting toxicity
DOR: duration of response
DRF: discrepancy resolution form
ECOG: eastern cooperative oncology group
eGFR: estimated glomerular filtration rate
FISH: fluorescence in situ hybridization
FLC: free light chain
FSH: follicle stimulating hormone
GCP: good clinical practice
HBcAb: hepatitis B core antibody
HBsAb: hepatitis B surface antibody
HBsAg: hepatitis B surface antigen
HBV: hepatitis B virus
HRT: hormonal replacement therapy
HSC: haemopoietic stem cell
ICH: international conference on harmonisation
IEC: institutional ethics committee
IgM: immunoglobulin M
IMiD: immunomodulatory drug
IMWG: international myeloma working group
INR: international normalized ratio
IRB: institutional review board
ITT: intent to treat
IV: intravenous
LDH: lactate dehydrogenase
LPI: last patient in
mAb: monoclonal antibody
MDRD: modified diet in renal disease
MM: multiple myeloma
MR: minimal response
MRD: minimal residual disease
MTD: maximum tolerated dose

ORR:	overall response rate
OS:	overall survival
PD:	progression of disease
PFS:	progression free survival
PI:	proteasome inhibitor
PK:	pharmacokinetics
PR:	partial response
PS:	performance status
PT:	prothrombin time
Q2W:	once every 2 weeks
QW:	once weekly
RBC:	red blood cell
RP2D:	recommended Phase 2 dose
RRMM:	relapse and refractory multiple myeloma
SAE:	serious adverse event
sCR:	stringent complete response
SCT:	stem cell transplant
SPD:	sum of the products of the maximal perpendicular diameters of measured lesions
TEAE:	treatment-emergent adverse event
TTR:	time to response
ULN:	upper limit of the normal range
VGPR:	very good partial response
WBC:	white blood cell

4 INTRODUCTION AND RATIONALE

4.1 INTRODUCTION

4.1.1 CD38

CD38 is a type II glycosylated 45 kilodalton (kDa) membrane protein that was identified as a lymphocyte marker (1). CD38 has a role in leukocyte homeostasis through modulation of hematopoietic cell survival and differentiation (2). 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 (2). 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 (3). These reaction products are implicated in calcium mobilization and intracellular signaling.

The expression of CD38 in healthy humans can be detected on 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, 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 CLL. The expression of CD38 is especially notable in multiple myeloma (MM) as >98% of patients are positive for this protein (4, 5). 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.

4.1.2 PD-1

The importance of intact immune surveillance in controlling outgrowth of neoplastic transformation has been known for decades (6). The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control (7). The normal function of PD-1, expressed on the cell surface of activated T cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene Pdcd1) is an Ig superfamily member related to CD28 and CTLA-4, which has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2). The structures of murine PD-1 alone (8) and in complex with its ligands were first resolved (9, 10) and more recently the NMR-based structure of the human PD-1 extracellular region and analyses of its interactions with its ligands were also reported (11). PD-1 and family members are type I transmembrane glycoproteins containing an Ig Variable-type (V-type) domain responsible for ligand binding and a cytoplasmic tail which is responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif (ITIM) and an immunoreceptor tyrosine-based switch motif (ITSM). Following T cell stimulation, PD-1 recruits the tyrosine phosphatases SHP-1 and SHP-2 to the ITSM motif within its cytoplasmic tail, leading to the dephosphorylation

of effector molecules, such as CD3ζ, PKCθ and ZAP70, which are involved in the CD3 T cell signaling cascade (12). The mechanism by which PD-1 down-modulates T cell responses is similar to, but distinct from that of CTLA-4 (13). PD-1 was shown to be expressed on activated lymphocytes, including peripheral CD4+ and CD8+ T cells, B cells, T regs and Natural Killer cells (14). Expression has also been shown during thymic development on CD4-CD8- (double negative) T cells (15) as well as subsets of macrophages (16) and dendritic cells (17). The ligands for PD-1 (PD-L1 and PD-L2) are constitutively expressed or can be induced in a variety of cell types (18). PD-L1 is expressed at low levels on various non-hematopoietic tissues, most notably on vascular endothelium, whereas PD-L2 protein is only detectably expressed on antigen-presenting cells found in lymphoid tissue or chronic inflammatory environments (18).
Both ligands are type I transmembrane receptors containing both IgV- and IgC-like domains in the extracellular region and short cytoplasmic regions with no known signaling motifs. Binding of either PD-1 ligand to PD-1 inhibits T cell activation triggered through the T cell receptor. PD-L2 is thought to control immune T cell activation in lymphoid organs, whereas PD-L1 serves to dampen unwarranted T cell function in peripheral tissues. Although healthy organs express little (if any) PD-L1, a variety of cancers were demonstrated to express abundant levels of this T cell inhibitor (19, 20) which, via its interaction with the PD-1 receptor on tumor-specific T cells, plays a critical role in immune evasion by tumors (21). As a consequence, the PD-1/PD-L1 pathway is an attractive target for therapeutic intervention in cancer (22).

Two anti-PD1 antibodies, nivolumab and pembrolizumab, are now approved in melanoma and lung cancer. The promise of anti-PD1 antibodies is starting to be explored also in hematologic malignancies such as Hodgkin disease (22, 23), and the rationale for the use of anti-PD1 antibodies in MM is elucidated in the following Section 4.3.2.2.

4.1.3 Multiple myeloma (MM)

Multiple myeloma is a malignant plasma cell disease that is characterized by clonal proliferation of plasma cells in the bone marrow and the production of excessive amounts of a monoclonal immunoglobulin (usually of the IgG or IgA type or free 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, anaemia, infections, hypercalcaemia and renal dysfunction (24). The disease course for MM varies with the aggressiveness of the disease and related prognostic factors. Median survival is approximately 3 years; however, some patients can live longer than 10 years (25).

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 later 2 regimens are associated with higher toxicity (24). Newer treatments with Velcade® (bortezomib) alone, bortezomib combinations, and Revlimid® (lenalidomide) plus dexamethasone show some promise as induction therapy, and these agents demonstrate higher response rates and lower toxicity (24, 26). 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 (RRMM) patients previously treated with IMiDs and PI, supporting the use of CD38 antibody in MM (27).

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 3 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.

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 (28).

Studies have shown the expression of PD-L1 on MM cells, and T and NK cells within the MM microenviroment expression PD-1(29).

4.2 DESCRIPTION OF INVESTIGATIONAL MEDICINAL PRODUCT

4.2.1 Isatuximab

Isatuximab (SAR650984) is a 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), antibody-dependent cellular-mediated phagocytosis (ADCP), complement-dependent cytotoxicity (CDC) and direct induction of apoptosis (pro-apoptosis) without crosslinking. Isatuximab treatment of CD38 expressing cells also results in inhibition of CD38 enzymatic activity (30).

Please refer to the isatuximab Investigator's Brochure for more information on the current safety and efficacy of isatuximab.

4.2.2 Cemiplimab

Cemiplimab (REGN2810) is a high affinity hinge-stabilized IgG4P human antibody to the PD-1 receptor (PDCD1, CD279) that blocks PD-1/PD L1-mediated T cell inhibition. Cemiplimab displayed a robust, dose-dependent suppression of MC38.Ova tumors in the syngeneic mouse tumor model. The nonclinical activity of cemiplimab is similar to two in-house generated anti-PD-1 comparator antibodies with identical amino acid sequence to nivolumab and pembrolizumab (based on publically available sequence data).

4.2.2.1 Clinical data

As of 20 Jan 2017, 459 patients have been treated with cemiplimab either as monotherapy or in combination with radiotherapy and/or other cancer therapy in the three ongoing studies. The majority of patients (n=353) have been treated in Study 1423. Study 1423 is a first-in-human study in patients with advanced malignancies of repeat dosing of cemiplimab as monotherapy, as well as in combination with hypofractionated radiation therapy (hfRT) and/or cyclophosphamide (CTX), or in combination with hfRT, CTX, and Granulocyte Macrophage Colony-Stimulating Factor, or in combination with docetaxel or docetaxel plus carboplatin. As of 20 Jan 2017, in Study 1423, a total of 353 patients have been enrolled and treated with 4 different dose levels (n=27 at 1 mg/kg, n=300 at 3 mg/kg, n=6 at 10 mg/kg, and n=20 a flat dose of 200 mg). The study design includes 60 patients in dose escalation cohorts and the rest in a series of expansion cohorts. As of 20 Jan 2017, the majority of patients (300 of 353) have been treated with 3 mg/kg cemiplimab. All patients except 12 patients have been treated on a Q2W schedule. There have been no patients with hematologic malignancies treated in Study 1423.

Cemiplimab has been generally well tolerated, and the reported AEs have been similar to what have been observed with other PD-1 inhibitors. In study 1423, the most common treatment-emergent adverse events (TEAEs) occurring in 10% or more of patients were fatigue, nausea, decreased appetite, anemia, constipation, arthralgia, diarrhea, dyspnea, cough, pyrexia, vomiting, asthenia, and back pain. No protocol-defined dose limiting toxicities have been observed. Potential immune-related TEAEs (irTEAEs) have been observed in33.7% patients including Grade 3 or higher in 8.2% patients. Treatment-related irTEAE occurring in more than 1% of patients included arthralgia (8.2%), diarrhea (6.5%), pruiritus (4.5%), hypothyroidism (4.2%), rash maculo-papular (3.7%), AST increased (3.4%), rash (2.8%), ALT increased (2.5%), pneumonitis (2.3%), rash pruritic (1.7%), stomatitis (1.7%), hyperthyroidism (1.1%) 5.1% patients experienced serious irTEAE. Events of Grade 3 or higher occurring in more than 1 patient included: AST increase (n=3, 0.8%), pneumonitis (n=3, 0.8%), ALT increased (n=2, 0.6%) and diabetic ketoacidosis (n=2, 0.6%). Events occurring in 1 patients (0.3%) included: arthralgia, autoimmune hepatitis, colitis, hepatic failure, hyperbilirubinaemia, hyperthyroidism, paraneoplastic encephalomyelitis, transaminases increased. the events of paraneoplastic encephalomyelitis and hepatic failure were with fatal outcome. Five patients (1.4%) experienced a total of 8 cemiplimab-related infusion-related reactions (IRRs), all were non-serious and Grade 2 except 1 Grade 1 event. One patient treated at 10 mg/kg monotherapy in Study 1423 with soft tissue sarcoma died because of anti-HuD paraneoplastic encephalomyelitis; 16 other patients died due to progression of disease.

330 patients were evaluable to tumor response, with 17.6% objective response and 57.6% disease control. As of 20 January 2017, no patients with multiple myeloma have been treated with cemiplimab. However, in study 1504, as of 15 Jun 2016, 12 patients with hematologic malignancies (6 with Hodgkin's lymphoma and 6 with non-Hodgkin's lymphoma) have been enrolled and treated Q2W with cemiplimab as monotherapy (1 mg/kg [n=6] and 3 mg/kg [n=6]). The safety profile appears similar to that seen with cemiplimab in study 1423. After the data cut off, one fatal case of toxic epidermal necrolysis was reported in a patient with follicular lymphoma who had a protracted course of skin rash and stomatitis (Grade 3 highest grade) one month after discontinuation of idelalisib (administered as a prior treatment) that resolved 2 weeks prior to initiation of cemiplimab. No efficacy information is available for this study at the present time.

Please refer to the cemiplimab Investigator's Brochure for more information on the current safety and efficacy of cemiplimab.

4.3 RATIONALE

4.3.1 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 (28).

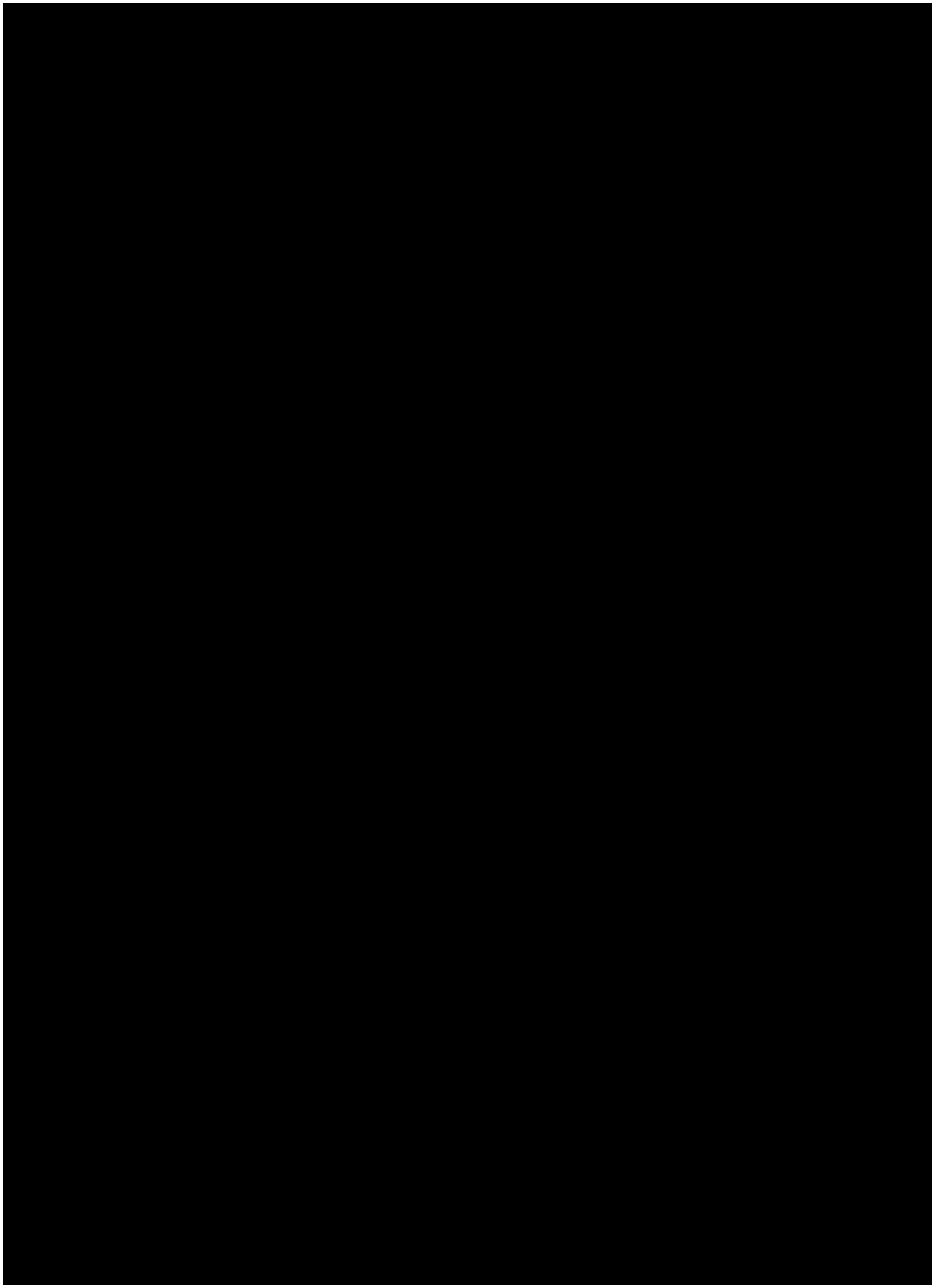
Clinically, isatuximab single agent has shown clinical response in RRMM patients and the treatment effect is enhanced by combination with immuno-modulation (IMiDs).

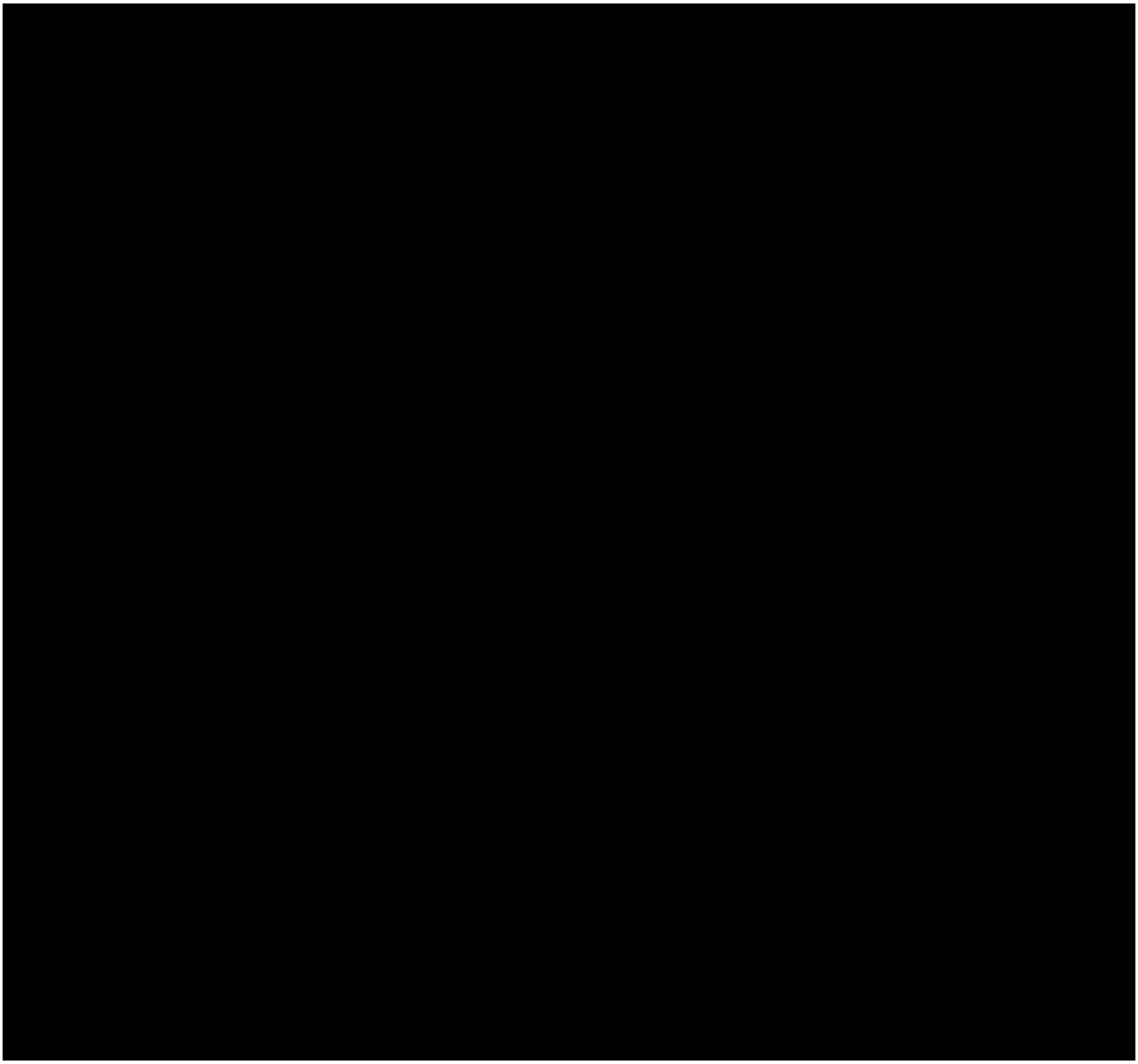
As a single agent, nivolumab (anti-PD-1) had minimal activity in RRMM, with a stable disease rate of 63% in a Phase I trial; PR or better were not seen, with the exception of one CR occurring after local radiation therapy (31). Recent report shown that combined PD-L1 and CD38 inhibition improves tumor response in animal model (32).

Based on preclinical studies indicating that isatuximab induced ADCC can be enhanced through the inhibition of PD-1, the combination therapy of isatuximab and cemiplimab (an anti-PD1 antibody currently in clinical development) may provide another option for the treatment of RRMM.

4.3.1.1 Pre-clinical data

PD-1 and its ligand PD-L1 are reported to be expressed in the multiple myeloma tumor micro-environment; PD-L1 in the plasma cells (33, 34) and PD-1 in T and NK cells (35, 36). More recently, data showing that PD-L1 blockade enhances NK and T cell mediated lysis of MM cells has been published (37).





4.3.2 Rationale for dose selection

4.3.2.1 Isatuximab

Isatuximab as a single agent has 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 does not demonstrate major differences in efficacy between 10 and 20 mg/kg with comparable response rate in heavily pretreated patients. Pharmacokinetics/pharmacodynamics (PK/PD) 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/PD analyses, the dose selected for further isatuximab combination studies is 10 mg/kg QW x 4 administrations followed by 10 mg/kg Q2W.

Based on these data, the dose of isatuximab 10 mg/kg has been selected in combination therapies.

4.3.2.2 Cemiplimab

Similar to the experience observed with other anti-PD-1 antibodies, cemiplimab dosing has been escalated safely in the FIH study R2810-ONC-1423. As of 15 June 2016, a total of 222 patients have been enrolled in study R2810-ONC-1423, including 71 patients in monotherapy cohorts at 1, 3, and 10 mg/kg Q2W and at 200 mg Q2W flat dose, and 151 patients in combination therapy cohorts (eg, combinations with chemotherapy and/or hypo-fractionated radiation therapy). As of 15 June 2016, no DLTs have been observed across the treatment regimens studied. Preliminary efficacy was observed with cemiplimab in several tumor types at all doses tested. Evidence of rapid and durable responses with cemiplimab was also observed in study R2810-ONC-1423, at all doses tested with no clear dose-response relationship, similar to the observations with other anti-PD-1 antibodies (38, 39).

While the PK of cemiplimab in animals is described as non-linear with target-mediated elimination, linear kinetics are observed in the clinic at the dose levels between 1 and 10 mg/kg Q2W. The observed linear PK in patients is consistent with saturation of the target-mediated clearance pathway and a flat dose-response is observed across the treatment regimens studied, suggesting saturation of PD-1 binding at these doses. The 3 mg/kg Q2W dose was initially administered for maintenance therapy in the FIH study and was subsequently used in several other studies of the program. Based on feedback from regulatory authorities, it was subsequently decided to switch from body weight adjusted dosing to fixed flat dosing across the cemiplimab program.

The preference for a fixed flat dose over a body-weight-adjusted dose for anti-PD-1 monoclonal antibodies is supported by a wide safety margin (no maximum tolerated dose observed), a flat E-R relationship for safety and efficacy over the therapeutic dosing range, and similar variability in exposure (CV%) after flat and body-weight-adjusted doses (40).

Simulations of cemiplimab exposure at steady state in 1,000 patients using population PK analyses have demonstrated that the variability in cemiplimab exposure was similar for body weight-adjusted doses as compared to fixed flat doses, 250 mg Q2W doses of cemiplimab produced results similar to those after the 3 mg/kg Q2W doses over a similar treatment period.

In the FIH study with cemiplimab, both the 1 mg/kg Q2W and the 3mg/kg Q2W doses had yielded preliminary efficacy signals in a number of tumor types. Acceptable safety data have also been obtained following a 10 mg/kg Q2W regimen with no DLTs observed as of 15 June 2016; Translated into a fixed flat dose, a 3 mg/kg Q2W dose would correspond to a 250 mg Q2W dose of cemiplimab, which are acceptable as a starting dose when cemiplimab is given in combination with isatuximab. Therefore, to match the weekly and bi-weekly dosing schedule for isatuximab (10 mg/kg QWx4 followed by 10 mg/kg Q2W), a fixed flat 250 mg Q2W dosing regimen of cemiplimab is preferred for patient's convenience.

Since changing the exposure of check point inhibitors such as nivolumab in combination with ipilimumab altered the safety, tolerability and efficacy of these drugs in NCSLC (41), two fixed flat dosing regimens of cemiplimab in combination with isatuximab will be assessed in this study: 250 mg Q2W (DL1) and 250 mg Q4W (DL-1 and DL-2).

4.3.3 Study design rationale

This is the first study of isatuximab in combination with cemiplimab. To evaluate the safety and clinical activity in RRMM, the study is designed in 2 parts.

The Phase 1 part is to confirm the feasibility of the isatuximab / cemiplimab combination and select a recommended dose for Phase 2. The maximum tolerated dose (MTD) defined as the highest dose intensity at which 0 out of 3 or no more than 1/6 patients have DLT. Given the promising early signs of the activity and the acceptable safety profile of each of the two antibodies, and that MTD has not been reached in either one as monotherapy with isatuximab 20 mg/kg QW and cemiplimab 10 mg/kg, no typical dose escalation is planned. A cohort of 3 patients will be treated at starting dose of 10 mg/kg QWx4 followed by Q2W for isatuximab and 250 mg Q2W for cemiplimab,which have been shown to be clinically active with an acceptable safety profile both as monotherapy and in combinations with other standard therapies. If necessary, dose will be de-escalated with typical 3+3 design rule.

The Phase 2 part is a proof of concept study to determine the efficacy of the combination of isatuximab and cemiplimab in RRMM patients using ORR as primary endpoint, and to further evaluate the safety of the combination therapy. The efficacy of single-agent isatuximab and other CD38 drugs is well established in patients with RRMM who have received at least three prior lines of therapy including a PI and an IMiD or whose disease is double refractory to PI and IMiD (42, 43). A control arm consisting of isatuximab given as a single agent will be used in Phase 2 to characterize the treatment benefit and risk profile when cemiplimab is combined with isatuximab, and will serve to detect the risk ascribable to cemiplimab when it is combined to isatuximab in RRMM. To ensure that the most effective and safe dose of cemiplimab will be used in this study, two different doses will be assessed if it is permitted based on the MTD finding from Phase 1. Patients will be randomized in the 3 study arms of Phase 2.

Patients will be followed until progression of disease (PD) or death for a maximum of 2 year after last patient is treated. This will allow the study to have a proper evaluation of the combination in term of PFS and OS.

5 STUDY OBJECTIVES

5.1 PRIMARY OBJECTIVE(S)

- To determine the safety and tolerability of the combination of isatuximab and cemiplimab.
- Phase 2 only: To compare the overall response rate (ORR, defined as CR+VGPR+PR) of the combination of isatuximab and cemiplimab versus isatuximab alone in patients with RRMM based on International Myeloma Working Group (IMWG) criteria (44).

5.2 SECONDARY OBJECTIVE(S)

- To determine the following efficacy measurements (Phase 2 only):
  - Clinical benefit rate (CBR, CR + VGPR + PR + Minimal response [MR]),
  - Duration of response (DOR),
  - Time to response (TTR),
  - Progression free survival (PFS),
  - Overall survival (OS).
- To determine the pharmacokinetic profile of isatuximab and cemiplimab when given in combination.
- To assess the immunogenicity of isatuximab and cemiplimab when given in combination.

5.3 EXPLORATORY OBJECTIVE(S)

- To explore the minimal residual disease (MRD) in patients achieving a CR.
- To assess the relationship between immune phenotypes, immune regulatory marker expression, adaptive immune response and parameters of clinical response.
- To explore central/effector memory T cell proliferation.

6 STUDY DESIGN

6.1 DESCRIPTION OF THE STUDY

This is a Phase 1/2 study to evaluate the safety, tolerability, efficacy and PK of isatuximab in combination with cemiplimab in RRMM.

The study will be conducted in 2 parts:

- The Phase 1 (lead in) part is to confirm the feasibility of the isatuximab / cemiplimab combination.
- The Phase 2 part will further evaluate the safety, efficacy and PK of the combination versus isatuximab monotherapy. Patients will be randomized in 1:1:1 in 3-arms or 1:1 in 2-arms study using an IRT.

Isatuximab and cemiplimab are defined in this protocol as “study treatments”.

6.2 PART 1

6.2.1 Starting dose and dose de-escalation design

Given the promising early signs of anti-cancer activity and the acceptable safety profile of each of the two antibodies (no MTD has been reached with either one as monotherapy), the starting dose will be 10 mg/kg QW for 4 weeks followed by Q2W for isatuximab and 250 mg Q2W for cemiplimab.

Dose de-escalation will be performed if necessary as defined in the Table 1 below:

Table 1 - Treatment dose and schedule

Dose level	Isatuximab	Cemiplimab
Dose level 1 (DL1)	10 mg/kg QWx4 >Q2W	250 mg Q2W
Dose level -1 (DL-1)	10 mg/kg QWx4 >Q2W	250 mg Q4W
Dose level -2 (DL-2)	10 mg/kg Q2W	250 mg Q4W

Patients will continue treatment until disease progression, unacceptable adverse events, consent withdrawal, or any other reason.

At dose level 1 (DL1), 3 patients will be enrolled for DLT evaluation in Cycle 1:

- If 0/3 patient has DLT, no more patients will be enrolled in Phase 1, and DL1 will be the recommended Phase 2 dose (RP2D).
- If 1/3 patients has DLT, additional 3 patients will be enrolled at DL1 for DLT assessment:
  - If a total of 1/6 patient has DLT at DL1, the DL1 will be the RP2D,

- If a total of ≥2/6 patients have DLT at DL1, dose will be de-escalated to dose level minus 1 (DL-1).

- If ≥2/3 patients have DLT, dose will be de-escalated to dose level minus 1 (DL-1).

At DL-1, the same DLT observation rule will be applied for selecting a RP2D and for dose de-escalation.

At DL-2, the same DLT observation rule will be applied for selecting a RP2D. If ≥2/6 patients have DLT, study committee will analyze all the data collected up to this point and determine whether the study is to be terminated without proceeding to Phase II or if alternative doses and schedules could be further examined in Phase I, or changes in the study design could be made based on the perceived benefit/risk to patients and on the PK results.

In Case 2 DLTs are observed before completion of enrollment no additional patients will be enrolled. Enrollment of patients within and between cohorts are staggered by at least 3 days.

For DLT definition, see Section 9.1.1.

The DLT observation period is 1 cycle (28 days). However, all AEs during treatment, unless due to disease progression or an obviously unrelated cause, will be taken into consideration by the Study Committee for the determination of the MTD and RP2D.

The NCI CTCAE version 4.03 Appendix C will be used to assess the severity of AE, causal relationship is to be determined by the investigator. The DLTs will be confirmed by the Study Committee.

6.2.2 Maximum administered dose / maximum tolerated dose

The MAD is defined as the highest dose intensity at which at least 2 out of 3 or 2 out of 6 patients experienced DLTs during the initial DLT observation period (Cycle 1). The MTD is defined as the highest dose intensity at which 0 out of 3 or no more than 1 out of 6 patients experienced DLT.

6.3 PART 2

Phase 2 will have 3 arms (if the MTD or RP2D is at DL1 or DL-1) or 2 arms (if the MTD or RP2D is at DL-2) to assess the treatment response and safety of the combination therapy compared with isatuximab alone. After confirmation of eligibility criteria, patients will be randomly assigned using an interactive response technology (IRT), in a 1:1:1 ratio or 1:1 ratio in 1 of the 3- or 2-arm, respectively, with 35 patients in each arms.

If RP2D is DL1:

- Arm 1 (control): isatuximab 10 mg/kg QWx4 followed by Q2W.
- Arm 2 (DL1): isatuximab 10 mg/kg QWx4 followed by Q2W + cemiplimab 250 mg Q2W.

- Arm 3 (DL-1): isatuximab 10 mg/kg QWx4 followed by Q2W + cemiplimab 250 mg Q4W.

If RP2D is DL-1:

- Arm 1 (control): isatuximab 10 mg/kg QWx4 followed by Q2W.
- Arm 2 (DL-1): isatuximab 10 mg/kg QWx4 followed by Q2W + cemiplimab 250 mg Q4W.
- Arm 3 (DL-2): isatuximab 10 mg/kg Q2W + cemiplimab 250 mg Q4W.

If RP2D is DL-2:

- Arm 1 (control): isatuximab 10 mg/kg QWx4 followed by Q2W.
- Arm 2 (DL-2): isatuximab 10 mg/kg Q2W + cemiplimab 250 mg Q4W.

6.3.1 Anti-CD38 refractory cohort

Patients who received anti-CD38 mAb within 6 months before study entry and had disease progression while on treatment or within 60 days after the last treatment will be enrolled in a separate cohort. A decision will be made to start the cohort after the planned Phase 2 interim analysis suggested a treatment benefit of the combination therapy including pass the futility check. The dose and schedule will be determined based on the efficacy and safety findings in the interim analysis

6.4 RETREATMENT OF PATIENTS

Study treatment can continue until disease progression, unacceptable adverse reactions, or patient/investigator decision to continue.

A cycle is 28 days, and deemed to have been delayed if the treatment is >3 days beyond the theoretical day of treatment. The reason for dose delay will be provided.

In the event of toxicity, in order for patients to be retreated, see Section 6.5 and Appendix G for retreatment recommendations.

6.5 DOSE DELAYS/ MODIFICATIONS

6.5.1 General rules

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

Dose modifications different from those stated in the protocol should only be made in consultation with the Sponsor unless required for immediate patient safety.

Dose adjustment and/or cycle delay are permitted in case of toxicity. Dose adjustments will be made according the worst grade of toxicity observed within a cycle. If a patient experiences several toxicities and there are conflicting recommendations, the most conservative dose adjustment recommended should be followed. Once a dose has been decreased, intra-patient re-escalation back to the previous dose level is not permitted.

Administration of the study treatment will be discontinued in the event of a TEAE that persists despite appropriate dose modifications or any other AE that, in the opinion of the Investigator, warrants discontinuation.

If one of the 2 drugs (cemiplimab or isatuximab) is prematurely permanently discontinued, the other drug can be continued until disease progression, unacceptable adverse reaction, patient's refusal of further treatment, or in the absence of a clear benefit from therapy. The end of treatment assessment in this case will be 30 day after the date of the last IMP administration.

All changes to study treatment administration must be recorded in the eCRF.

6.5.2 Dose delay and dose omission

Within a cycle, the treatment window is ±1 day for each of the weekly administrations, ±2 days for each of the Q2W administrations and ±4 days for each of the Q4W administration. A dose is deemed to have been delayed if the treatment is ≥2 days beyond the theoretical day of treatment for weekly dose, ≥3 days beyond the theoretical day of treatment for Q2W dose and ≥5 days beyond the theoretical day of treatment for Q4W dose. The reason for dose delay will be captured. Patient will receive the next infusion after recovery of the toxicity as described in Section 6.5.3 and Section 6.5.4. If infusion has been delayed by 2 days within a cycle, next study treatment should be administered at the planned time interval between 2 administrations (eg, Day 15 Cycle 1 administration is actually administered on Day 17, the planned Day 22 should be administered on Day 24).

Patients may have dose omission if toxicity occurs and does not recover according to following rules:

- In Cycle 1 if toxicity occurs and does not recover on the day of planned infusion or within the following 3 days, infusion of isatuximab and/or cemiplimab may be omitted.
- In Cycle 2 and beyond, if toxicity occurs and does not recover on the day of planned infusion or within the following 7 days, infusion of isatuximab and/or cemiplimab may be omitted for patient on Q2W dose schedule.

In case of consecutive dose omissions for the recovery of toxicity, following rules should be followed for restart or discontinue the treatment:

- Dose interruption (cycle delay) up to 14 days, it is per Investigator's decision to restart the treatment of cemiplimab and isatuximab.
- After dose interruption of >14 days, it is per Investigator's decision to restart the treatment of cemiplimab and isatuximab, if a clear benefit from therapy is observed and after consultation with the sponsor.

- Treatment with isatuximab and cemiplimab must be definitely discontinued if the interruption is longer than 84 days.

6.5.3 Dose modifications

Dose reduction of cemiplimab is permitted for patients treated at the starting dose level and will consist in time interval increase between 2 planned infusions (Table 2).

Table 2 - Dose reduction guidance

	Isatuximab*		Cemiplimab	
Dose level	**Dose (mg/kg)**	**Frequency**	**Dose (mg)**	**Frequency**
Starting dose	10	QW x4 >Q2W	250 mg	Q2W
Dose reduction	10	QW x4 >Q2W	250 mg	Q4W

* No dose reduction for isatuximab

Guidelines for isatuximab and cemiplimab dose modifications and treatment discontinuation due to hematological and non-hematological adverse reactions in general are outlined in Table 3.

See Section 6.5.4 and Appendix G for guidance for immune-related AEs (irAEs) correlated with cemiplimab, and Section 6.5.5 for infusion associated reactions (IARs) correlated with isatuximab and cemiplimab.

The final decision will be per Investigator's judgment for the best interest of the patient.

Table 3 - Isatuximab and cemiplimab dose modification guidelines

Toxicity NCI CTCAE V4.03	**Isatuximab dose management**	**Cemiplimab Dose management**	**Action and Guidelines**
Hematological toxicity			
Grade 1, 2, 3	No change in dose		Patient should be given supportive care and monitored closely.
Grade 3 thrombocytopenia lasting >7 days or associated with bleeding	Delay the dose until bleeding is controlled and platelet >50 000/mm^3. Restart treatment with same dose and schedule.		Patient should be given supportive care and monitored closely. Permanent discontinuation should be considered if toxicity does not resolve within 84 days of last infusion.
Grade 4	Delay the dose until ANC>1000/mm^3, Platelet >50 000/mm^3. Restart with same dose and schedule. Grade 4 lymphopenia: no change in dose		
Febrile neutropenia and/or neutropenic infection	Delay the dose until fever and infection recover and ANC>1000/mm^3. Restart with same dose and schedule.		

Toxicity NCI CTCAE V4.03	Isatuximab dose management	Cemiplimab Dose management	Action and Guidelines
Non-hematological toxicity (other than irAE and IAR)			
Grade 1	No Change in Dose	No Change in Dose	N/A
Grade 2	Delay the dose until improves to Grade ≤1 or baseline. Restart treatment at same dose and schedule	Delay the dose until improves to Grade ≤1 or baseline. Restart at same dose and schedule	It is up to the investigator's judgment whether to restart the treatment of isatuximab and cemiplimab if the interruption is within 14 days. If the treatment interruption is longer than 14 days, before restarting the treatment, the investigator must discuss with sponsor; if it is determined that it is to the best interest of the patient, the treatment may be restarted. If the interruption is longer than 84 days, the treatment must be definitely discontinued.
Grade 3	Delay the dose until improves to Grade ≤1 or baseline. Restart at same dose and interval	Delay the dose until improves to Grade ≤1 or baseline. 1st episode lasts <14 days: restart at same dose 1st episode lasts >14 days or recurrence: restart with first reduction dose (Q4W administration if began at Q2W starting dose). If began at DL-1, consider discontinuation 2nd episode lasts >14 days or multiple recurrences discontinue treatment.	
Grade 4	Permanent discontinue treatment for treatment related AEs		
Immune-related AE (irAE): see Table 4 and Appendix G for dose modification and patient management guideline)			
Infusion Associated Reaction (IAR): see Table 5 for IAR management guideline			

6.5.4 General guidelines for the management of immune-related adverse events

Investigators must be extremely vigilant and be ready to intervene early in the management of immune-related AE (irAEs) because the onset of symptoms of irAEs (eg, pneumonitis) may be subtle.

- Detailed guidance for the management of specific irAEs (Colitis, Endocrine AE, Pneumonitis, Renal AE, Dermatologic AE, Hepatitis, Ophthalmologic AE [Uveitis]), plus Nausea and Vomiting is provided in Section 19, Appendix G.
- General guidance is provided in Table 4.
- If a patient experiences several irAEs which involve different recommendations, the most conservative recommendation should be followed.

The recommendations provided in Table 4 and Appendix G should be seen as guidelines, and the treating physician should exercise clinical judgment based on the symptoms and condition of the individual patient.

Any patient currently receiving cemiplimab who was previously treated with a phosphatidylinositol 3-kinase (PI 3-K) inhibitor and who develops stomatitis or mucositis should temporarily suspend study treatment. If this or any other immune-related AE occurs among these patients, the sponsor should be informed as soon as possible to discuss further management of the patient. An irAE of any grade in a patient previously treated with a PI 3-K inhibitor should be reported as an adverse event of special interest (AESI).

Table 4 - General guidelines for immune related adverse events

Severity	Withhold/Restart /Discontinue isatuximab Treatment	Withhold/Restart/Discontinue cemiplimab Treatment	Supportive Care
Grade 1	No action	No action	Provide symptomatic treatment.
Grade 2	No action	May delay the dose until Grade ≤1	Consider systemic corticosteroids (Prednisone 0.5 to 1 mg/kg/day or equivalent) in addition to appropriate symptomatic treatment.
Grade 3 Grade 4	Delay the dose Restart treatment when Toxicity improves to Grade ≤1 or baseline.	Delay the dose Restart treatment Toxicity improves to Grade ≤1 or baseline Discontinue if unable to reduce corticosteroid dose to <10 mg per day prednisone equivalent within 12 weeks of toxicity.	For any Grade 3-4 immune-related adverse event, if symptoms worsen or do not improve on adequate corticosteroids (Prednisone 1 to 2 mg/kg/day or equivalent) within 48 to 72 hours), consider additional immunosuppressive agents (to be selected from agents such as: infliximab, cyclophosphamide, cyclosporine, and mycophenolate mofetil). Referral of the patient to a specialized unit for assessment and treatment should be considered.

6.5.5 General guidelines for the management of IARs

See Appendix H.

Patients should routinely receive premedications prior to isatuximab infusion as detailed in Section 8.2 to reduce the risk and severity of IARs commonly observed with mAbs.

Infusion associated reactions (which include NCI-CTCAE, version 4.03 terms "allergic/hypersensitivity reactions" and "cytokine release syndrome/acute infusion reaction") typically occurs within 24 hours from the start of the infusion. If an IAR is observed, patients must also be informed of the potential risk of recurrent allergic reactions at subsequent infusions.

Summary of IAR management is provided in Table 5.

Patients who experience Grade 2 IARs may resume cemiplimab/isatuximab infusion after temporary interruption, under close monitoring and with therapy as needed. Patients may receive additional medication per the judgment of the Investigator. Additional recommended medications

are: diphenhydramine 25 mg IV (or equivalent) and methylprednisolone 100 mg IV (or equivalent).

Once a Grade 2 IAR has improved or resolved to Grade ≤1, the infusion may be restarted:

- For cemiplimab, the infusion should be restarted at one half the original infusion rate.
- For isatuximab, the infusion should be restarted at one half the original infusion rate, see Section 8.4 for 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 Grade 3 or 4 IAR must have cemiplimab and/or isatuximab permanently discontinued and appropriate therapy should be administered:

If a Grade 3 or high IAR occurred during cemiplimab infusion, cemiplimab should be permanently discontinue. Patient can continue treatment with isatuximab.

If a Grade 3 or high IAR occurred after the start of isatuximab infusion, patient should be permanently discontinue the treatment of both cemiplimab and isatuximab.

Should an IAR of Grade ≥2 occur, additional blood sampling during the AE is required for analysis of cytokine levels (TNF-α, , IL-6, IL-1-β, and IFN-γ), markers of complement activation (C3a, C4, CH50), serum tryptase, and markers of potential TLS (uric acid, lactate dehydrogenase [LDH], BUN/creatinine, potassium, phosphate, corrected calcium or ionized calcium). The infusion reaction and the therapy administered must be documented in the CRF.

Grade 2 or higher IARs must be reported as AESIs (see Section 10.5). Study personnel should consult the Medical Monitor for further guidance regarding re-treatment of patients with infusion reactions and regarding issues of premedication management (eg, alternative medications for patients allergic or intolerant to premedication agents) or to determine if locally used equivalent medications are acceptable.

Table 5 - IAR management

Infusion Related Reaction grading (NCI-CTCAE v4.03 criteria)	Recommendation
Mild Grade 1 Infusion interruption or intervention not indicated	Continuation of cemiplimab/ isatuximab infusion is per the judgment of the Investigator following close direct monitoring of the patient's clinical status. Cemiplimab/Isatuximab infusion may be stopped at any time if deemed necessary. If stopped, IAR will be classified as Grade 2 as per NCI-CTCAE definition.
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 hrs)	Stop cemiplimab/isatuximab infusion. Give additional medication(s) with IV diphenhydramine 25 mg IV (or equivalent) and/ or IV methylprednisolone 100 mg (or equivalent) as needed. cemiplimab*/Isatuximab** may be resumed only after patient recovery, with close monitoring. Blood samples for safety labs must be collected at listed as below: Important: additional blood sampling during the AE is required for analysis of cytokine levels (TNF-α, , IL-6, IL-1-β, and IFN-γ), markers of complement activation (C3a, C4, CH50), serum tryptase, and markers of potential TLS

Infusion Related Reaction grading (NCI-CTCAE v4.03 criteria)	Recommendation
Severe or Life-threatening 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 cemiplimab/isatuximab infusion. Give additional medication(s) with diphenhydramine 25 mg IV (or equivalent) and/ or IV methylprednisolone 100 mg (or equivalent) and/or epinephrine as needed. If IAR occurred during cemiplimab infusion, permanently discontinue cemiplimab. Continue treatment with isatuximab. If IAR occurred after the start of isatuximab infusion, permanently discontinue both cemiplimab and isatuximab. Blood samples for safety labs must be collected at listed as below: Important: additional blood sampling during the AE is required for analysis of cytokine levels (TNF-α, , IL-6, IL-1-β, and IFN-γ), markers of complement activation (C3a, C4, CH50), serum tryptase, and markers of potential TLS

* Cemiplimab: The prepared infusion bag should be kept no more than 8 hours at room temperature between +15°C to +25°C (59°F to 77°F), or no more than 24 hours at 5°C (with an acceptable operating range of 2°C to 8°C refrigerator).

** Istuximab: the resulting solution for infusion should be used within 16 hours at room temperature between +15°C to +25°C (59°F to 77°F) from the bag preparation to the end of IV infusion of the patient or a new infusion should be prepared with the remaining dose to be administered the same day.

6.5.6 Guidelines for the management of potential tumor lysis syndrome (TLS)

In case of TLS, study treatment should be held until all serum chemistries have resolved. To ensure normal hydration, correct laboratory abnormalities, fluid overload, electrolyte or acid-base deviation. Management must be done according to the local site guideline. Use of xanthine oxidase or urate oxidase is allowed.

TLS complications including renal function should be monitored, and study treatment can be reinstituted at full doses after resolution.

Possible clinical and laboratory abnormalities which can be associated with TLS are presented in Table 6 (45).

Table 6 - Laboratory and clinical abnormalities possibly consistent with TLS

Laboratory	Clinical
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[a] <7.0 mg/dL(<1.75 mmol/L) or ionized calcium <1.12 mg/dL (<0.3 mmol/L)	• 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/hr for 6 hours • Seizures, cardiac dysrhythmia, neuromuscular irritability (tetany, paresthesias, muscle twitching, carpopedal spasm, Trousseau's sign, Chvostek's sign, laryngospasm, bronchospasm), hypotension, or heart failure probably or definitely caused by hypocalcemia • Dysrhythmias probably or definitely caused by hyperkalemia

a The corrected calcium level in milligrams per deciliter = measured calcium level in milligrams per deciliter + 0.8x (4-albumin in grams per deciliter)

6.5.7 Guidance in case of hepatitis B reactivation occurring under study treatment

Patient still on treatment at the time of amended protocol 05 will be tested for HBV serology and HBV viral DNA once at any time if HBV status was unknown before treatment started; test will be repeated if clinically indicated.

In case of viral reactivation during study treatment (greater than 1 $\log_{10}$ IU/mL increase in HBV DNA or reappearance of hepatitis B surface antigen (HBsAg) or detection of HBV DNA in patients with resolved infection) study treatment will be held and specialist consulted for initiation of anti-viral treatment and monitoring of the patient. Resolved infection means previous known history of acute or chronic hepatitis B or the presence of total anti-hepatitis B core antibody (HBcAb) with/without anti-hepatitis B surface antibody (HBsAb); HBsAg negative; undetectable serum HBV DNA; and normal ALT levels. Restart of study treatment should be agreed between the Sponsor, the Investigator and specialist (hepatologist) if infection is controlled. ALT and AST will be closely monitored every month up to study treatment discontinuation. HBV DNA to be done as per specialist advice.

6.6 DURATION OF STUDY PARTICIPATION

6.6.1 Duration of study participation for each patient

The duration of the study for a patient will include a period for screening of up to 21 days. The cycle duration is 28 days. Patients will continue treatment until disease progression, unacceptable adverse events, consent withdrawal, or any other reason.

After study treatment discontinuation, patients will return to the study site 30 days (+5 days) after the last dose of study treatments for end-of-treatment assessments. The post-treatment follow-up period include an extended safety follow-up period of 90 days after the last dose of study treatment, and further follow up period beyond 90 days after the last dose of study treatments until death or final study cut-off date, whichever occurs first.

The further follow up schedule beyond 90 days after last treatment is adjusted according to the disease progression:

- Patients who discontinue study treatment due to PD: follow-up visit will be done every 3 months from the date of last study treatment administration until death or final study cut-off date.
- Patients who discontinue the study treatment without PD: will be followed every month for disease assessment until confirmation of PD or start treatment with another anti-cancer therapy whichever comes first. After PD patient will be followed every 3 months as described just above until death or final study cut-off date.

6.6.2 Determination of end of clinical trial (all patients)

The cutoff date for primary analysis of ORR and reporting of other study endpoints will be 6 months after last patient first treatment.

The final analysis cutoff date for OS analysis and updated analysis of ORR and other secondary endpoints will be approximately 12 months after last patient first treatment date.

Interim analysis

For Phase 2 part, a formal interim analysis of response rate (including confirmed and unconfirmed responses) will be performed when the first 15 randomized patients in each arm completed 2 cycles of treatment or permanently discontinue treatment. The purpose of the analysis is to stop combination arm early for futility when conditional power is <30%. Details can be found in Section 13.5.

In addition, formal safety review by DMC are planned approximately every 3 months to examine unblinded patient safety data and quality of trial conduct.

6.7 STUDY COMMITTEES

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

The 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 sponsor 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.

The DMC will convene every 3 months for regular safety and efficacy review, or on ad hoc basis when required. In addition, the DMC will also review the results from the interim analysis (see Section 13.5). After each meeting, the DMC will advise the sponsor's representatives on recommendations regarding the continued safety of treating ongoing and future study patients, as well as the course of action regarding the conduct of the trial.

The Study Committee will be comprised of the Investigators and Sponsor representatives. The Study Committee will be review clinical data on a regular basis, with a review being performed at least at the end of each dose level cohort, and at the end of the Phase 1 of the study.

The Study Committee will convene regularly during Phase 1, eg, every 2 weeks, or ad hoc when required.

7 SELECTION OF PATIENTS

7.1 NUMBER OF PATIENTS

Approximately 108 to 138 patients.

7.2 INCLUSION CRITERIA

I 01. Age ≥18.

I 02. Patients must have a known diagnosis of multiple myeloma with evidence of measurable disease, as defined below:

- Serum M-protein ≥1 g/dL (≥0.5 g/dL in case of IgA disease),

AND/OR

- Urine M-protein ≥200 mg/24 hours,

OR

- In the absence of measurable M-protein, serum immunoglobulin free light chain ≥10 mg/dL, and abnormal serum immunoglobulin kappa lambda free light chain ratio (<0.26 or >1.65).

I 03. Patients must have received prior treatment with an IMiD (for ≥2 cycles or ≥2 months of treatment) and a proteasome inhibitor (for ≥2 cycles or ≥2 months of treatment).

I 04. Patients must have received at least 3 prior lines of therapy (Note: Induction therapy and stem cell transplant ± maintenance will be considered as one line).

I 05. Patients, must have achieved MR or better with anyanti-myeloma therapy (ie, primary refractory disease is not eligible).

I 06. Patients understand and have signed the Written Informed Consent form and arewilling and able to comply with the requirements of the trial.

I 07. Anti-CD38 refractory cohort only: Patients who received anti-CD38 mAb within 6 months before study entry and had disease progression while on treatment or within 60 days after the last treatment.

7.3 EXCLUSION CRITERIA

Patients who have met all the above inclusion criteria listed in Section 7.2 will be screened for the following exclusion criteria:

E 01. Has any concurrent hematology malignancy other than multiple myeloma, including:
- Active primary AL amyloidosis,
- Concomitant plasma cell leukemia.

E 02. Has prior exposure to:
- Isatuximab or participated clinical studies with isatuximab,
- Any agent (approved or investigational) that blocks the PD-1/PD-L1 pathway.

E 03. Diagnosed or treated for another malignancy within 3 years prior to the study treatment with the exception of resected/ablated basal or squamous cell carcinoma of the skin, or carcinoma in situ of the cervix, or other local tumors considered cured by local treatment, or low risk prostate cancer after curative therapy;

E 04. Evidence of other immune related disease /conditions, including:
- Ongoing or recent (within 2 years) evidence of significant autoimmune disease that required systemic immunosuppressive treatment (ie, with use of disease modifying agents, corticosteroids or immunosuppressive drugs.). Replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc) is not considered a form of systemic treatment,
- History of moderate immune-mediated acute drug reactions (eg, colitis, hepatitis, etc).

E 05. History of non-infectious pneumonitis requiring steroids or current pneumonitis; history of the thoracic radiation.

E 06. Has received a live-virus vaccination within 30 days of planned treatment start. Seasonal flu vaccines that do not contain live virus are permitted.

E 07. Known to be HIV+, HBV+ or hepatitis A, B, or C active Infection, or active tuberculosis, or severe and active infection requiring systemic antibiotics, antivirals or antifungals within 2 weeks prior to first dose (except when used for chronic prophylaxis).

E 08. Has allogenic HSC transplant.

E 09. Has prior exposure to treatment, including:
- Prior treatment with idelalisib (an PI3K inhibitor)
- Any anti-myeloma drug treatment including dexamethasone within 14 days before study entry (90 days if prior anti-CD38 treatment),
- Patients who received anti-CD38 mAb within 6 months before study entry and had disease progression while on treatment or within 60 days after the last treatment will be excluded except the anti-CD38 refractory cohort.
- Any major procedure within 14 days before the initiation of the first study treatment: plasmapheresis, major surgery (kyphoplasty is not considered major procedure), radiotherapy (palliative radiotherapy may be given to control pain).
- Any investigational drugs within 28 days or 5 half-lives from the 1st study treatment, whichever is longer.

E 10. Congestive heart failure (New York Heart Association class III to IV) myocardial infarction within 6 months or with reduced ejection fraction, symptomatic coronary artery disease, major clinically significant electrocardiogram (ECG) and echocardiogram abnormalities, significant ventricular arrhythmias.

E 11. Ongoing adverse events Grade ≥2 (excluding alopecia and those listed in eligibility criteria) from any prior anti-cancer therapy (NCI-CTC v4.03).

E 12. Eastern Cooperative Oncology Group (ECOG) performance status (PS) >2. See Appendix B for ECOG performance status scale.

E 13. Inadequate hematological function including:

- Platelets <50 000/mm^3. Patient should be platelet transfusion independent for 2 weeks prior to screening lab values),
- ANC ≤1000/mm^3 (1 x 10^9/L). (use of colony-stimulating factors to achieve these counts is allowed),
- Hemoglobin <8.0 g/dL (patients may receive red blood cell transfusion or receive supportive care such as erythropoietin and darbepoetin in accordance with institutional guidance).

E 14. Inadequate liver findings including:

- Total bilirubin >2 x ULN,
- AST and/or ALT >3 x ULN.

E 15. Inadequate renal function: Estimated glomerular filtration rate (eGFR) <30 mL/min/1.73m^2 (MDRD Formula). See Appendix A for MDRD equation.

E 16. Corrected serum calcium >14 mg/dL (>3.5 mmol/L).

E 17. Pregnant or breastfeeding female patients.

E 18. Women of childbearing potential and male subjects with female partners of childbearing potential who are not willing to avoid pregnancy by using effective contraceptive (prior to initial dose, during the course of study and up to 6 months after the last study treatment). See Appendix J for guidance of the contraceptive and collection of pregnancy information.

E 19. Known intolerance or hypersensitivity to any component of isatuximab and/or cemiplimab.

E 20. Patient is a dependent on the sponsor or investigator (in conjunction with Section 1.61 of the ICH-GCP Ordinance E6), employees of the clinical study site or any other individuals directly involved in the conduct of the study, or immediate family members of such individuals.

E 21. Patients who are accommodated in an institution because of regulatory or legal order, or prisoners or subjects who are legally institutionalized, or patients with any severe acute or chronic medical condition, including psychological disorder, which could impair the ability of the patient to participate in the study or interfere with interpretation of study results or patient unable to comply with the study procedures.

8 STUDY TREATMENTS

8.1 INVESTIGATIONAL MEDICINAL PRODUCT

8.1.1 Isatuximab

8.1.1.1 Pharmaceutical form

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

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

For administration to patients, the appropriate volume of isatuximab will be diluted in an infusion bag of 0.9% sodium chloride solution or 5% dextrose 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 Dose of drug per administration

Starting dose of isatuximab is 10 mg/kg, see Section 6.2.1.

8.1.1.3 Preparation, reconstitution and administration

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

Infusion via a central line is preferred if available. In case of patients with local intolerance after peripheral IV infusion, 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 treatment to allow calculation of the isatuximab dose.

For infusion, an IV tubing administration set with a 0.20-µm in-line filter will be used; 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.

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

8.1.2 Cemiplimab

8.1.2.1 Pharmaceutical form

Cemiplimab drug product concentrated solution 50 mg/mL in 10 mL vials with 5.0 mL or 7.0 mL withdrawable, containing 10 mM histidine, 5% (w/v) sucrose, 1.5% (w/v) L-proline, and 0.2% (w/v) polysorbate 80, pH 6.0.

8.1.2.2 Dose of drug per administration

Starting dose of cemiplimab is 250 mg, see Section 6.2.1.

8.1.2.3 Preparation, reconstitution and administration

Cemiplimab 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 cemiplimab 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.

For infusion, an IV tubing administration set with a 0.20-µm in-line filter will be used; 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.

8.2 NONINVESTIGATIONAL MEDICINAL PRODUCT(S)

Patients should routinely receive premedication **30 to 60 minutes prior to the start of the isatuximab infusion** to reduce the risk and severity of IARs commonly observed with monoclonal antibodies.

Patients who do not experience an IAR during the first 4 administrations of SAR650984 may have the need for subsequent pre-medication reconsidered at the investigator’s discretion in consultation with the sponsor.

The recommended premedication agents and are listed below:

- Acetaminophen 650 mg to 1000 mg PO (or equivalent).
- Ranitidine 50 mg IV (or equivalent: other approved H2 antagonists [eg, cimetidine], oral proton pump inhibitors [eg, omeprazole, esomeprazole]).
- 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).

- Methylprednisolone 100 mg IV (or equivalent).

The order of pre-medications should be:

- Acetaminophen, ranitidine, diphenhydramine, and then methylprednisolone when methylprednisolone is administered via IV route.
- Methylprednisolone (PO), acetaminophen (PO), ranitidine (IV), diphenhydramine (IV) when methylprednisolone is given via PO route.

8.2.1 Acetaminophen or equivalent

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

8.2.2 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.

8.2.3 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.

8.2.4 Methylprednisolone or equivalent

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

8.3 DOSING REGIMEN AND SEQUENCE

8.3.1 Dosing regimen

Isatuximab:

- For isatuximab alone as control, and at DL1 and DL-1: 10 mg/kg QW for 4 weeks followed by Q2W (ie, on Days 1, 8, 15 and 22 in Cycle 1, and on Days 1 and 15 in Cycle 2 and beyond, of a 28-day cycle).
- For DL-2: 10 mg/kg Q2W (ie, on Days 1 and 15 every cycle, of a 28-day cycle).

Cemiplimab:

- For DL1: 250 mg Q2W (ie, on Days 1 and 15 in all cycles of a 28-day cycle).
- For DL-1 and DL-2: 250 mg Q4W (ie, on Day 1 in all cycles of a 28-day cycle).

8.3.2 Doing sequence

In Phase 1, all patients will receive isatuximab and cemiplimab.

In Phase 2, patients will be randomized to receive isatuximab alone or Isatuximab and cemiplimab.

Emergency equipment and medication for the treatment of IARs (eg, antihistamines, bronchodilators, IV saline, corticosteroids, acetaminophen, and/or epinephrine) must be available for immediate use.

- Dosing sequence for patients receive isatuximab and cemiplimab administration:
  - Pre-medications as described in Section 8.2,

    followed by
  - Cemiplimab infusion over 30 minutes,

    followed by
  - Isatuximab iv infusion over approximately 2-4 hours.
- Dosing sequence for patient receive isatuximab administration only:
  - Pre-medications as described in Section 8.2,

    followed by
  - Isatuximab iv infusion over approximately 2-4 hours.

8.4 RATE AND DURATION OF INFUSION

The duration of infusion for cemiplimab is 30 minutes.

For isatuximab, 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 6.5.5.

8.5 PACKAGING AND LABELING

8.5.1 Isatuximab

Isatuximab is packaged in 30 mL glass vials fitted with elastomeric closure. More detail information is provided in the pharmacy manual.

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

8.5.2 Cemiplimab

Cemiplimab is packaged in USP Type 1 clear glass, 10 mL vial with 20 mm gray chlorobutyl rubber stopper with FluroTec® coating and 20 mm red flip-off seal.

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

8.6 STORAGE CONDITIONS AND SHELF LIFE

8.6.1 Isatuximab

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

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

Isatuximab is to be stored at +2°C to +8°C (36°F to 46°F). All vials must be kept in their box until use. No protection from light is required for storage in the infusion bags.

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

8.6.2 Cemiplimab

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

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

Cemiplimab 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.

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

8.7 METHOD OF ASSIGNING PATIENTS TO TREATMENT GROUP IN PHASE 2

Phase 2 will have 3 arms (if the MTD or RP2D is at DL1 or DL-1) or 2 arms (if the MTD or RP2D is at DL-2) to assess the treatment response and safety of the combination therapy with isatuximab alone as control. Patients will be randomized in study arms. IRT will be used for randomization.

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

8.8 RESPONSIBILITIES

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

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

Under no circumstances will the Investigator supply IMP to a third party, allows the IMP to be used other than as directed by this clinical trial protocol, or dispose of IMP in any other manner.

8.8.1 Treatment accountability and compliance

Administration of the IMP will be supervised by the Investigator or Subinvestigator.

The person responsible for drug dispensing is required to maintain adequate records of the IMP. These records (eg, drug movement form) include the date the IMP 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 drug administration to the patient will record precisely the date and the time of the drug administration to the patient.

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 TREATMENT

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 the first study treatment, at any time during the study in addition to the IMP are regarded as concomitant treatments and the type, dose and route of administration must be documented on the appropriate pages of the e-CRF.

Concomitant medications should be kept to a minimum during the study. However, if these are considered necessary for the patient's welfare and are unlikely to interfere with the IMP, they may be given at the discretion of the investigator and recorded in the e-CRF.

- Supportive treatment as medically indicated for the patient’s well-being may be prescribed at the Investigator’s discretion. Every medication or treatment taken by the patient during the trial and the reason for its administration must be recorded on the e-CRF.

8.9.1 Prophylaxis for opportunistic infections

A recent study suggests that infections are the leading therapy-related causes of death in MM patients. Based on the NCCN guideline Version 1.2018, MM patients are at an intermediate risk of infection, prophylaxis for opportunistic infections is appropriate in this study. Broad-spectrum antimicrobial agents should be used in high-risk patients, per investigator’s discretion.

8.9.2 Prohibited concomitant treatments:

- 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 are prohibited, except used in the premedication as defined in the study protocol Inhaled glucocorticosteroids whenever indicated is allowed.

- Live vaccines should be avoided. However, giving 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.
- Prophylactic use of hematopoietic growth factors (eg, G-CSF, GM-CSF, erythropoietin) during the DLT observation period. Curative treatment is allowed.

8.9.3 Contraceptive measures and pregnancy counseling

Females of child bearing potential or male subjects with female partners of childbearing potential shall be required to use effective contraceptive methods (double barrier method, intrauterine device, oral contraception or abstinence) prior to first study treatment, while on therapy and for 5 months following the last dose of Isatuximab and 6 months following the last dose of cemiplimab.

A woman is considered of childbearing potential (WOCBP), ie, fertile, following menarche and until becoming post- menopausal unless permanently sterile.

The following highly effective methods of contraception are accepted:

- Sexual abstinence,
- Diaphragm and spermicide PLUS male condom, or,
- Intrauterine device PLUS male condom, or,
- Medical method (such as hormonal contraceptive) PLUS male condom.

The choice of effective method is left to Investigator judgment, in accordance to local regulation. Sterilized or infertile subjects are exempt from the requirement to use of contraception. In order to be considered sterilized or infertile, subjects must have undergone surgical sterilization (vasectomy/bilateral tubectomy, hysterectomy, bilateral ovariectomy) or be a postmenopausal woman defined as 12 months or more with no menses prior to enrollment and 50 years of age.

9 ASSESSMENT OF INVESTIGATIONAL MEDICINAL PRODUCT

9.1 SAFETY

The first co-primary objective of this study is to determine the safety and tolerability of the combination of isatuximab and cemiplimab in patients with RRMM.

The safety profile will be assessed from the findings of physical examination (preferably by the same physician in each center), laboratory tests and reports of AEs, etc, and will be based on incidence, severity (as graded by the NCI-CTCAE v. 4.03), and cumulative nature of TEAEs (defined as AEs that develop or worsen in grade or become serious during the TEAE period).

9.1.1 Dose-limiting toxicities (Phase 1 only)

Potential DLTs are defined as the occurrence of any of the following adverse reactions at first cycle:

Hematological DLT is defined as any of the followings unless due to disease progression or an obviously unrelated cause:

- Grade 4 neutropenia lasting more than 7 consecutive days.
- Grade 3 to 4 neutropenia complicated by fever (temperature ≥38.5°C on more than one occasion) or microbiologically or radiographically documented infection.
- Grade 3 to 4 thrombocytopenia associated with clinically significant bleeding that requiring clinical intervention.

  Note: Platelet transfusions in the absence of bleeding will not be considered a DLT because thrombocytopenia is an anticipated complication of MM, particularly in a heavily pretreated patient population, and patients can enter the study with pre-existing thrombocytopenia.

Non-hematologic DLT is defined as any of the followings unless due to disease progression or an obviously unrelated cause:

- Grade 4 non-hematologic AE.
- Grade ≥2 uveitis.
- Grade 3 non-hematological AE lasting >3 days despite optimal supportive care. **except**:
  - Grade 3 fatigue,
  - Allergic reaction/hypersensitivity attributed to isatuximab or cemiplimab,
  - Laboratory abnormality that worsens to Grade 3 or 4 but is not clinically significant per investigator and study committee.
- Delay in initiation of the 2nd cycle >14 days due to treatment related laboratory abnormalities/ AE.

In addition, any other AE that the investigator / Study Committee deem to be dose limiting, regardless of its grade, may also be considered as DLT.

At the end of Cycle 1, each patient must be assessed by the Investigator as to whether or not the patient experienced a DLT. This information must be recorded on the appropriate eCRFs, and an electronic DLT notification (either DLT or not) will be sent to the Sponsor, before a subsequent cycle may begin.

Potential and IMP-related DLTs will be considered as adverse event of special interest (AESI). As such, the Investigators will be required to report them to the Sponsor within 24 hours of the Investigator becoming aware of each event. The Investigator will complete the specific DLT form in the eCRF.

The reported potential DLTs will be reviewed by the Study Committee in order to determine their relationship to the IMP.

9.1.2 Adverse events

Adverse events will be collected from the signing of the study main informed consent up to 30 days after the last IMP administration. During the follow-up period, ongoing SAEs regardless of relationship to IMP and ongoing or new study treatment related AEs will be followed until resolution or stabilization. Adverse events encountered before the start of study treatment will be summarized separately.

Adverse events will be graded according to the NCI CTCAE v.4.03, and will be coded to a "Preferred Term" and associated primary "System Organ Class" using MedDRA (Medical Dictionary for Regulatory Activities).

The study-specific and general safety criteria are developed in Section 10.

9.1.3 Laboratory safety variables

Please refer to "Study Procedures" Section 12.

9.1.4 Clinical examinations

Please refer to "Study Procedures" Section 12.

9.1.5 Immunogenicity

It is of utmost importance to collect all blood samples at the specified times and according to the specifications for collection, storage, and shipment as defined in a separate laboratory manual.

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

The cemiplimab and isatuximab ADA sampling times for blood collection can be found in the PK Flow Chart (Section 1.2 and Section 1.3).

- For cemiplimab during treatment phase, samples for immunogenicity assessment are to be collected every third Cycle from C5 (ie, on D1 of C5, C8, C11, C14, etc) till the last study treatment. In response to AEs of special interest, such as anaphylaxis or hypersensitivity, ADA samples closer to the event may be collected, based on the judgment of the Investigator and/or medical monitor. If isatuximab is stopped and cemiplimab treatment continues, cemiplimab ADA samples should be collected as planned per PK/PD flow-chart.
- For isatuximab, samples for immunogenicity assessment are to be collected during the course of the study. However, collection can be stopped earlier based on the updated knowledge of isatuximab immunogenicity (note that collection was indeed interrupted at cut-off date of primary efficacy analysis 6 months after LPI). At FU 90 (±7) days after last IMP administration if ADA is positive or inconclusive no further ADA will be sampled. The ADA results will be communicated to investigational sites on an ongoing basis.

Bioanalytical methods used for immunogenicity assessment are summarized in Table 7.

Table 7 - Bioanalytical methods for immune response assessment

Analyte	ANTI ISATUXIMAB ANTIBODY	ANTI CEMIPLIMAB ANTIBODY
Matrix	Plasma	Serum
Analytical technique	PandA method	Non-quantitative bridging immunoassay
Lower Limit of Quantification	Not applicable	Not applicable
Site of bioanalysis	Covance Harrogate (UK))	Regeneron Pharmaceuticals, Inc. (Tarrytown, NY)

9.2 EFFICACY

9.2.1 Primary endpoint (Phase 2 only)

The second co-primary endpoint of the study is to determine the efficacy of the combination as assessed by ORR. ORR is defined as the proportion of patients with CR (including sCR), VGPR and PR as assessed by investigators using the IMWG response criteria (44).

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:

- M-protein quantification (serum and urine) (local laboratory).
- FLC quantification (local laboratory).
- Quantitative immunoglobulins (local laboratory).

- In addition, other examinations for disease assessment will be done as clinically indicated (eg, to confirm a response, suspected PD) as below (local laboratory):
  - Bone marrow aspiration,
  - Bone disease assessment,
  - Extramedullary disease (plasmacytoma) assessment (including bone plasmacytoma).

Response/progression will be determined according to IMWG criteria (44) (Appendix D). Response/progression based on M-protein and FLC will be confirmed based on 2 consecutive assessments.

Progressive disease is defined for patients with measurable disease with one of the following:

- Increase of ≥25% in serum M-protein from nadir (the absolute increase must be ≥0.5 g/dL) in 2 consecutive assessments; serum M-protein increases ≥1 g/dL in 2 consecutive assessments are sufficient to define relapse if starting M-protein t is ≥5 g/dL and/or,
- Increase of ≥25% in urine M-protein from nadir (the absolute increase must be ≥200 mg/24 h) in 2 consecutive assessments and/or,
- Only in subjects without measurable serum and urine M-protein levels: increase of ≥25% in the difference between involved and uninvolved FLC levels and absolute increase must be >10 mg/dL 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 ORR.

Measurable disease is defined by at least one of the following measurement:

- Serum M-protein ≥1g/dL or ≥0.5 g/dL for patients with IgA MM.
- Urine M-protein ≥200 mg/24h.
- In the absence of measurable M-protein, serum immunoglobulin FLC level ≥10 mg/dL provided abnormal serum immunoglobulin kappa lambda FLC ratio (<0.26 or >1.65).

9.2.2 Secondary endpoints (Phase 2 only)

- CBR: defined as the proportion of patients with CR (including sCR), VGPR, PR and minimal response (MR) as assessed by investigators using the IMWG response criteria.
- DOR: defined as the time from the date of the first response (≥PR) that is subsequently confirmed to the date of first confirmed disease progression or death, whichever happens first PD will be determined according to IMWG criteria (See Appendix D). In the absence of the confirmation of subsequent disease progression or death before the analysis cut-off date or the date of initiation of a further anticancer treatment, the DOR will be censored at the date of the last valid disease assessment not showing disease progression performed

prior to initiation of a further anticancer treatment and the analysis cut-off date, whichever is earlier. DOR will not be calculated for patients that do not achieve a PR or better.

- TTR: defined as time from first study treatment administration (C1D1) to first response (PR or better) that is subsequently confirmed.
- PFS: defined as time from the first study treatment administration to the date of first documentation of progressive disease (PD) that is subsequently confirmed or the date of death from any cause. Same censoring rules as DOR will be used.
- OS: defined as the time from the first study treatment administration to death from any cause. Patients without death prior to the analysis cutoff date will be censored at the last date the patient was known to be alive or the cutoff date whichever comes first.

9.3 PHARMACOKINETIC EVALUATION

9.3.1 Sampling time

It is of utmost importance to collect all blood samples at the specified times and according to the specifications for collection, storage, and shipment as defined in a separate laboratory manual.

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

The cemiplimab and isatuximab PK sampling times for blood collection can be found in the PK Flow Chart (Section 1.2 and Section 1.3).

For isatuximab, samples for PK assessment are to be collected during the course of the study. However, collection can be stopped earlier based on the updated knowledge of isatuximab PK (note that collection was indeed interrupted before Amendment 05).

9.3.2 Pharmacokinetic sample handling procedure

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

9.3.3 Bioanalytical methods and bioanalytical sites

Bioanalytical methods are summarized in Table 8.

Table 8 - Bioanalytical methods for isatuximab and functional cemiplimab pharmacokinetic analysis

Analyte	Isatuximab	Cemiplimab
Matrix	Plasma	Serum
Analytical technique	Immunoassay	Immunoassay
Lower limit of quantification	0.500 µg/mL	78.0 ng/mL
Site of bioanalysis	Covance Harrogate, UK	Regeneron Pharmaceuticals, Inc. (Tarrytown, NY)

9.3.4 Pharmacokinetic parameters

9.3.4.1 Non-compartmental analysis

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

Table 9 - List of pharmacokinetic parameters and definitions

Parameters	Analyte		Definition
	cemiplimab	Isatuximab	
C_{eoi}	•	•	Concentration observed at the end of intravenous (IV) infusion
C_{max}	•	•	Maximum concentration observed after the first infusion
t_{max}	•	•	Time to reach C_{max}
C_{last}	•	•	Last concentration observed above the lower limit of quantification after the first administration
t_{last}	•	•	Time of C_{last}
C_{trough}	•	•	Concentration observed just before treatment administration during repeated dosing
$AUC_{0\text{-}14d}$ or $AUC_{0\text{-}28d}$	•		Area under the concentration versus time curve calculated using the trapezoidal method over the dosing interval (DL1=14 days and DL-1=28 days) after the first administration
$AUC_{0\text{-}7d}$		•	Area under the concentration versus time curve calculated using the trapezoidal method over the dosing interval (7 days) after the first administration

9.3.4.2 Population approach

Populations PK approaches may be used for both compounds and PK estimates may be used to conduct exploratory exposure-response analyses for safety and efficacy and PK/PD analyses for relevant biomarkers. If done, the data generated will be reported in stand-alone report(s).

9.4 SPECIFIC ASSESSMENTS: ISATUXIMAB IAR LABS - CYTOKINES, MARKERS OF ACTIVATED COMPLEMENTS AND SERUM TRYPTASE

Baseline sample will be drawn for assessment of cytokines (IL-1β, IL-6, TNFα and IFNγ), markers of activated complement (C3a, C4 and CH50), lactate dehydrogenase [LDH] and serum tryptase, prior to first isatuximab administration at Cycle 1. Then if an isatuximab infusion associated reaction (IAR) ≥Grade 2 occurs, additional blood sampling during the AE is required for analysis.

Samples not collected, missed or lost, for any reason should be documented. Actual dates and times of blood collection should be recorded in the eCRF. The dates and the times of study treatment administration should also be precisely recorded.

Special procedures for collection, storage, and shipment as well as bioanalysis methods and bioanalysis location will be provided in a separate Laboratory Manual.

9.5 EXPLORATORY BIOMARKER ANALYSES

Bone marrow and blood samples will be collected for the following biomarker analyses:

- Correlation of multiple myeloma molecular subtype (as defined by marker expression, cytogenetics) with parameters of clinical response. Cytogenetics analysis (including, but may not limited to, 17p deletion, t[4, 14] and t[14, 16]) will be performed. Baseline bone marrow samples will be collected for FISH analyses. In addition, results of local FISH/cytogenetic tests performed the most recently prior to patient enrollment may also be collected through report or access to data.
- Correlation of immunophenotype in bone marrow and/or peripheral blood with parameters of clinical response. Blast cells and immune cell populations (including MDSC cell, T-cell, NK-cell subsets and Treg/CD8 effector ratio) will be characterized by multiparametric flow cytometry analysis on the expression of cell surface markers. The proportion of cells positive for a given marker or set of markers (eg, regulatory T cells [Tregs]) will be correlated with response to SAR650984. Bone marrow aspirate and blood will be collected at baseline and Day 1 of Cycle 3 and blood samples only will be collected at EOT.
- Whenever possible, PD-L1 expression in malignant plasma and immune cells will be determined and correlated with clinical response. Access to archival bone marrow biopsy material will be requested at screening and if available, retrospective expression analysis will be performed by IHC assay.
- Correlation of adaptive immune response (TCR repertoire profiling) with parameters of clinical response. Blood and bone marrow samples will be collected at screening, D1 of Cycle 3 (blood only) and at CR.
- Correlation of adaptive immune response (humoral and cellular immune responses to myeloma-related tumor antigens) with parameters of clinical response. Blood will be collected prior to pre-medication and IMP administration on D1 of Cycle 1, Cycle 2, Cycle 4, Cycle 7 and Cycle 10 and in disease progression patients at EOT. Humoral response will be assessed in all sites. Cellular response will be assessed in patients at selected sites.

- MRD will be assessed by sequencing and/or flow cytometry in bone marrow samples from CR patients and correlated with parameters of clinical response. Method to measure MRD include multi-parametric flow cytometry (MFC) and more recently next generation sequencing to amplify and sequence immunoglobulin gene segments present in myeloma clone is a quantitative method for MRD detection. Bone marrow samples will be collected at CR.
- Additional analysis, not specified in the protocol but related to the drug action and/or effect of isatuximab/cemiplimab, may be conducted on remaining samples pending evolving literature.

10 PATIENT SAFETY

10.1 SAFETY ENDPOINTS ASSESSED IN THIS TRIAL

Refer to Section 9.1 for definition of safety criteria, parameters to be analyzed and method of sample collection.

10.2 SAFETY INSTRUCTIONS

The safety of the patients in this clinical trial is primarily dependent on the clinical Investigators' monitoring and assessment of their patients. Please refer to Section 9.1.2 Adverse Events monitoring

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

10.3 DEFINITIONS OF ADVERSE EVENT AND SERIOUS ADVERSE EVENT

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

A **Serious Adverse Event** 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 intervention to prevent one of the other outcomes listed in the definition above.

Note: Examples of such events (list is not exhaustive) are intensive treatment in an emergency room or at home (for allergic bronchospasm, blood dyscrasias, or convulsions) or asymptomatic ALT increase ≥10 ULN that does not result in hospitalization, or development of drug dependency or drug abuse.

10.4 OBLIGATION OF THE INVESTIGATOR REGARDING SAFETY REPORTING

10.4.1 Adverse events

All AEs regardless of seriousness or relationship to the IMP, spanning from the signature of the informed consent form (ie, occurring during the baseline period even in the absence of any administration of IMP), up to 30 days following the last administration of study treatment, are to be recorded on the corresponding page(s) included in the eCRF.

Whenever possible, diagnosis or single syndrome should be reported instead of symptoms. The Investigator should specify the date of onset, intensity, action taken with respect to IMP, 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 IMP.

Vital signs or ECG abnormalities are to be recorded as AEs only if they are symptomatic and/or requiring corrective treatment and/or leading to treatment discontinuation and/or modification of dosing and/or fulfilling a seriousness criterion and/or is defined as an AESI (see Section 10.3).

Laboratory abnormalities are to be recorded as AEs only if they lead to treatment discontinuation and/or modification of dosing and/or fulfill a seriousness criterion and/or are defined as an AESI (DLT) (see Section 10.3).

10.4.2 Timely handling of certain AEs

In the case of a SAE, an AESI, a pregnancy report, or an overdose, the Investigator must immediately:

- ENTER (within 24 hours) the information related to the SAE in the appropriate screens of the e-CRF; the system will automatically send e-notification to the monitoring team after approval of the Investigator within the e-CRF or after a standard delay.
- There may be instances when copies of medical records for certain cases are requested by Sanofi. In such case, care should be taken to ensure that the patient's identity is protected and the patient's identifiers in the study are properly mentioned on any copy of a source document provided to the Company. For laboratory results, include the laboratory normal ranges
- All further data updates should be recorded in the e-CRF as appropriate within 24 hours of knowledge. In addition, every effort should be made to further document each SAE that is fatal or life threatening within the week (7 days) following initial notification.
- A back-up plan is used (using paper flow) when the e-CRF system does not work.

10.4.3 Follow-up

- The Investigator should take all appropriate measures to ensure the safety of the patients, notably he/she should follow up the outcome of any AEs (clinical signs, laboratory values or other, etc) until the return to normal or consolidation of the patient's condition. Ongoing related AEs at the end of study treatment will be followed until resolution or stabilization.

- In case of any SAE/AESI, the patient must be followed up until clinical recovery is complete and laboratory results have returned to normal, or until outcome has been stabilized. This may imply that follow-up may continue after the patient has discontinued study treatment or has left the clinical trial and that additional investigations may be requested by the monitoring team;
- In case of any AE or AESI 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.

10.4.4 Treatment discontinuation due to nonserious adverse event

In the case of a treatment discontinuation due to a nonserious AE:

- ENTER (within 24 hours) the information related to treatment discontinuation due to a non-SAE in the appropriate screens of the e-CRF (AE with the box "action taken with IMP" ticked "permanently discontinued", together with the end of treatment form with reason that should be ticked "AE"); the system will automatically send the notification to the monitoring team after approval of the Investigator within the e-CRF or after a standard delay.

10.5 ADVERSE EVENT OF SPECIAL INTEREST

An 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 conditions are considered AESIs and as such, the Investigators will be required to report them to the Sponsor within 24 hours of the Investigator becoming aware of the event:

- **Grade ≥2 acute infusion associated reactions** (IARs; Section 6.5.4 for manifestation/ symptoms typical of an IAR). An IAR occurs typically within 24 hours from the start of the infusion.
- **Grade ≥3 immune-related TEAEs.**
- Any grade of **immune-related TEAEs** in a patient previously treated with a PI 3-K inhibitor.
- **DLTs** (as defined in Section 9.1.1) are considered as AESIs, and as such, the Investigators will be required to report them to the Sponsor within 24 hours of the Investigator becoming aware of the event. The Investigator will attach the DLT-specific CRF page to the DLT/AESI form.
- **Pregnancy** of a female subject entered in a study as well as pregnancy occurring in a female partner of a male subject entered in a study with IMP/NIMP.

- 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. It will be qualified as an SAE only if it fulfills one of the seriousness criteria (see Section 10.4),
- In the event of pregnancy in a female participant, treatment with the 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.

- **Symptomatic overdose** (serious or nonserious) with IMP/NIMP (see Section 10.4.2):
  - An overdose (accidental or intentional) with the isatuximab or cemiplimab is defined as increase of at least 30% of the intended administered dose at each infusion expressed in unit per body weight) to be administered in the specified duration or if the dose is administered in less than half the recommended duration of administration,
  - An overdose (accidental or intentional) with the NIMP is defined as increase of at least 30% of the intended administered dose at each administration expressed in unit per body weight),
  - In case of accidental or intentional overdose with the IMP/NIMP, 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.

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

10.5.1 Laboratory abnormalities

Laboratory abnormalities should be monitored, documented, and managed according to the related flowchart (see Section 1.1). Laboratory values will be reported in the appropriate pages of e-CRF.

Laboratory abnormalities should be reported as AE in case they lead to an action on study treatment, if they are serious, or AESIs (see Section 10.4.1).

10.6 OBLIGATIONS OF THE SPONSOR

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

- All SAEs that are unexpected and are at least reasonably related to the IMP (ie, suspected unexpected serious adverse reactions), to the regulatory authorities, Institutional 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 (eg, DLT) to those regulatory authorities who require such reporting.

Adverse events that are considered expected are specified in the reference safety information (current IB of each of the two IMPs).

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

11 HANDLING OF PATIENT TEMPORARY AND PERMANENT TREATMENT DISCONTINUATION AND OF PATIENT STUDY DISCONTINUATION

Pregnancy will lead to definitive treatment discontinuation in all cases.

11.1 PERMANENT TREATMENT DISCONTINUATION WITH INVESTIGATIONAL MEDICINAL PRODUCT(S)

11.1.1 List of criteria for permanent treatment discontinuation

Isatuximab or cemiplimab can be discontinued prematurely. Patients will remain on study treatment until the last IMP (isatuximab or cemiplimab) is discontinued. The reason for premature discontinuation will be captured in the appropriate eCRF page.

Patients may withdraw from treatment with IMP if they decide to do so, at any time and irrespective of the reason, or this may be done at the discretion of the Investigator. All efforts should be made to document the reason(s) for discontinuation and this should be documented in the e-CRF.

Treatment with the IMP should be discontinued in any of the following cases:

- At the patient's request, at any time and irrespective of the reason (consent's 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. 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.
- 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 6.5.7.

11.1.2 Handling of patients after permanent treatment discontinuation

All permanent treatment discontinuation should be recorded by the Investigator in the appropriate screen of e-CRF when considered as confirmed. After study treatment is discontinued, patients should complete a follow-up visit 30 days after the last administration of the IMP as described in Section 12.4.3.

Patients who have been withdrawn from the study treatment cannot be re-entered into the study.

11.2 REPLACEMENT OF PATIENTS

During the dose Phase 1 part of the study, a patient may be considered not evaluable for DLT and may be replaced at the same dose level as described in Section 6.2.2.

12 STUDY PROCEDURES

12.1 VISIT SCHEDULE

During the course of the study, all patients entering the study must be evaluated according to the schedule outlined in the flow charts in Section 1.1, Section 1.2 and Section 1.3 and described below. The results of the evaluation will be recorded in the e-CRF pages until the patient is not followed anymore.

12.2 SCREENING/BASELINE EVALUATION

The screening assessments are to be performed within 21 days prior to first study treatment, 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.
- Demography (age, gender and race) and medical/surgical history (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 (less than 7 days prior to first study treatment) 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, respiration rate and body temperature.
- Prior medication use within 21 days prior to the first study treatment administration.
- 12-lead ECG.
- ECOG PS.
- All AEs/SAEs occurring after signed informed consent for all patients.
- Chest X-ray.

Local laboratory assessments

- Serum pregnancy test to be performed within 7 days prior first study treatment administration for females of childbearing potential.

- 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 eGFR (MDRD Formula), urea or BUN, fasting glucose, albumin and total protein. Thyroid stimulating hormone (TSH), and free T4.
- Hematology: hemoglobin, hematocrit, RBC, WBC with differential (including ANC), and platelet count.
- Coagulation: prothrombin time (PT) or international normalized ration (INR) and activated partial thromboplastin time (aPTT).
- Quantitative urinalysis: red blood cells, leukocytes, protein, glucose, ketone, pH, bilirubin, Na, K, Ca, Cl, nitrates, specific gravity.
- Serum β2-microglobulin.

Disease assessment:

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

  Note: One additional serum sample will be collected for testing potential interference of isatuximab in M protein assessment. The sample will be collected at the same time as for serum M protein sample above (central laboratory).
- 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),
  - BMA for MRD assessment (central laboratory),
  - Bone marrow plasma cell infiltration (local laboratory).
- Bone disease assessment: Skeletal survey or low-dose whole-body CT scan: including skull, all long bones, pelvis and chest (local assessment)
- Plasmacytoma assessment (PET-CT, CT scan or MRI) in patients with known or suspected have plasmacytoma (local assessment):

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

Other assessment

- Bone marrow biopsy/aspirates and blood samples for exploratory biomarkers analysis (central laboratory):
  - Adaptive immune response (including TCR repertoire) (blood and BMA),
  - Immunophenotyping (blood and BMA),
  - PD1-PDL1 expression (archival bone marrow biopsy).
- A blood sample for blood typing interference test (local laboratory).

12.3 REGISTRATION/RANDOMIZATION

Registration 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.

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.

Re-screening is allowed once.

12.4 TREATMENT PERIOD

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

The following procedures are to be performed/assessed **on D1, D8, D15 and D22 prior to study treatment administration unless specified otherwise**:

- 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 prior to start of each infusion, every hour during the infusion and at the end of infusion.
- ECOG PS.
- Body weight.
- Study treatment administration.
- All AEs/SAEs throughout the cycle.
- Concomitant medications from registration and used throughout the cycle.

Laboratory assessments (not required to be repeated at Cycle 1 Day 1 if performed within 3 days prior to first study treatment administration at screening and results were normal or not clinically significant.

- Serum pregnancy test to be performed on Day1 of each cycle prior to study treatment administration for females of childbearing potential.

- In case of viral reactivation during study treatment (greater than 1 log_{10} IU/mL increase in HBV DNA or reappearance of HBsAg or detection of HBV DNA in patients with resolved infection), ALT and AST will be closely monitored every month up to study treatment discontinuation. HBV DNA to be done as per specialist advice.
- Blood chemistry prior Day 1, Day 8, Day 15, and Day 22 administration: 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 eGFR (MDRD Formula), urea or BUN, fasting glucose albumin, total protein.
- Hematology, to be done weekly prior Day 1, Day 8, Day 15, and Day 22 administration: hemoglobin, hematocrit, RBC, WBC with differential (including ANC), and platelet count.
- Dipstick (qualitative) on D1 and D15.
- IAR laboratory tests on D1 prior to first isatuximab administration: (TNF- α, IL-1-β, IL-6, and IFN-γ), markers of activated complement (C3a, C4 and CH50) and serum tryptase, lactate dehydrogenase [LDH]. If an 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-6, and IFN-γ), markers of complement activation (C3a, C4, CH50), serum tryptase (central laboratory) and LDH.

Blood sample collection for PK and ADA evaluation (see Section 1.2, Section 1.3) (central laboratory).

Disease assessment on C1D1 (unless the disease assessment for the screening is done in the 3 days prior first administration) (local laboratory):

- Serum M-protein,
- Urine M-protein,
- sFLC.

  Note: One additional serum sample will be collected for testing potential interference of isatuximab in M protein assessment. The sample will be collected at the same time as for serum M protein sample above (central laboratory).

Other assessment:

- Blood samples for exploratory biomarkers analysis (central laboratory):
  - Adaptive immune response (humoral and cellular response): prior to pre-medication and IMP administration on Day 1.

If clinically indicated only:

- Coagulation at any time during the cycle.
- Quantitative urinalysis: RBC, leukocytes, protein, glucose, ketone, pH, bilirubin, Na, K, Ca, Cl, nitrates, specific gravity. at any time during the cycle.

- Markers for TLS (uric acid, creatinine/BUN, 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.

12.4.2 Subsequent cycles (Day 1 and 15 both ±2 days)

The following procedures are to be performed/assessed **on D1 and 15 prior to study treatment administration unless specified otherwise, and as clinically indicated**:

- 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, respiration rate and body temperature.
- ECOG PS.
- Weight.
- Study treatment administration.
- All AEs/SAEs throughout the cycles.
- Concomitant medications used throughout the cycle.

Laboratory assessments (safety assessment)

- Serum pregnancy test to be performed on Day1 of each cycle prior to study treatment administration for females of childbearing potential
- In case of viral reactivation during study treatment (greater than 1 $\log_{10}$ IU/mL increase in HBV DNA or reappearance of HBsAg or detection of HBV DNA in patients with resolved infection), ALT and AST will be closely monitored every month up to study treatment discontinuation. HBV DNA to be done as per specialist advice.
- 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 eGFR (MDRD Formula), urea or BUN, fasting glucose, albumin and total protein. Thyroid stimulating hormone (TSH) and free T4 will be assessed every second cycle.
- Hematology: hemoglobin, hematocrit, RBC, WBC with differential (including ANC), and platelet count.
- Dipstick (qualitative).
- Quantitative urinalysis if hematuria or clinically indicated only: red blood cells, leukocytes, protein, glucose, ketone, pH, bilirubin Na, K, Ca,, Cl, nitrates, specific gravity.
- Serum β2 microglobulin prior to D1 of each cycle.

Disease assessment

- Laboratory disease assessment: on Day 1 each cycle prior study treatment administration (reference value to assess response will be the value from the last lab taken before 1st treatment administration) (local laboratory).
  - 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 involved/non-involved),
  - Immunoglobulins: IgG, IgA, IgM, IgD and IgE (IgD or E only if the heavy chain component of the disease is known to be E or D.

  Note: One additional serum sample will be collected for testing potential interference of isatuximab in M-protein assessment. The sample will be collected at the same time as for serum M protein sample above (central laboratory).
- Bone marrow aspirate (or biopsy as clinically indicated):
  - Bone marrow plasma cell infiltration to confirm CR, or if suspicion of disease progression in the absence of biochemical progression and as clinically indicated. (local laboratory)
  - BMA for MRD assessment in case of CR. 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 (central laboratory).
- Bone disease assessments: skeletal survey or low-dose whole-body CT scan including skull, all long bones, pelvis and chest (Local assessment).
  - If clinically indicated.
- Plasmacytoma assessment (PET-CT, CT scan or MRI) (local assessment):
  - If known extramedullary disease, to be repeated every 12 weeks (±1 week), and if clinically indicated,
  - To be done in case of suspicion of progression or if clinically indicated in a patient with no previous positive image for extramedullary disease.

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

Other assessment:

- 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-6, and IFN-γ), markers of complement activation (C3a, C4, CH50), serum tryptase (central laboratory) and LDH.
- Blood sample collection for PK and ADA evaluation (see Section 1.2, Section 1.3) (central laboratory).
- C2D1 only, a blood sample for blood typing interference test (local laboratory).
- Bone marrow biopsy/aspirates and blood samples for exploratory biomarkers analysis (central laboratory):
  - Adaptive immune response (including TCR repertoire): at C3D1 (blood only) and in case of CR (blood and BMA),
  - Adaptive immune response (humoral and cellular response): prior to pre-medication and IMP administration at C2D1, C4D1, C7D1 and C10D1 (blood),
  - Immunophenotyping at C3D1 (blood and BMA),
  - PD1-PDL1 expression at C3D1 (optional bone marrow biopsy).

If clinically indicated only:

- Coagulation at any time during the cycle.
- Quantitative urinalysis: RBC, leukocytes, protein, glucose, ketone, pH, bilirubin Na, K, Ca, Cl, nitrates, specific gravity at any time during the cycle.
- Markers for TLS (uric acid, creatinine/BUN, potassium, phosphate, calcium and corrected calcium) at any time during the cycle.
- Any other exams clinically indicated.

12.4.3 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.
- Weight.
- ECOG PS.
- All AEs/SAEs occurring up to 30 days after last study treatment administration (will be collected in last treatment cycle).
- Concomitant medications up to 30 days from last study treatment administration.

Local laboratory tests

- Serum pregnancy test for females of childbearing potential.
- 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 eGFR (MDRD Formula), urea or BUN, fasting glucose, albumin and total protein.
- Hematology: hemoglobin, hematocrit, RBC, WBC with differential (including ANC), and platelet count.
- Quantitative urinalysis: red blood cells, leukocytes, protein, glucose, ketone, pH, bilirubin, Na, K, Ca, Cl, nitrates, specific gravity.
- Serum β2-microglobulin.

Disease assessment

- Laboratory disease assessment (local laboratory):
  - 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 FLC in case of CR (quantification and ratio involved/non-involved),
  - Immunoglobulins: IgG, IgA, IgM, IgD and IgE (IgD or E only if the heavy chain component of the disease is known to be E or D).

    Note: One additional serum sample will be collected for testing potential interference of isatuximab in M-protein assessment. The sample will be collected at the same time as for serum M-protein sample above (central laboratory).
- Bone marrow aspirate (or biopsy as clinically indicated): bone marrow plasma cell infiltration to confirm CR, or if suspicion of disease progression in the absence of biochemical progression and as clinically indicated (local laboratory).
- Bone disease assessments: skeletal survey or low-dose whole-body CT scan including skull, all long bones, pelvis and chest (Local assessment).
  - If clinically indicated.
- Plasmacytoma assessment (PET-CT, CT scan or MRI) (local assessment):
  - If clinically indicated.

Other assessment

- Blood sample collection for PK and ADA evaluation (see Section 1.2, Section 1.3).
- Bone marrow biopsy/aspirates and blood samples for exploratory biomarkers analysis:

- Adaptive immune response (humoral and cellular response) in disease progression patients (blood).
- Immunophenotyping (blood only).
- PD1-PDL1 expression (optional bone marrow biopsy).

12.4.4 Post treatment follow up

12.4.4.1 60 and 90 days after last treatment visit

The following procedures are to be performed at the 60 and 90 days visit:

- Physical examination.
- Vital signs.
- 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, including drug administered and best response.
- Second primary malignancies.
- Concomitant medications related to AE/SAE.

Local laboratory tests

- Serum pregnancy test for females of childbearing potential every month for 5 months following the last dose of isatuximab or 6 months following the last dose of cemiplimab, whichever comes last.
- 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 eGFR (MDRD Formula), urea or BUN, fasting glucose, albumin and total protein.
- Hematology: hemoglobin, hematocrit, RBC, WBC with differential (including ANC), and platelet count.
- Quantitative urinalysis: red blood cells, leukocytes, protein, glucose, ketone, pH, bilirubin, Na, K, Ca, Cl, nitrates, specific gravity.

Blood sample for PK and ADA evaluation (see Section 1.2, Section 1.3).

Disease assessment (only for patients without confirmed disease progression and patients who have not yet started treatment with another anticancer therapy)

- Laboratory disease assessment (local laboratory):

- Serum M-protein: immunoelectrophoresis,
- Urine M-protein: immunoelectrophoresis,
- Serum FLC in case of CR (quantification and ratio involved/non-involved),
- Immunoglobulins: IgG, IgA, IgM, IgD and IgE (IgD or E only if the heavy chain component of the disease is known to be E or D),

  Note: One additional serum sample will be collected for testing potential interference of isatuximab in 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).

- Bone marrow plasma cell infiltration to confirm CR, or if suspicion of disease progression in the absence of biochemical progression and as clinically indicated (local laboratory).
- Bone disease assessments if applicable:
  - Skeletal survey or low-dose whole-body CT if clinically indicated.
- Extramedullary disease (plasmacytoma) assessment (including bone plasmacytoma) if applicable (PET-CT, CT scan or MRI):
  - If known extramedullary disease, and if clinically indicated,
  - To be done in case of suspicion of progression or if clinically indicated in a patient with no previous positive image for extramedullary disease.

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

12.4.4.2 Further follow-up visits until 12 months after LPI

For patients with confirmed disease progression (at EOT or during follow-up):

The post-treatment follow-up period includes visits (or phone call) 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.
- Pregnancy test for females of childbearing potential every month for 5 months following the last dose of isatuximab or 6 months following the last dose of cemiplimab, whichever comes last.
- Further anti-myeloma therapy, include drug administered and best of responses.
- Survival status (every 3 months).

For patients discontinued without disease progression and have not yet started treatment with another anticancer therapy:

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 or start treatment with another anti-cancer therapy whichever comes first:

- Disease assessment
  - Laboratory tests
  a) Serum M-protein: immunoelectrophoresis and if M protein undetectable, immunofixation will be performed,
  b) Urine M-protein: immunoelectrophoresis and if M protein undetectable, immunofixation will be performed,
  c) Serum free light chains in case of CR (sFLC, quantification and ratio involved/non-involved),
  d) Immunoglobulins: IgG, IgA, IgM, IgD and IgE (IgD or E only if the heavy chain component of the disease is known to be E or D),

  Note: One additional serum sample will be collected for testing potential interference of isatuximab in 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).
  - Bone marrow aspirate (or biopsy as clinically indicated): bone marrow plasma cell infiltration to confirm CR, as clinically indicated (Local assessment).
  - Bone disease assessments: Skeletal survey or low-dose whole-body CT scan if clinically indicated.
  - Plasmacytoma assessment:
  a) If known extramedullary disease, if clinically indicated,
  b) 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; PET-CT, CT or MRI) should be used throughout the study for each individual patient.
- 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.
- Pregnancy test for females of childbearing potential every month for 5 months following the last dose of isatuximab or 6 months following the last dose of cemiplimab, whichever comes last.
- Further anti-myeloma therapy, include drug administered and best response.
- Survival status (every 3 months).

12.4.5 Post OS final study cut-off date

Patients still on study treatment after the final analysis cut-off date (12 month after last patient first treatment) can continue study treatment until at least 1 treatment discontinuation criterion as defined in Section 6.5.7 is met. The following information will be collected during the study treatment administration:

- IP administration.
- All SAEs regardless of relationship to study treatment and adverse events considered related to study treatment.
- Pregnancy test for females of childbearing potential every month for 5 months following the last dose of isatuximab or 6 months following the last dose of cemiplimab, whichever comes last.
- End of treatment reason.

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.

13 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.

13.1 DETERMINATION OF SAMPLE SIZE

This study aims to determine the safety and efficacy of the combination of isatuximab and cemiplimab.

In Phase 1 part, the objective is to determine the RP2D based on DLT occurrence. The actual sample size will depend on DLTs observed and number of dose levels actually explored. It is anticipated that 3 to 18 DLT-evaluable patients will be treated in the Phase 1 part of the study.

In Phase 2 randomization part, the objective is to evaluate the efficacy and safety of the combination therapy. Assuming ORR = 20% in control arm (isa alone arm) and ORR = 50% in combination arms, using Fisher's exact test to compare the ORR in control vs combination arms, given an overall 1-sided type I error of 5% for each combination arm, 35 patients per arm is required to achieve a power 79% power for each combination arm.

A separate anti-CD38 refractory cohort with 15 patients might be enrolled if a treatment benefit is suggested for the combination therapy including pass the futility check at the interim analysis. Assuming ORR =20% or more in the combination therapy, a size of 15 patients is required to test against a null hypothesis of ORR ≤1% (ie, no activity in the Isa alone arm) with a one-sided α of 0.05 and 82% power.

Therefore, the total expected number of patients treated in the study (Phase 1 and 2) is 108 to138 patients.

13.2 PATIENT DESCRIPTION

13.2.1 Disposition of patients

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

The number of screened patients as well as the number and percentage of patients included in the analysis populations defined in Section 13.3 will be provided.

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

13.2.2 Protocol deviations

Major protocol deviations which compromise the evaluation of the safety and efficacy will be derived adequately and determination of deviations will be finalized based on data review conducted prior to database lock. Decisions made on a patient's status will be documented.

13.3 ANALYSIS POPULATIONS

13.3.1 All-treated/safety population

For Phase 1, the all treated/safety population is defined as all screened patients who received at least one dose or a part of a dose of the study treatments, regardless of the amount of treatment administered. For Phase 2 randomization part, the all treated/safety population is defined as all randomized patients who received at least one dose or a part of a dose of the study treatments, regardless of the amount of treatment administered. Patients will be analyzed according to the treatment actually received. For Phase 2 anti-CD38 refractory cohort, the all treated/safety population is defined as patients who received as least one dose/a part of a dose of the study treatment, regardless of the amount of treatment administered.

This population is the primary population for the analysis of all exposure and safety parameters (except for DLT evaluation). Phase 1 and Phase 2 patients will be analysed separately.

13.3.2 ITT population

For Phase 2 randomization part, the ITT population include all patients with a signed informed consent form who have been allocated a randomization number by the IRT, regardless of whether the patient was treated or not. Patient will be analyzed according to the treatment group allocated by IRT, regardless of treatment (if any) the patients actually received.

For any patient randomized more than once, only the data associated with the first randomization will be used for analysis.

For Phase 2 anti-CD38 refractory cohort, the ITT population include all patients with a signed informed consent form and received at least one dose /a part of a dose of the study treatment.

This population is the primary population for all efficacy analyses.

13.3.3 Patients evaluable for DLT assessment

For isatuximab/cemiplimab combination, the DLT evaluable population is defined as patients in the Phase 1 part receiving the planned doses of isatuximab and cemiplimab during Cycle 1, and who completed the DLT observation period of 28 days after the first IMP administration, unless they discontinue the study treatment(s) due to DLT. Dose-limiting toxicity will be validated by the Study Committee. Patients not evaluable for DLT will be replaced.

13.3.4 Pharmacokinetic population

The PK population will include patients from the treated/safety population with at least one non-missing drug concentration after the study drug administration (whatever the cycle and even if dosing is incomplete).

13.3.5 ADA evaluable population

ADA population includes all patients from the treated/safety population with at least one ADA non-missing result after study drug administration.

13.4 STATISTICAL METHODS

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

Unless otherwise specified, analyses will be descriptive and performed separately for Phase 1 and Phase 2 patients, based on the analysis population defined in Section 13.3. The baseline for a given parameter is defined as the last non-missing assessment for this parameter before first administration of study treatments.

Continuous data will be summarized using number of available data, mean, SD, median, minimum and maximum for each dose level (if applicable). Summary tables will be presented by dose level(s) and overall (in case of more than 1 dose level), unless otherwise noted.

13.4.1 Demographics and baseline characteristics

Demographic and baseline characteristics (including age, gender, race, ethnicity, ECOG performance status), medical or surgical history, MM characteristics at diagnosis and at study entry will be summarized with descriptive statistics for the safety population in Phase 1 or ITT population in Phase 2.

Prior anti-myeloma therapies

The following parameters regarding prior anticancer will be summarized:

- Prior anticancer treatment: number of prior lines (defined in Appendix E), number of prior regimen, main anticancer treatments (Alkylating agents, proteasome inhibitors, immunomodulators, monoclonal antibodies).
- Refractory status to main anticancer treatments.
- Description of last regimen given prior to study entry:
  - Time from completion of last regimen of treatment to first study treatment (months),
  - Main treatments,
  - Best response to last regimen,
  - Duration of last regimen of therapy,
  - Refractory status as defined above.
- Prior transplant: number (%) of patients with transplant, type of transplant, time from last transplant to first study treatment (months).
- Prior surgery: number (%) of patients with prior surgery, type of surgery and time from last surgery to first study treatment (months).

- Prior radiotherapy: number (%) of patients with prior radiotherapy, intent and time from last radiotherapy to first study treatment (months).

13.4.2 Extent of investigational medicinal product exposure

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:

  - Date of last dose of isatuximab + 7 days if last cycle is QW cycle or date of last dose of isatuximab + 14 days if last cycle is Q2W,
  - Date of last dose of cemiplimab + 14 days if last cycle is Q2W cycle or date of last dose of cemiplimab + 28 days if last cycle is Q4W cycle (if applicable).

The first day of first cycle is defined as the date patient receive first isatuximab or/and cemiplimab.

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

- 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 QW cycle or [date of last dose of isatuximab + 14 days - first dose of isatuximab]/7 if last cycle is Q2W cycle,
  - For cemiplimab: [date of last dose of cemiplimab + 14 days - first dose of isatuximab]/7 if last cycle is Q2W cycle or [date of last dose of isatuximab + 28 days - first dose of isatuximab]/7 if last cycle is Q4W cycle.
- Number of infusions.
- Cumulative dose (in mg/kg) for isatuximab/cemiplimab: 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.
- 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 a 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. Infusion delay is not applicable to the 1st dose of each cycle.
- Cemiplimab infusion delays within a cycle (only if RP2D is Q2W schedule): a dose is a dose is deemed to have been delayed if the study treatment is ≥3 days beyond the theoretical day of treatment. Infusion delay is not applicable to 1st dose of each cycle.
- Infusion interruption (isatuximab and/or cemiplimab): administration of treatment was stopped during the infusion before it is completed regardless it is further restarted or not.
- Dose omission: Partially administered cycle: Cycle with at least one isatuximab/ cemiplimab dose omitted.

13.4.3 Prior/concomitant medication/therapy

Prior and concomitant medications will be summarized on the safety population in Phase 1 or ITT population in Phase 2 according to the WHO-DD dictionary, considering the first digit of the ATC class (anatomic category) and the first three digits of the ATC class (therapeutic category). All ATC codes corresponding to a medication will be summarized patients will be counted once in each ATC categories (anatomic or therapeutic) linked to the medication.

13.4.4 Analyses of efficacy variables

All efficacy analyses will be performed using the all ITT population in Phase 2 unless otherwise specified.

13.4.4.1 Analysis of primary efficacy endpoint

The ORR will be summarized by treatment arms/cohort with descriptive statistics. A 95% two-sided confidence interval(s) will be computed using Clopper-Pearson.

For Phase 2 randomization part of the study, the Fisher's exact test will be performed to compare the ORR in control arm vs each of the combination arm, using a 1-sided significance level of 0.10 with Hochberg adjustment, (at time of primary analysis of ORR; ie, cutoff date 6 months after last patient first dose). If the maximum p-value (of two p-values) is less than 0.1, the null hypothesis for both combination arms will be rejected; else if minimal p-value is less than 0.05, the null hypothesis will be reject for this corresponding arm only. If only one combination arm is continued in addition to the control arm, then ORR will be tested using a 1-sided significant level of 0.05.

Subgroup analyses of BOR will be performed including but not limited to the following variables listed:

- Age: <70 years versus ≥70 years.
- Number of previous lines of therapy: ≤3 vs >3.

- ISS staging at study entry: I vs II vs III.
- High risk cytogenetic (such as del (17), t (4:14) or t (14:16) abnormality): Yes vs No.
- Baseline creatinine clearance : <60 mL/min vs ≥60 mL/min.
- Refractory to prior anticancer treatments (eg, IMiD, PI): Yes vs No.
- PD-L1 level at baseline: ≥50% vs <50%

For Phase 1 all treated population, a listing of response data will be provided.

13.4.4.2 Analysis of secondary efficacy endpoints

The following secondary endpoints will be analyzed by treatment arms / cohort (in case of more than 1 dose level):

- CBR will be summarized with descriptive statistics.
- Rate of patients ≥VGPR as BOR will be summarized with descriptive statistics.
- DOR and TTR: Kaplan-Meier estimates such as median and Kaplan-Meier curves will be provided for DOR for patients who achieved a response (sCR, CR, VGPR and PR).
- PFS and OS: the PFS and OS will be analyzed using the Kaplan-Meier method. The Kaplan-Meier estimates of the 25th, 50th and 75th percentiles and the 95% confidence intervals of median will also be computed. The Kaplan-Meier curves will be plotted.

Subgroup analyses for secondary endpoints may be performed if relevant.

13.4.5 Analyses of safety data

13.4.5.1 Dose-limiting toxicities

The DLTs will be listed by patient on the patients evaluable for DLT population.

13.4.5.2 Analyses of adverse events

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 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 are reported during the post-treatment period.

The 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.

13.4.5.2.1 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, pregnancy if any, and overdose if any will be presented separately.
- IARs of Grade ≥3.
- Potential immune-related TEAEs and immune-related reactions.
- 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, IARs, TEAEs leading to permanent/premature discontinuation , TEAEs leading to dose modification, serious TEAEs, TEAEs with fatal outcome and AEs/SAEs occurring during the extended safety follow-up period and 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.

13.4.5.3 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.
- 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.

A listing of deaths will be provided.

13.4.5.4 Clinical laboratory evaluations

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 all grades together each grade 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.

13.4.5.5 Other safety evaluations

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 will also be summarized.

Others

Cytokines (TNF-α, IL-1-β, , IL-6, IFN-γ), markers of complement (C3a, C4, CH50), serum tryptase will be summarized with descriptive statistics. A listing of patients with second primary malignancies will be summarized.

Immunogenicity

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

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

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

Definitions:

- Pre-existing ADA, defined as ADA that are present in samples drawn during the pretreatment period.
- Treatment-induced ADA, defined as ADA that developed at any time during the ADA on-study observation period in patients without pre-existing ADA (including patients without pretreatment samples).
- Treatment boosted ADA, defined as pre-existing ADA with a significant increase in the ADA titer during the study compared to the baseline titer.
- ADA positive patients, defined as patients with at least one treatment-induced or treatment-boosted ADA positive sample at any time following the first study treatment administration.
- ADA prevalence, defined as the sum of the number of patients with pre-existing ADA and the number of patients with treatment induced ADAs, divided by the number of evaluable patients.
- ADA incidence, defined as the number of ADA positive patients divided by the number of evaluable patients.

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

ADA prevalence and ADA incidence will be also described.

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

13.4.6 Analyses of pharmacokinetic variables

Individual concentrations and PK parameters of isatuximab and cemiplimab will be summarized by descriptive statistics (such as mean, geometric mean, median, standard deviation, standard error of the mean, coefficient of variation, minimum, and maximum) under the responsibility of Sanofi, Pharmacokinetic, Dynamic & Metabolism department. Individual and mean profiles will be presented graphically.

13.5 INTERIM ANALYSIS

For the isatuximab/cemiplimab combination, preliminary interim analysis of safety and efficacy may be performed when the first 15 randomized patients in each arm of the Phase II part complete 2 cycles of treatment or permanently discontinue treatment. Interim efficacy data will be analyzed for futility stopping of the arm(s).

The analysis will include the first 15 randomized patients from each arm in the ITT population. Given the observed response rate from each combination arm, and assuming the numbers of response follow binomial distribution with response rate = 20% in control arm, and 50% in combination arm for the remaining 20 patients in each arm, the conditional power can be calculated based on 1-sided Fisher's exact test at 0.05 significance level (for each arm separately) at the end of the trial. If the conditional power is <30% for a combination arm, the arm will be stopped early for futility.

14 ETHICAL AND REGULATORY CONSIDERATIONS

14.1 ETHICAL AND REGULATORY STANDARDS

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

Information regarding the 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.

14.2 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 study, 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, with the name of the patient filled in and personally dated by the patient or by the patient’s legally acceptable representative, and by the person who conducted the informed consent discussion. A copy of the signed and dated written informed consent form will be provided to the patient.

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

14.3 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 ethics committee (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, Investigator’s CV, etc.) and the date of the review should be clearly stated on the written ethics committee (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 ethics committee (IRB/IEC) should be informed as soon as possible. They should also be informed of any event likely to affect the safety of patients or the continued conduct of the clinical trial, in particular any change in safety. All updates to the Investigator's Brochure will be sent to the ethics committee (IRB/IEC) and to health authorities (competent regulatory authority), as required by local regulation.

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

15 STUDY MONITORING

15.1 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 e-CRF, discrepancy resolution form [DRF], or other appropriate instrument) in an accurate manner according to the instructions provided and to ensure direct access to source documents by the 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.

15.2 RESPONSIBILITIES OF 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 e-CRFs. 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.

15.3 SOURCE DOCUMENT REQUIREMENTS

According to the ICH GCP, the Monitoring team must check the CRF entries against the source documents, except for the preidentified source data directly recorded in the CRF. the informed consent form will include a statement by which the patient allowing 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 CRF (eg, patient's medical file, appointment books, original laboratory records). These personnel, bound by professional secrecy, must maintain the confidentiality of all personal identity or personal medical information (according to confidentiality rules).

15.4 USE AND COMPLETION OF CASE REPORT FORMS AND ADDITIONAL REQUESTS

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

Should a correction be made, the corrected information will be entered in the e-CRF 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 e-CRF.

The computerized handling of the data by the Sponsor when available in the e-CRF 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 e-CRF.

15.5 USE OF COMPUTERIZED SYSTEMS

Procedures shall be employed and controls designed to ensure the confidentiality of electronic records. Such procedures and controls shall include validation of systems to ensure accuracy and reliability, ability to generate accurate and complete copies of records, protection of records to enable retrieval, use of secure, computer-generated, time-stamped entries, use of operational system checks, use of device checks to determine validity of source data input, determination that person who develop, maintain, or use such systems have adequate education and training, the establishment and adherence of written policies to deter record falsification, the use of appropriate controls over systems documentation including the distribution of or use of documentation for system operation and maintenance, and revision and change control procedures which document time-sequenced development and modifications of systems documentation.

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.

16 ADDITIONAL REQUIREMENTS

16.1 CURRICULUM VITAE

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

16.2 RECORD RETENTION IN STUDY SITES(S)

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

It is recommended that the Investigator retain the study documents at least 15 years after the completion or discontinuation of the clinical trial.

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

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

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

16.3 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 e-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 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.

16.4 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 regarding 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.

16.5 DATA PROTECTION

- The patient's personal data, which may be 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 the 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.

16.6 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 as required by applicable law. An insurance certificate will be provided to the IECs/IRBs or regulatory authorities in countries requiring this document.

16.7 SPONSOR AUDITS AND INSPECTIONS BY REGULATORY AGENCIES

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

The Investigator agrees to allow the auditors/inspectors to have direct access to his/her study records for review, being understood that these personnel 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/she will inform the Sponsor and authorize the Sponsor to participate in this inspection.

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

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

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

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

16.8.1 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 IMP 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 by the Investigator or Subinvestigator, or delegated staff with any provision of the clinical trial protocol, or breach of any applicable laws, regulations, or ICH GCP guidelines.
- 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.

16.8.2 By the Investigator

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

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

16.9 CLINICAL TRIAL RESULTS

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

16.10 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 his approval.

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

17 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 of 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 recollected if necessary.

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19 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 ECOG 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

Appendix C National Cancer Institute common terminology criteria for adverse events

Refer to NCI CTCAE v. 4.03 (46) in the Study Reference Manual, or online at the following NCI website: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40

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.

An accurate baseline prior to therapy is essential.

Appendix D IMWG response criteria

Disease response will be assessed using the updated International Myeloma Working Group Response Criteria (IMWG) (44). A confirmation assessment for disease response within 4 weeks is required in this protocol (either PR or better, or PD).

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

Adapted from updated International Myeloma Working Group Response Criteria

IMWG MRD criteria (requires a complete response as defined below)	
Sustained MRD-negative	MRD negativity in the marrow (NGF or NGS, or both) and by imaging as defined below, confirmed minimum of 1 year apart. Subsequent evaluations can be used to further specify the duration of negativity (eg, MRD-negative at 5 years)
Flow MRD-negative	Absence of phenotypically aberrant clonal plasma cells by NGF on bone marrow aspirates using the EuroFlow standard operation procedure for MRD detection in multiple myeloma (or validated equivalent method) with a minimum sensitivity of 1 in 10^5 nucleated cells or higher
Sequencing MRD-negative	Absence of clonal plasma cells by NGS on bone marrow aspirate in which presence of a clone is defined as less than two identical sequencing reads obtained after DNA sequencing of bone marrow aspirates using the LymphoSIGHT platform (or validated equivalent method) with a minimum sensitivity of 1 in 10^5 nucleated cells or higher
Imaging-positive MRD-negative	MRD negativity as defined by NGF or NGS plus disappearance of every area of increased tracer uptake found at baseline or a preceding PET/CT or decrease to less mediastinal blood pool SUV or decrease to less than that of surrounding normal tissue
Standard IMWG response criteria	
Response	**IMWG criteria**
CR	• Negative immunofixation on the serum and urine and • disappearance of any soft tissue plasmacytomas and • <5% plasma cells in bone marrow aspirates. • A normal FLC ratio of 0.26–1.65 is required. **Two consecutive assessments are needed. No known evidence of progressive disease or new bone marrow lesions if radiographic studies were performed**
sCR	CR as defined above plus: • normal FLC ratio (0.26 to 1.65) and • absence of clonal cells in bone marrow by immunohistochemistry (κ/λ ratio ≤4:1 or ≥1:2 for κ and λ patients, respectively, after counting ≥100 plasma cells) **Two consecutive assessments of laboratory parameters are needed. No known evidence of progressive disease or new bone marrow 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. • FLC only: a ≥90% decrease in the difference between involved and uninvolved FLC levels. **Two consecutive assessments are needed. No known evidence of progressive disease or new bone marrow 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 • If serum and urine M-protein are unmeasurable, a ≥50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria • If serum and urine M-protein are unmeasurable, and serum-free light assay is also unmeasurable, ≥50% reduction in plasma cells is required in place of M-protein, provided baseline bone marrow plasma-cell percentage was ≥30%. 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 marrow 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 marrow 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 marrow 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) • In patients without measurable serum and urine M-protein levels, the difference between involved and uninvolved FLC levels (absolute increase must be >10 mg/dL) • In patients without measurable serum and urine M-protein levels and without measurable involved FLC levels, bone marrow plasma-cell percentage irrespective of baseline status (absolute increase must be ≥10%) • 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; ≥50% increase in circulating plasma cells (minimum of 200 cells per µL) if this is the only measure of disease **Two consecutive assessments are needed. No known evidence of progressive disease or new bone marrow lesions if radiographic studies were performed**

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

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

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

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

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

- Any response (sCR, CR, VGPR, PR) or progression needs to be confirmed by two consecutive disease assessments according to the Study Flow Chart. A disease assessment at one time point not matched by the same disease assessment at the next time point will be considered unconfirmed (except for progression by imaging, bone marrow PC counts, where one time point is adequate for confirmed progression).
- Urine M-protein is not needed to document partial response or minor response if baseline urine M-protein was not measurable; however, it is still required for complete response and very good partial response.
- Serum FLC levels should only be used for response assessment when both the serum and urine M-component levels are deemed not measurable.
- 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 value before suspected progression will be used 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.

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.)

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-L, et 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.)

Appendix G Recommended dose modification or discontinuation and supportive care guidelines for specific cemiplimab drug related adverse events

Colitis Adverse Event Management

Colitis events CTCAE v4.03	Isatuximab Dose Management	Cemiplimab Dose Management	Actions and Guidelines	Diagnostic considerations
Grade 1 Bowel obstruction Colitis Colitis microscopic	No change in dose	No change in dose	• For diarrhea, treat symptomatically (loperamide, oral hydration, electrolyte substitution and ADA colitis diet). Endoscopy is recommended if symptoms persist. • Grade 1 diarrhea that persists for >I week should be treated with the addition of oral diphenoxylate hydrochloride and atropine sulfate four times daily and budesonide 9 mg daily.	All attempts should be made to rule out other causes such as metastatic disease, bacterial or parasitic infection, gastroenteritis or the first manifestation of an inflammatory bowel disease by examination for stool leukocytes, stool cultures, and a Clostridium difficile titer.
Grade 2 Enterocolitis hemorrhagic Gastrointestinal (GI) perforation Necrotizing colitis Diarrhea: all patients who experience diarrhea should be advised to drink liberal quantities of clear fluids. If sufficient oral intake is not feasible, fluid and electrolytes should be substituted via IV infusion.	Delay or omit dose until ≤Grade 1 (See Section 6.5.2)	Delay or omit dose until ≤Grade 1 (See Section 6.5.2)	• GI consultation and endoscopy is recommended to confirm or rule out colitis for Grade 2 diarrhea that persists >1 week or Grade 1-2 diarrhea with rectal bleeding 9additional guidelines for the treatment of persistent colitis are provided below). • Grade 2 diarrhea should be treated with addition of oral diphenoxylate hydrochloride and atropine sulfate four times daily and budesonide 9 mg daily. • Grade 2 diarrhea with diffuse ulceration and bleeding seen on endoscopy may require oral steroids with prolonged taper and represent an increased risk for the development of bowel perforation. • When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. • In patients with Grade 2 enterocolitis, cemiplimab should be withheld and anti-diarrheal treatment should be started. If symptoms are persistent for more than 1 week, systemic corticosteroids should be initiated (eg, 0.5 mg/kg/day of prednisone or equivalent). When symptoms improve to Grade 1 or less, corticosteroid taper should be started and continued over at least 1 month.	

Colitis events CTCAE v4.03	Isatuximab Dose Management	Cemiplimab Dose Management	Actions and Guidelines	Diagnostic considerations
Grade 3 Grade 4	Grade 3: delay or omit dose until ≤Grade 1 (See Section 6.5.2) Grade 4: discontinue treatment	Delay or Omit dose until ≤Grade 1 (See Section 6.5.2) Discontinue if unable to reduce corticosteroid dose to <10 mg/day prednisone equivalent within 12 weeks of toxicity.	• Patients with Grade 3 enterocolitis, drug will be permanently discontinued and treatment with systemic corticosteroids should be initiated at a dose of 1-2 mg/kg/day prednisone or equivalent. When symptoms improve to Grade 1 or less, corticosteroid taper should be started and continued over at least 1 month. • For **Grade 3-4 diarrhea** (or Grade 2 diarrhea that persists after initial steroid treatment): - Rule out bowel perforation. Imaging with plain films or computed tomography (CT) can be useful. - Consider consultation with gastroenterologist and confirmation biopsy with endoscopy. - Treat with intravenous (IV) steroids (methylprednisolone 125 mg) followed by high dose oral steroids (prednisone 1-2 mg/kg once per day or dexamethasone 4 mg every 4 hours). When symptoms improve to Grade 1 or less, corticosteroid taper should be started and continued over no less than 4 weeks. Taper over 6-8 weeks in patients with diffuse and severe ulceration and/or bleeding. - If IV steroids followed by high-dose oral steroids does not reduce initial symptoms with 48-72 hours, consider treatment with infliximab at 5 mg/kg once every 2 weeks. Discontinue infliximab upon symptom relief and initiate a prolonged steroid taper over 45-60 days. If symptoms worsen during steroid reduction, initiate a re-tapering of steroids starting at a higher dose of 80 or 100 mg followed by a more prolonged taper and administer infliximab. CAUTION: Infliximab is contraindicated in patients with bowel perforation or sepsis. - If symptoms persist despite the above treatment a surgical consult should be obtained.	All attempts should be made to rule out other causes such as metastatic disease, bacterial or parasitic infection, gastroenteritis or the first manifestation of an inflammatory bowel disease by examination for stool leukocytes, stool cultures, and a Clostridium difficile titer. If symptoms are persistent and/or severe, endoscopic evaluation should be considered.

Endocrine Adverse Event Management

Endocrine events CTCAE v4.03	IsatuximabDose Management	Cemiplimab Dose Management	Actions and Guidelines	Diagnostic considerations
Grade 1-2 Hyperthyroidism Hypothyroidism Thyroid disorder Thyroiditis	No change in dose	No change in cemiplimab dose	• Monitor thyroid function or other hormonal level tests and serum chemistries more frequently (every 3-6 weeks) until returned to baseline values. • Replacement of thyroid hormone or thyroid suppression therapy as indicated.	All attempts should be made to rule out other causes such as brain metastases, sepsis, and/or infection. An endocrinology consultation Is recommended.
Grade 3-4 Hyperthyroidism Hypothyroidism Thyroid disorder Thyroiditis	Delay or omit dose until resolves to Grade ≤2 (see Section 6.5.2)	Delay or omit dose until on stable replacement dose as determined by resolution of symptoms and normalization of hormone levels. (see Section 6.5.2)	• Consider endocrine consultation. • Rule out infection and sepsis with appropriate cultures and imaging. • Replacement of thyroid hormone or thyroid suppression therapy as indicated.	
Grade 1-4 Adrenal insufficiency Hypophysitis Hypopituitarism Pan-hypopituitarism	Grade 1, 2: no change in dose, Grade 3, 4: delay or omit dose until resolves to Grade ≤2 (see Section 6.5.2)	Delay or omit dose until on stable replacement dose. (see Section 6.5.2)	• Thyroid hormone and/or steroid replacement therapy to manage adrenal insufficiency. • If Grade 1-2 hypophysitis is considered, pituitary gland imaging should be considered (magnetic resonance imaging [MRI] with gadolinium and selective cuts of the pituitary can show enlargement or heterogeneity and confirm the diagnosis). • Grade 3-4 hypophysitis with clinically significant adrenal insufficiency and hypotension, dehydration, and electrolyte abnormalities (such as hyponatremia and hyperkalemia) constitutes adrenal crisis. Hospitalization and IV methylprednisolone should be initiated.	All attempts should be made to rule out other causes such as brain metastases, sepsis, and/or infection. An endocrinology consultation Is recommended

Pneumonitis Adverse Event Management

Pneumonitis events CTCAE v4.03 Grade	Isatuximab Dose Management	cemiplimab Dose Management	Actions and Guidelines	Diagnostic considerations
Grade 1 Pneumonitis Interstitial lung disease Acute interstitial pneumonitis	No change in Dose	Consider delay or omit dose. (see Section 6.5.2). cemiplimab may be continued with close monitoring.	• Radiological findings should be followed on serial imaging studies at least every 3 weeks. • Monitor for symptoms every 2-3 days. • Consider pulmonary consultation and/or bronchoscopy if clinically indicated.	All attempts should be made to rule out other causes such as metastatic disease, bacterial or viral infection.
Grade 2 Pneumonitis Interstitial lung disease Acute interstitial pneumonitis	Delay or omit dose until resolves to Grade ≤1. (see Section 6.5.2)	delay or omit dose until resolves to Grade ≤1. (see Section 6.5.2)	To rule out other causes such as infection: • Consider pulmonary consultation with bronchoscopy and biopsy/bronchoalveolar lavage (BAL). • Consider pulmonary function tests • Follow radiological findings on serial imaging studies every 1-3 days If the patient is determined to have study drug-associated pneumonitis • Monitor symptoms daily, consider hospitalization • Treat with systemic corticosteroids at a dose of 1-2 mg/kg/day prednisone or equivalent. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. • Treatment with cemiplimab may be resumed if the event improves to ≤Grade 1 within 12 weeks and corticosteroids have been reduced to the equivalent of methylprednisolone 10 mg by mouth daily or less. Repeat chest imaging monthly as clinically indicated. For Grade 2 pneumonitis that improves to ≤Grade 1 within 12 weeks, the following rules should apply: • First episode of pneumonitis: may decrease the dose to 1 mg/kg in subsequent cycles. • Second episode of pneumonitis: Discontinue cemiplimab if upon rechallenge the patient develops a second episode of ≥Grade 2 pneumonitis.	

Pneumonitis events CTCAE v4.03 Grade	Isatuximab Dose Management	cemiplimab Dose Management	Actions and Guidelines	Diagnostic considerations
Grade 3-4 Pneumonitis Interstitial lung disease Acute interstitial pneumonitis	Grade 3: delay or oimt dose until resolves to Grade ≤1. (see Section 6.5.2) Grade 4: discontinue treatment	Discontinue cemiplimab	• Consider pulmonary function tests with pulmonary consult. • Bronchoscopy with biopsy and/or BAL is recommended. • Treat with intravenous (IV) steroids (methylprednisolone 125 mg). When symptoms improve to Grade 1 or less, a high dose oral steroid (prednisone 1-2 mg/kg once per day or dexamethasone 4 mg every 4 hours) taper should be started and continued over no less than 4 weeks. • Add prophylactic antibiotics for opportunistic infections. • If IV steroids followed by high-dose oral steroids does not reduce initial symptoms with 48-72 hours, consider treatment with infliximab at 5 mg/kg once every 2 weeks. Discontinue infliximab upon symptom relief and initiate a prolonged steroid taper over 45-60 days. If symptoms worsen during steroid reduction, initiate a re-tapering of steroids starting at a higher dose of 80 or 100 mg followed by a more prolonged taper and administer infliximab.	All attempts should be made to rule out other causes such as metastatic disease, bacterial or viral infection.

Renal Adverse Event Management

Renal events CTCAE v4.03 Grade	Isatuximab Dose Management	Cemiplimab Dose Management	Actions and Guidelines	Diagnostic considerations
Grade 1 Nephritis Nephritis autoimmune	No change in Dose	Consider delay or omit dose if event does not improve with symptomatic treatment (see Section 6.5.2)	• Provide symptomatic treatment. • Monitor creatinine weekly: when it returns to baseline, resume routine creatinine monitoring per protocol.	All attempts should be made to rule out other causes such as obstructive uropathy, progression of disease, or injury to other chemotherapy agents. A renal consultation is recommended.
Grade 2 Renal failure	Delay or omit dose until resolves to Grade ≤1 (see Section 6.5.2)	Consider delay or omit dose. (see Section 6.5.2)	• Systemic corticosteroids at a dose of 1-2 mg/kg/day of prednisone or equivalent may be indicated. When symptoms improve to Grade 1 or less, corticosteroid taper should be started and continued for at least 1 month. • Consider prophylactic antibiotics for opportunistic infections. • Consider renal biopsy. • If elevations persist >7 days or worse, treat as Grade 4.	
Grade 3-4 Renal failure acute	Grade 3: delay or omit dose until resolves to Grade ≤1. (see Section 6.5.2) Grade 3: discontinue treatment	Discontinue cemiplimab	• Renal consultation with consideration of ultrasound and/or biopsy as appropriate. • Monitor creatinine daily. • Treat with systemic corticosteroids at a dose of 1-2 mg/kg prednisone or equivalent once per day. • When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. • Discontinue cemiplimab if unable to reduce corticosteroid dose for irAEs to ≤10 mg. • Cemiplimab treatment may be restated and the dose modified as specified in the protocol.	

Dermatologic Adverse Event Management

Skin events CTCAE v4.03	Isatuximab Dosing managment	Cemiplimab Dosing managemnt	Action and Guidelines	Diagnostic Considerations
Grade 1, 2	No change in dose	No change in dose	Symptomatic treatment should be given such as topical glucocorticosteroids (eg, betamethasone 0.1% cream or hydrocortisone 1%) or urea-containing creams in combination with oral antipruitics (eg, diphenhrdeamine HCl or hydroxyzine HCl) Treament with oral steroids is at investigator discretion for Grade 2 events.	All attemps should be made to rule out other causes such as metastatic disease, infectious, or allergic dermatitis.
Grade 3	No change in dose	Delay or omit dose until Grade ≤2. (see Section 6.5.2)	Consider dermatology consultation and biopsy for confirmation of diagnosis. Treatment with oral steroids is recommended, starting with 1 mg/kg prednisone or equivalent once daily or dexamethasone 4 mg 4 times per day. When symptoms improve to Grade ≤1, steroids taper should be started and continue over no leass than 4 weeks.	
Grade 4	Delay or omit dose until Grade ≤3 (see Section 6.5.2)	Discontinue treatment	Dermatology consultation and consideration of biopsy and clinical dermatology photograph. Initiate with oral steroids with 1 mg/kg prednisone or equivalent. When symptoms improve to Grade ≤1, steroids taper should be started and continue over no leass than 4 weeks.	

Hepatitis Adverse Event Management

Hepatitis CTCAE v4.03	Isatuximab Dosing managment	Cemiplimab Dosing managemnt	Action and Guidelines	Diagnostic Considerations
Grade 1, 2	No change in dose	Delay or omit dose if there is a treatment-emergent concurrent elevation of ALT and bilirubine that corresponds to an upward shift of 2 or more grades in both parameters. (see Section 6.5.2)	Monitor liver function tests more frequently until returned to baseline values	All attemps should be made to rule out other causes such as metastatic disease, progressive liver disease, viral hepatitis, alternative drug toxicity, infectious caurses and/or myositis.
Grade 3, 4	Delay or omit dose until Grade ≤2 (see Section 6.5.2)	Discontinue treatment if: ASTor ALT ≥5xULN Bilirubine ≥3xULN	Consider appropriate consultation and liver biopsy to establish etiology of hepatic injury, if neccessary. Treat with high-dose IV glucocorticostroids for 24-48hours. When symptoms improves to Grade ≤1, a steroid taper with dexamethasone 4 mg every 4 hours or prednisone at 1-2 mg/kg shouldbe started and continued over no less tahn 4 weeks. If AST/ALT levels bot not decease 48 hours after initiation of systemic steroids, oral mycophenolate mofdtil 500 mg every 12 hours may be given. Inflixmab is not recommended due to its potential for hepatotoxicity. Several courses of steroids taper may be necessary as symtoms may worsen when the stroids dose is decreasesd.	

Ophthalmology (Uveitis) Adverse Event Management

Uveitis CTCAE v4.03	**Isatuximab Dosing managment**	**Cemiplimab Dosing managemnt**	**Action and Guidelines**	**Diagnostic Considerations**
Grade 1	No change in dose	Discontinue treatment if symptoms persist despite treatment with topical immunosuppressive therapy	Evaluation by an ophthalmologist is strongly recommended Treat with topical steroids such as 1% prednisolone acetate suspension and iridocyclitis	All attemps should be made to rule out other causes such as metastatic disease, infection, or other oculas disease (eg, glaucoma or cataracts)
Grade 2	No change in dose	Discontinue treatment if symptoms persist despite treatment with topical immunosuppressive therapy, and do not improve to Grade 1 within the retreatment period or requires systemic treatment		
Grade ≥3	Delay or omit dose until Grade ≤2 (see Section 6.5.2)	Discontinue treatment	Treatment with systemic corticosteroids such as prednisolone at a dose of 1-2 per day. When symtoms improve to Grade ≤1, steroid taper should be started and continued over no less than 4 weeks.	

Nausea and Vomiting Adverse Event Management

Nauea and Vomiting CTCAE v4.03	Isatuximab Dosing managment	Cemiplimab Dosing managemnt	Action and Guidelines	Diagnostic Considerations
Grade 1	No change in dose	No change in Dose	Nausea and vomiting should be treated aggressively, and consideration should be given in subsequent cycles to the administration of prophylactic antiemetic therapy according to standard institution practice. Patients should be strongly encouraged to maintain liberal oral fluid intake.	
Grade 2	Delay or omit dose until ≤Grade 1. (see Section 6.5.2) Restart treatment at same dose level.	Delay or omit dose until ≤Grade 1. (see Section 6.5.2) If patient treated with 3 mg/kg, may consider decrease the dose to 1 mg/kg if persisted Grade 2 >14 days despite the anti-emetic.		
Grade 3	Delay or omit dose until ≤Grade 1. (see Section 6.5.2) Restart at same dose level.	Delay or omit until ≤Grade 1. (see Section 6.5.2) If patient treated with 3 mg/kg, consider decrease the dose to 1 mg/kg if persisted Grade 2 >14 days for the 1st occurrence despite the anti-emetic, or recurrence.		
Grade 4	Discontinue treatment			

Appendix H Infusion associated reactions observed with Isatuximab

Types of infusion associated reactions

- Anaphylactic reaction.
- Cytokine release syndrome.
- Drug hypersensitivity.

Symptoms typically associated with infusion associated reactions

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

Appendix I CD38 blood test interference guideline AABB2016

Advancing Transfusion and Cellular Therapies Worldwide

Association Bulletin #16-02

Date: January 15, 2016
To: AABB Members
From: [redacted]
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),

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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-

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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 J Contraceptive guidance and collection of pregnancy information

No reproductive toxicology studies have been conducted with isatuximab, so the most conservative contraceptive recommendation has to be followed.

DEFINITIONS

Nonreproductive potential

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

Reproductive potential

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

CONTRACEPTIVE GUIDANCE

Male subjects

- Male subjects with heterosexual partners of reproductive potential (WOCBP) are eligible to participate if they agree to use the following during the protocol defined timeline:
  - Refrain from donating sperm

    and
  - At least 1 of the following conditions applies:
  - Are and agree to remain abstinent from penile-vaginal intercourse on a long term and persistent basis, when this is their preferred and usual lifestyle

    or

- Agree to use a male condom plus an additional contraceptive method with a failure rate of <1% per year (see table for female subjects).

- Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom for the time defined in the protocol.

Female subjects:

Highly Effective Contraceptive Methods That Are User Dependent *Failure rate of <1% per year when used consistently and correctly*[a]
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b] - Oral. - Intravaginal. - Transdermal.
• Progestogen-only hormone contraception associated with inhibition of ovulation[b] - Oral. - Injectable.
Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[b]
• IUD
• IUS
• Bilateral tubal occlusion
• Vasectomized partner *(Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method(s) of contraception should be used. Spermatogenesis cycle is approximately 90 days.)*
• Sexual abstinence *(Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the subject.)*
NOTES: *a* Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for subjects participating in clinical studies. *b* Hormonal contraception may be susceptible to interaction with the study treatment, which may reduce the efficacy of the contraceptive method. In this case 2 highly effective methods of contraception should be used during the treatment period and for at least 5 months after the last dose of isatuximab or 6 months after cemiplimab, whichver comes lasts.

Appendix K Protocol amendment history

The Protocol Amendment Summary of Changes Table for the current amendment is located before the Clinical Trial Summary.

The reasons for amendment for other all other amendments are provided below:

1. Amended clinical trial protocol 01 based on Amendment 01 (30-May-2017)

Reason for amendment:

- **Change dose limiting toxicities (DLT) definition**

In section(s): tabulated clinical trial summary, Sections 6.2.1 and 9.1.1 of the protocol

Rationale: Per FDA request

- **Added physical examinations, Hematology, biochemistry and urinalysis lab tests at visits 60 and 90 days after last dose of study treatment**

In section(s): tabulated clinical trial summary, Sections 1.2, 6.6.1 and 12.4.4.1 of the protocol

Rationale: Per FDA request.

2. Amended clinical trial protocol 02 based on Amendment 02 (17-Nov-2017)

Reasons for amendment:

- **Revised Phase 1 and Phase 2 study design**

In section(s): tabulated clinical trial summary, sections 1.1, 1.2, 1.3, 4.3, 5.1, 5.2, 6.1, 6.2, 6.3, 6.5, 6.7, 7.1, 7.2, 8.3, 8.7, 9.2.1, 13.1, 13.3, 13.4 of the protocol

Rationale: recently FDA released statement regarding the risks associated with the use another anti-PD-1 (pembrolizumab) in combination with dexamethasone, and an immunomodulatory agent (lenalidomide or pomalidomide) for the treatment of patients with multiple myeloma. FDA confirmed that the imbalance in deaths observed in the pembrolizumab trials were due to toxicity and not disease progression. It is not clear if this safety risk is due to an interaction between the anti-PD-1 and the IMiD or anti-PD-1 in multiple myeloma. Therefore, the Phase 1 and Phase 2 study design is revised to:

- Changed dose de-escalation in Phase 1 to 3+3 design.
- Added a control arm with isatuximab alone in Phase 2 for better assessment of benefit and risk profile when cemiplimab is combined with isatuximab.
- In published data, for the combination of nivolumab and ipilimumab in NCSLC, changing the exposure of check point inhibitors altered the safety, tolerability and efficacy. To ensure that the most effective and safe dose of cemiplimab will be used in this study, two different doses will be assessed if it is permitted based on the MTD finding from Phase 1. Patients will be randomized in the 3 study arms of Phase 2.

- Changed patient population to include relapsed and /or refractory multiple myeloma (RRMM) patients received at least 3 prior lines of anti-cancer therapy.
- **Body weight based dose is changed to flat dose**

In section(s): tabulated clinical trial summary, Sections 6.1 and 8.3 of the protocol

Rationale: Based on feedback from regulatory authorities, it was subsequently decided to switch from body weight adjusted dosing to fixed flat dosing across the cemiplimab program.

- **Added a DMC**

In section(s): tabulated clinical trial summary, sections 6.8 of the protocol

Rationale: to have an independent committee monitory patient safety and to provide the sponsor with appropriate recommendations in due time to ensure the safety of the patients.

- **Add an exclusion criteria: Patients who have previously been treated with idelalisib (a PI3K inhibitor).**

In section(s): tabulated clinical trial summary, Sections 7.3 of the protocol.

Rationale: In study R1979-ONC-1504, recent safety findings for 3 patients with indolent lymphoma previously treated with idelalisib, a phosphatidylinositol 3-kinase (PI 3 K) inhibitor. Following a single dose of cemiplimab monotherapy in each case, 2 patients experienced severe stomatitis and/or skin reactions. The third patient experienced myositis and myasthenia gravis after 2 doses of cemiplimab.

- **Add additional safety guidance language added for the management of patients developing stomatitis or mucositis.**

In section(s): Sections 6.5.4 of the protocol.

Rationale: based on recent safety findings mentioned above.

- **An adverse event of special interest (AESI) has been added to the list of AESIs: an irAE of any grade in a patient previously treated with a PI 3-K inhibitor and additional safety guidance language added for the management of patients developing stomatitis or mucositis.**

In section(s): Sections 10.5 of the protocol.

Rationale: based on recent safety findings mentioned above.

- **Clarify plasmacytoma assessment at screening: in patients with known or suspected extramedullary disease.**

In section(s): Sections 1.2 and 12.2 of the protocol.

Rationale: further clarification.

- **Change REGN2810 to cemiplimab.**

In section(s): entire document.

Rationale: to be consistent with the usage of product name for both investigational products

3. Amended clinical trial protocol 03 based on Amendment 03 (06-Aug-2018)

Reasons for amendment:

The main reasons of this amendment are to add a separate cohort in Phase 2 for patients with disease refractory to anti-CD38 Mab as the most recent treatment, to add assessment of humoral and cellular immune responses to myeloma-related tumor antigens in blood and their correlation with clinical response,

Other modifications made in the document to either improve the clarity/consistency or correct errors.

- **Add a anti-CD38 refractory cohort in Phase 2**

In section(s): tabulated clinical trial summary, Sections 6.3 and 7.3 of the protocol.

Rationale: Patients who received anti-CD38 mAb within 6 months before study entry and had disease progress while on treatment or within 60 days after the last treatment will be enrolled in a separate cohort. The enrollment will start only if a treatment benefit of the combination therapy is demonstrated in the interim analysis including pass the futility check.

- **Add assessment of humoral and cellular immune responses to myeloma-related tumor antigens in blood and their correlation with clinical response**

In section(s): tabulated clinical trial summary, Sections 1.1 and 9.5 of the protocol.

Rationale: to further understand the mechanism of action of the combination therapy.

- **Update PK/PD flowcharts**

In section(s): Section 1.2 and Section 1.3 of the protocol.

Rationale: to improve the clarity.

- **Added an appendix of contraceptive guidance and collection of pregnancy information and provided reference in exclusion criteria No. 18**

In section(s): Section 7.2 and appendix.

Rationale: provide further clarification.

- **Extended overall survival (OS) follow up period to 24 months after last patient first dose, best of response for post anticancer therapy will be collected during this study follow up period**

In section(s): CTS, Section 12.4 of the protocol.

Rationale: to explore if the study treatment has benefit for OS and the effect of the study treatment to the response of next anti-cancer therapy.

- **Changed DMC review for every 4 months to every 3 months**

In section(s): Sections 6.7 and 6.8 of the protocol.

Rationale: in response to ANSM's request.

- **Updated cemiplimab clinical information**

In section(s): Section 4.2.2.1 of the protocol.

Rationale: based on new information provided in IB ed.05 dated 12-May-2017.

- **Added an instruction for prophylaxis of opportunistic infections**

In section(s): Section 8.9 of the protocol.

Rationale: in response to health authority's request.

- **Added additional exclusion criterion**

In section(s): CTS and Section 7.3 of the protocol.

Rationale: in response to health authority request.

4. Amended protocol [04] (11 June 2019)

This amended protocol (amendment 04) 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
Section 8.9,3 Contraceptive measures and pregnancy counseling	Amended to indicate that females of child bearing potential or male subjects with female partners of childbearing potential shall be required to use contraception for 5 months following the last dose of isatuximab.	Changed from 3 months due to re-estimation of isatuximab plasma half-life
Study flowchart and Section 12.4.4.1 60 and 90 days after last treatment visit	Amended to indicate that monthly pregnancy tests will be required for 5 months following the last dose of Isatuximab or 6 months following the last dose of cemiplimab, whichever comes last.	Due to re-estimation of isatuximab plasma half-life

5. Amended protocol 05 (14 August 2020)

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.

OVERALL RATIONALE FOR THE AMENDMENT

Based on updated analysis of primary endpoint (overall response rate [ORR]) planned six months after last patient in (LPI) and other secondary endpoints (including overall survival [OS]) performed at the planned cutoff date 1 year after LPI, the addition to cemiplimab to SAR650984 only resulted in marginal additive efficacy. No safety concerns were observed during periodic Data Monitoring Committee (DMC) review. No further efficacy data collection at longer follow-up will be performed. Per DMC recommendation, the final OS analysis planned at 24 months after LPI will not be performed and the follow-up will stop after the extended safety period of 90 days after last study treatment dose. Participants under treatment will continue to be treated as long as they benefit from it.

A risk of hepatitis reactivation has been identified in the SAR650984 Investigator's Brochure Edition 11 (30-Apr-2020).

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Clinical trial summary; 1.1 Study flowchart; 1.2.2 ISATUXIMAB QW/Q2W + CEMIPILIMAB Q2W (DL1) - Treatment phase: Cycle 2 and beyond (Sparse sampling); 1.2.3 ISATUXIMAB QW/Q2W + CEMIPILIMAB Q2W (DL1) - End of treatment and follow-up periods; 1.3.2 ISATUXIMAB QW/Q2W + CEMIPILIMAB Q4W (DL-1) - Treatment phase: Cycle 3 and beyond (Sparse sampling); 1.3.3 ISATUXIMAB QW/Q2W + CEMIPILIMAB Q4W (DL-1) - End of treatment and follow-up periods; 6.6.1 Duration of study participation for each patient; 6.6.2 Determination of end of clinical trial (all patients); 9.2.1 Primary endpoint (Phase 2 only); 12.4.4.2 Further follow-up visits until 12 months after LPI; 12.4.5 Post OS study cut-off date	Follow-up procedures after the extended safety period of 90 days after last study treatment dose will not be performed anymore after amended protocol 05 approval. The final OS analysis planned at 24 months after LPI will not be performed. Patients benefiting from study treatment may continue receiving treatment beyond amended protocol 05 implementation.	The addition to cemiplimab to SAR650984 only resulted in marginal additive efficacy. No safety concerns were observed during periodic DMC review. No further efficacy data collection at longer follow-up will be performed per DMC recommendation.
1.1 Study Flowchart; 6.5.7 Guidance in case of hepatitis B reactivation occurring under study treatment	Additional hepatitis viral serology if HBV status unknown before treatment start, to be repeated if clinically indicated.	A risk of hepatitis reactivation has been identified.
6.5.7 Guidance in case of hepatitis B reactivation occurring under study treatment	Description of study treatment discontinuation and restart procedure in case of viral reactivation.	A risk of hepatitis reactivation has been identified.
6.5.7 Guidance in case of hepatitis B reactivation occurring under study treatment; 12.4.1 Cycle 1 (Day 1, Day 8, Day 15 and Day 22 all ±1 day); 12.4.2 Subsequent cycles (Day 1 and 15 both ±2 days)	Description of monitoring of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) in case of viral reactivation.	A risk of hepatitis reactivation has been identified.
1.2.3 ISATUXIMAB QW/Q2W + CEMIPILIMAB Q2W (DL1) - End of treatment and follow-up periods; 1.3.3 ISATUXIMAB QW/Q2W + CEMIPILIMAB Q4W (DL-1) - End of treatment and follow-up periods; 9.1.5 Immunogenicity; 9.3.1 Sampling time	Anti-drug antibodies (ADA) and pharmacokinetics (PK) collection was stopped at cutoff date for primary efficacy analysis 6 months after Last Patient In.	Sufficient information on PK and immunogenicity of isatuximab is available. This change was already communicated through an administrative letter dated 10-Sep-2019 effective on 04-Oct-2019 for patients still on treatment and is brought in the protocol at the occasion of this amendment.
10.4.2 Timely handling of certain AEs	Hospitalization and examination reports for serious adverse events (SAEs), adverse events of special interest (AESI), pregnancy, or overdose will not be systematically requested	Only necessary copies of medical records are to be shared with the Sponsor.

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