NCT02812706

AMENDED CLINICAL TRIAL PROTOCOL NO. 05

COMPOUND (INN): SAR650984 (isatuximab)

A Phase I/ II Study of isatuximab (Anti-CD38 mAb) Administered as a Single Agent in Japanese Patients with Relapsed AND Refractory Multiple Myeloma

STUDY NUMBER: TED14095

STUDY NAME: Islands

VERSION DATE / STATUS: 15-Jul-2020 / Approved

Version Number:	1	EudraCT IND Number(s) PMDA CTN Number:	Not applicable Not applicable 28-0045
Date:	15-Jul-2020	Total number of pages:	122

NAMES AND ADDRESSES OF

COORDINATING INVESTIGATOR		Not Applicable
MONITORING TEAM'S REPRESENTATIVE	Name: Address: Tel: Fax: E-mail: Name: Address: Tel: Fax: E-mail:	
SPONSOR	Company: Address:	
OTHER EMERGENCY TELEPHONE NUMBERS	Tel for 24 hours alerting system: FAX for Safety Emergency: E-mail:	

PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY

Document	Country/countries impacted by amendment	Date, version
Amended Clinical Trial Protocol 05	Japan only	15-Jul-2020, Version number: 1 (electronic 5.0)
Amended Clinical Trial Protocol 04	Japan only	14-Dec-2018, Version number: 1 (electronic 4.0)
Amended Clinical Trial Protocol 03	Japan only	12-Oct-2017, Version number: 1 (electronic 3.0)
Protocol Amendment 03	Japan only	12-Oct-2017, Version number: 1 (electronic 1.0)
Amended Clinical Trial Protocol 02	Japan only	27-Jan-2017, Version number: 1 (electronic 2.0)
Protocol Amendment 02	Japan only	27-Jan-2017, Version number: 1 (electronic 1.0)
Amended Clinical Trial Protocol 01	Japan only	13-May-2016, Version number: 1 (electronic 1.0)
Protocol Amendment 01	Japan only	13-May-2016, Version number: 1 (electronic 1.0)
Clinical Trial Protocol	Japan only	01-Feb-2016, Version number: 1 (electronic 1.0)

AMENDED PROTOCOL 05 (15-JUL-2020)

OVERALL RATIONALE FOR THE AMENDMENT

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
1.5 Study Flowchart – Phase II part; 1.6 Footnotes for Study Flowcharts; 6.6.3 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.
6.6.3 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.
6.6.3 Guidance in case of hepatitis B reactivation occurring under study treatment; 12.3.1 Day 1 of Each Cycle; 12.3.4 Day 15 of Each Cycle	Description of monitoring of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) in case of viral reactivation.	A risk of hepatitis reactivation has been identified.
10.5.2 Serious Adverse Events, Adverse Events of Special Interest, Pregnancy and Symptomatic Overdose	Hospitalization and exams report for serious adverse events (SAEs), adverse events of special interest (AESI), pregnancy and symptomatic overdose will not be systematically requested.	Only necessary copies of medical records are to be shared with the Sponsor.
Whole document	Correction of typos.	

CLINICAL TRIAL SUMMARY

COMPOUND: isatuximab	**STUDY No: TED14095** **STUDY NAME: Islands**
TITLE	A Phase I/ II Study of isatuximab (Anti-CD38 mAb) Administered as a Single Agent in Japanese Patients with Relapsed AND Refractory Multiple Myeloma
INVESTIGATOR/TRIAL LOCATION	Japan
PHASE OF DEVELOPMENT	Phase I and Phase II
STUDY OBJECTIVE(S)	**Primary objective** **PHASE I PART** • To evaluate safety and tolerability of isatuximab in Japanese patients with relapsed and refractory multiple myeloma. **PHASE II PART** • To evaluate efficacy of isatuximab at recommended dose and to further evaluate the overall response rate (ORR) of isatuximab in Japanese patients with relapsed and refractory multiple myeloma. **Secondary objective(s)** • To evaluate the safety including immunogenicity of isatuximab. The severity, frequency and incidence of all adverse events will be assessed. • To evaluate the pharmacokinetic (PK) profile of isatuximab in the proposed dosing schedule. • To assess the efficacy using International Myeloma Working Group (IMWG) uniform response criteria. • To assess the relationship between baseline CD38 receptor density (RD) on multiple myeloma cells and efficacy. **Exploratory objective** • To assess minimal residual disease (MRD) in patients achieving Complete Response (CR) and correlate with clinical outcome. • To investigate the relationship of soluble CD38 and parameters of PK and clinical response. • To investigate the relationship between multiple myeloma molecular subtype (as defined by cytogenetics/ FISH) and parameters of clinical response. • To investigate the relationship between immune genetic determinants, immune phenotype and parameters of clinical response.

STUDY DESIGN	This is an open-label, non-randomized, single arm, local multi-center study conducted in 2 parts, Phase I and Phase II. In this study a cycle is 28 days. **Phase I part** The Phase I part is a dose escalation study of isatuximab administered as single agent as an intravenous (IV) infusion every week (QW) in Cycle 1 (4 weeks) followed by every 2 weeks (Q2W) in subsequent cycles to adult multiple myeloma patients. The initial dose and schedule of administration will be based on those defined in TED10893 study. The maximum tolerated dose (MTD) is defined as one level lower dose of the Maximum Administrated Dose (MAD). Dose escalation will be stopped when the Cohort 1 dosing level is considered as a MAD defined as the dose at which ≥33% of evaluable patients have experienced a DLT following the first administration of IMP and occurring during the first cycle from a cohort of 3 to 6 patients. Cohort 1 and 2 will include at least 3 evaluable patients if no potential confirmed DLT is reported, or up to 6 evaluable patients if a potential DLT is experienced by 1 of the first 3 patients. In Cohort 1, at least 7 calendar days must pass after dosing the first patient before dosing the second patient. Dose level for Cohort 1 will be the 1/2 of the global maximum administrated dose defined in TED10893 study. Dose level for Cohort 2 will be same as global recommended dose: • Cohort 1: 1/2 of global maximum administrated dose defined in TED10893 (ie. 10 mg/kg QW in Cycle 1 (4 weeks) followed by 10 mg/kg Q2W in subsequent cycles) • Cohort 2: Global recommended dose defined in TED10893 (ie. 20 mg/kg QW in Cycle 1 (4 weeks) followed by 20 mg/kg Q2W in subsequent cycles) Intrapatient dose escalation is not permitted. After completing the first cycle, patients may continue to receive additional administrations of isatuximab (at the same dosing level provided the patient is obtaining benefit from the treatment). If this dosing regimen is considered safe patients can continue the treatment (=isatuximab) until unacceptable adverse event, disease progression, withdrawal of consent and/or Investigator's decision. Additionally PK, safety and disease response will be assessed. Upon completion of enrollment and DLT observation period (Cycle 1) in each cohort, the Study Committee will review collected data and will make the decision to continue the enrollment in subsequent cohort/ phase. **Phase II part** The Phase II part is to commence after the Cohort 2 of Phase I part has completed enrollment and DLT evaluation. Patients enrolled in Phase II part will be given at the recommended dose determined in Phase I part.
STUDY POPULATION **Selection criteria**	Inclusion criteria: I 01. Males or females, age 20 years or older. I 02. Patient must have a known diagnosis of symptomatic multiple myeloma.

	I 03.	Patients must have received at least 3 prior lines of therapies which must include treatment with an Immunomodulatory Drug (IMiD) and a Proteasome Inhibitor (PI). The patients must have received an IMiD and a PI for ≥2 cycles or ≥2 months of treatment. OR Patients whose disease is double refractory to an IMiD and a PI. For patients who have received more than one type of IMiD and PI, their disease must be refractory to the most recent one. The patients must have received an IMiD and a PI for ≥2 cycles or ≥2 months of treatment.
	I 04.	Subject must have been responsive to at least one prior line of therapy (MR or better).
	I 05.	Refractory to the most recently received IMiD or PI included therapy. (Patient must progress during or within 60 days of completion of treatment with IMiD or PI)
	I 06.	Patients with measurable disease defined as at least one of the followings: IgG Type: Serum M-protein ≥1 g/dL (≥10 g/L) IgA or D Type: Serum M-protein ≥0.5 g/dL (≥5 g/L) Urine M-protein ≥200 mg/24 hours
	I 07.	ECOG Performance status ≤2
	I 08.	Life expectancy of at least 3 months.
	I 09.	Female patients of childbearing potential (FCBP) and male patients with female partners of childbearing potential who agreed to avoid pregnancy by using an adequate method of contraception for 2 weeks prior to screening, during and 6 months after the last administration of the IMP. Methods of contraception includes, 2-barrier method or 1 barrier method with a spermicide (spermicide is only available for purchase with condoms or diaphragm), oral hormonal contraception, intrauterine hormone-releasing system, vasectomy or intrauterine device. Adequate methods of contraception are provided as examples. Other acceptable and effective methods of birth control are also permitted. A FCBP is a sexually mature woman who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 24 consecutive months.
	I 10.	Voluntary written informed consent before performance of any study-related procedure not part of routine medical care with the understanding that consent may be withdrawn by the subject at any time without prejudice to future medical care.
	I 11.	Ability to understand the purpose and risks of the study and provide signed and dated informed consent and authorization to use protected health information (in accordance with national privacy regulations).
	<u>Exclusion criteria:</u>	
	E 01.	Patients treated with any anti-CD38 agent.
	E 02.	Patients with disease measurable only by serum free light chain analysis.
	E 03.	Diagnosed or treated for another malignancy within 5 years prior to enrollment, with the exception of complete resection of basal cell carcinoma or squamous cell carcinoma of the skin, an in situ malignancy, or low-risk prostate cancer after curative therapy.

	E 04. Prior anticancer therapy (chemotherapy, targeted agents, immunotherapy) within 21 days prior to the first drug infusion unless otherwise specified below, • Alkylating agents (eg, Melphalan) within 28 days prior to the first dose of IMP. • Steroids treatment (eg, prednisone >10 mg/day orally or equivalent except patients being Treated for adrenal insufficiency/replacement therapy or Treated for inhalation corticosteroids) within 14 days prior to the first dose of IMP. • Participated in another clinical trial within 30 days prior to the first dose of IMP. E 05. Patients treated with systemic radiation therapy within 4 weeks prior to the first dose of IMP or Localized radiation therapy within 1 week prior to the first dose of IMP. E 06. Major surgical procedure within 4 weeks prior to the first dose of IMP. E 07. Patients with laboratory values of:: • Absolute neutrophil count (ANC) <1,000 cells/μl (1.0 x 10^9/L) (G-CSF cannot be used within the previous 7 days of the laboratory test. Pegylated G-CSF cannot be used within the previous 3 weeks of the laboratory test.) • Platelet count <50,000/μL (without platelet transfusion during the 7 days previous to the laboratory test). • Hemoglobin <8.0 g/dL (patients may receive red blood cell transfusion) • AST or ALT >3.0 x upper limit of normal [ULN] • Total bilirubin >2.0 x ULN • Estimating glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2 using revised equation for eGFR in Japanese. • Serum calcium (corrected for albumin) level >ULN (treatment of hypercalcemia is allowed and subject may be enrolled if hypercalcemia returns to normal with standard treatment) E 08. Any toxicity Grade ≥2 (excluding alopecia, neutropenia or neuropathy) related to any prior anti-cancer therapy according to the NCI CTCAE version 4.03. E 09. Neuropathy Grade ≥3 or painful peripheral neuropathy Grade ≥2 E 10. History of significant cardiovascular disease unless the disease within the past 6 months is well-controlled. Significant cardiac diseases include, • Second/third degree atrioventricular block • Significant ischemic heart disease • QTc interval >450 msec at baseline (read by local cardiologist) • Poorly controlled hypertension • Congestive heart failure of NYHA Class III or worse (marked limitation of physical activity, comfortable at rest, but less than ordinary activity causes fatigue, palpitation, dyspnea or anginal pain) • LVEF <45%

	E 11. Previously received an allogenic stem cell transplant. E 12. Diagnosed Crow-Fukase (POEMS) syndrome or plasma cell leukemia. E 13. Patients with known or suspected amyloidosis. E 14. Patients with Waldenstrom's macroglobulinemia or Multiple myeloma IgM subtype. E 15. Patients with active infection requiring systemic antibiotics, antivirals or antifungals within 2 weeks prior to the first dose of IMP (except when used for chronic prophylaxis). E 16. Known human immunodeficiency virus (HIV) or active hepatitis B or C viral infection. E 17. Serious psychiatric illness, active alcoholism, or drug addiction that may hinder or confuse follow-up evaluation. E 18. Any medical conditions that, in the Investigator's opinion, would impose excessive risk to the patient (eg, poorly controlled diabetes or poorly controlled hypotension). E 19. Hypersensitivity or history of intolerance to boron or mannitol, sucrose, histidine (as base and hydrochloride salt) and polysorbate 80 or any of the components of study therapy that are not amenable to pre-medication with steroids and H2 blockers or would prohibit further treatment with these agents. E 20. Female subjects who are pregnant or lactating. If a female who stopped lactating before entering in the study, the female must stop lactating from the day of the first IMP administration until 6 months after the last administration of the IMP. E 21. Any subject who, in the judgment of the Investigator, is likely to be noncompliant during the study, or unable to cooperate because of a language problem or poor mental development. E 22. Any subject who cannot be contacted in case of emergency. E 23. Any subject who is the Investigator or any sub-investigator, research assistant, pharmacist, study coordinator, or other staff thereof, directly involved in conducting the study. Patients who have been withdrawn from the study treatment cannot be re-included in the study. Their inclusion and treatment number must not be re-used.
Total expected number of patients	Phase I part: 6 to 12 evaluable patients Phase II part: Approximately 30 patients
STUDY TREATMENT(s)	
Investigational medicinal product(s) **Formulation**	Isatuximab The drug product (isatuximab) 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 for parenteral administration as a sterile, non-pyrogenic, injectable, colorless, 20 mg/mL concentrate for solution for infusion that may contain white to off-white 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.

	The pH of the solution is 6.0 (5.7-6.3). The solution contains the following excipients: water for injection, 10% sucrose, 20 mM histidine (as base and hydrochloride salt) and 0.02% polysorbate 80.
Route(s) of administration	Intravenous infusion. The appropriate volume of isatuximab will be diluted in an infusion bag of 0.9% sodium chloride solution or 5% dextrose solution.
Dose regimen	**Phase I part** • Cohort 1: 1/2 of global maximum administrated dose defined in TED10893 (ie. 10 mg/kg QW in Cycle 1 (4 weeks) followed by 10 mg/kg Q2W in subsequent cycles.) • Cohort 2: Global recommended dose defined in TED10893 (ie. 20 mg/kg QW in Cycle 1 (4 weeks) followed by 20 mg/kg Q2W in subsequent cycles.) **Phase II part** • Recommended dose defined in Phase I part
ENDPOINT(S)	**Primary endpoint:** **Phase I part** The safety of Isatuximab will be evaluated using DLT criteria described as follows during the Cycle 1. The NCI CTCAE version 4.03 will be used to assess the severity of AE and serious adverse events (SAE). The DLTs will be determined by the Study Committee. Hematologic DLTs are defined as any of the following, attributed to isatuximab: • Grade 4 neutropenia lasting for ≥5 days. • Grade 3 to 4 neutropenia complicated by fever or Microbiologically or radiographically documented infection. • Grade 4 thrombocytopenia lasting for ≥5 days. • Thrombocytopenia if required platelet transfusion. • Treatment delay >14 days due to hematologic toxicity. Non-hematologic DLTs are defined as any of the following, attributed to isatuximab: • Grade ≥3 non-hematological AE, excluding Grade 3 fatigue, Grade 3 to 4 electrolyte abnormalities, Grade 3 nausea/vomiting/diarrhea if responsive to optimal medical management within 48 hours or allergic reaction/ hypersensitivity attributed to isatuximab. • AE that requires treatment delay for >14 days. • Grade 3 neuropathy will not be considered as a DLT if the patient began therapy with Grade 2 neuropathy at baseline. Any other toxicity that the Investigator and the sponsor deem to be dose limiting, regardless of the grade, may also be considered as DLT. Before starting Cohort 2 and Phase II part, all safety data, and the reported potential DLTs will be reviewed to determine their relationship to the IMP. Starting Cohort 2 or Phase II part decisions will be based on the assessment of IMP related DLTs by the Study Committee.

	Dose escalation will be stopped if ≥33% (≥2 in up to 6 patients) of patients experienced an IMP related DLT observed during the first cycles of treatment (4 weeks), according to the definition of MAD. **Phase II part** ORR is defined as the proportion of patients with stringent complete response (sCR), complete response (CR), very good partial response (VGPR), and partial response (PR) based on responses as assessed by the Independent Adjudication Committee (IAC) using the International Myeloma Working Group (IMWG) Uniform Response Criteria. Response evaluation will include: • M-protein quantification (serum and 24-hr urine) • Serum free light chain levels • Bone marrow aspiration and/ or biopsy • CT/MRI scan of plasmacytoma • Bone skeletal survey • Corrected serum calcium **Secondary endpoint:** Safety profile of isatuximab in terms of treatment-emergent adverse events/ serious adverse events (TEAE/SAE) and changes in laboratory parameters, vital signs, ECGs and assessment of physical examination. Assessment of efficacy: Efficacy will be determined using IMWG defined response criteria. Efficacy parameters will include Overall Response Rate (ORR), Clinical Benefit Rate (CBR), Overall Survival (OS), Progression Free Survival (PFS), Duration Of Response (DOR) and Time To Progression (TTP). PK assessments: • Concentration observed at the end of an intravenous (IV) infusion (C_{eoi}) • Maximum observed concentration (C_{max}) • Time to reach the maximum concentration (T_{max}) • Concentrations just before drug infusion (C_{trough}) • AUC over the dosing interval (AUC_{1week}) CD38 receptor density assessment: • CD38 receptor density from baseline bone marrow aspirates. Immune response: • Level of Anti -drug antibodies (ADA). Results of additional procedures performed as part of standard of care to assess the current disease status may also be collected. **Exploratory Endpoints:** • MRD by sequencing will be assessed in patients achieving a CR. • Bone marrow samples will be analyzed for multiple myeloma molecular subtype (by cytogenetics/ FISH). • Blood samples will be analyzed for immune genetic determinants (including FcγR polymorphisms, HLA and KIR genotypes).

	• Immune phenotype (such as B-cell, T-cell, and NK-cell subsets) in bone marrow and peripheral blood will be analyzed. • Blood samples will be analyzed for soluble factors including CD38. Additional molecular analysis, not specified in the protocol but related to the drug action and/or effect of Isatuximab, may be conducted on remaining samples pending evolving literature.
ASSESSMENT SCHEDULE	Assessment schedule will include the following (please see Study Flowcharts and PK flowcharts for additional details): **Safety evaluation** • DLT evaluation (Phase I part only) • AEs according to the NCI-CTC v. 4.03 grading scale • Vital signs • ECOG performance status • 12 lead Electrocardiogram (ECG) • 2-D Echocardiogram or Multigated Acquisition (MUGA) scan • Chest X-ray • Laboratory safety results (blood, urine) • Level of ADA **Pharmacokinetic evaluation** • PK samples will be collected per PK Study Flowcharts. **Efficacy evaluation** • M-protein quantification (serum and/or 24-hour urine, protein electrophoresis), immunofixation and serum FLC levels. • Serum β2-microglobulin, quantitative immunoglobulins and serum calcium. • Bone skeletal survey, computed tomography (CT) scan or magnetic resonance imaging (MRI) as clinically indicated • Radiologic imaging (CT/MRI scan) of plasmacytoma. • Survival status **Biomarkers/ exploratory evaluation** • Bone marrow aspiration and/or biopsy for minimal residual disease (MRD). • CD38 receptor density on plasma cells in bone marrow. • Soluble CD38 in plasma. • Cytogenetics/FISH: Probes for fluorescence in situ hybridization (FISH) analysis include, at minimum t(4;14), t(14;16) and del(17p). • Immune genetic determinants: includes Killer cell Ig-like receptors (KIR), HLA Typing and FcγR genes. • Immune phenotyping (peripheral blood and bone marrow samples).
STATISTICAL CONSIDERATIONS	**Determination of the sample size** Phase I Part The Phase I part of this study aims to determine the safety and tolerability of Isatuximab. It is anticipated that up to 6 to 12 evaluable patients will be enrolled. Patient(s) non evaluable for DLT will be replaced.

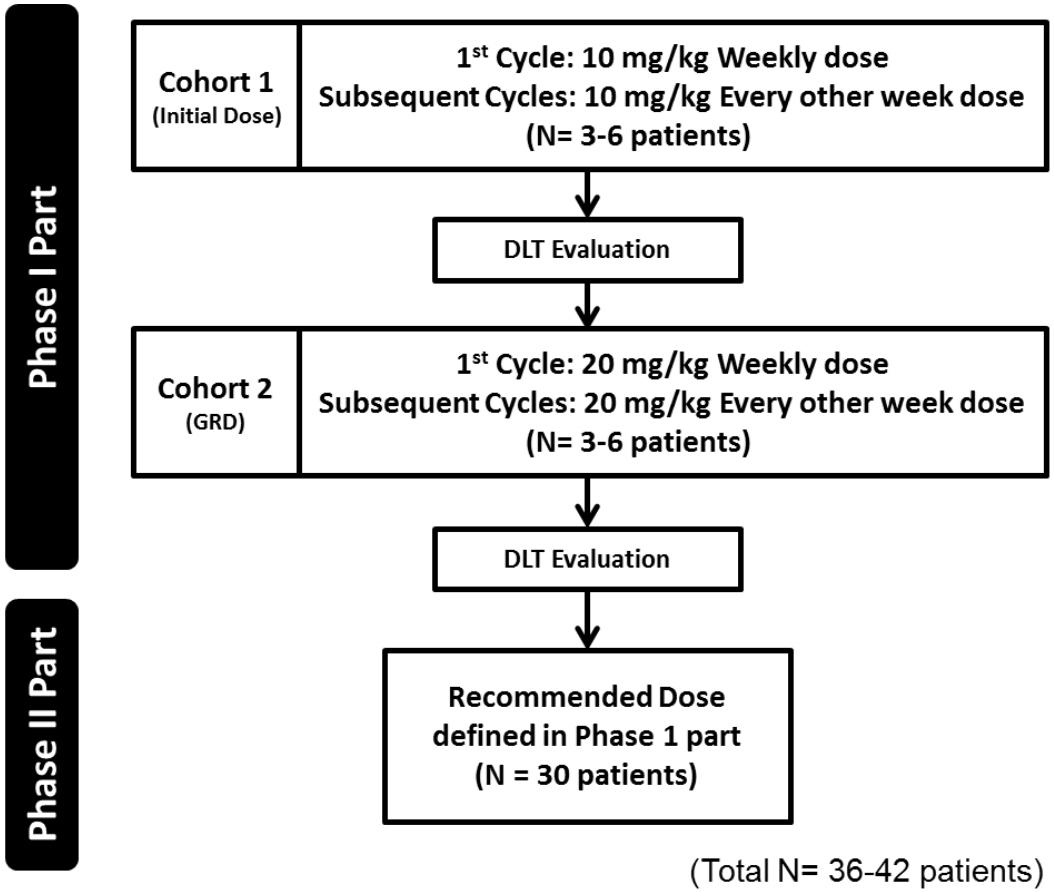
	Phase II Part The phase II part of the study aims to evaluate 33-36 patients which include the subjects in Phase I part at the recommended dose level. Given an assumed true ORR of 28%, the null hypothesis ORR ≤10% will be rejected using an exact binomial test at a one-sided alpha of 0.025 with at least 80% power. **Analysis populations** For both Phase I and Phase II parts of the study, the all treated/safety population will include all patients who have given their informed consent and who have received at least one dose (even incomplete) of Isatuximab. This population is the primary population for the analyses of efficacy and safety parameters. All analyses using this population will be based on the dose level actually received. In the Phase I part, the DLT evaluable population is the subset of patients from the all treated population who have completed the first cycle which consists of 4 administrations of the IMP, or they discontinued the IMP before completion of Cycle 1 for a DLT. The dose escalation will be determined on the DLT evaluable population. The pharmacokinetic population is the subset of patients from the all treated population who have a PK parameter. The activity/efficacy population is the subset of patients from the all treated population who have evaluable data for exploratory analysis. **General statistical approach** Basically, data from initial dose level and recommended dose level will be analyzed and reported separately. Only the efficacy evaluated in Phase I Cohort 2 and Phase II part is combined for recommended dose level. The separate tables will be presented by phase (when appropriate) unless otherwise noted. **Analysis of safety endpoints:** IMP related DLTs will be assessed and analyzed on DLT evaluable population. The same analysis below using all treated/safety population will be applied in Phase I and Phase II part. The treatment emergent adverse events (TEAEs) will be coded according to Medical Dictionary for Regulatory Affairs (MedDRA). Adverse events and laboratory abnormalities will be graded according to the NCI-CTCAE v. 4.03. Number (%) of patients experiencing treatment-emergent adverse events by primary system organ class and preferred term will be summarized by CTCAE grade (all grades and Grade ≥3) for the safety population. The same table will be prepared for drug related TEAEs, TEAEs leading to treatment discontinuation, serious TEAEs, TEAEs with fatal outcome, and drug-related SAEs occurred during the post treatment dosing period. 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. The descriptive statistics of all vital signs' variable will be calculated. **Analysis of pharmacokinetic and immune response endpoints:** The same analysis will be applied in Phase I and Phase II part. Pharmacokinetic and immune response endpoints and CD38 receptor density will be assessed and analyzed on PK population or activity/efficacy population.

	Pharmacokinetics parameters will be summarized with descriptive statistics (mean, geometric mean, median, standard deviation, coefficient of variation, minimum and maximum). Immune response, pharmacodynamics marker results will be descriptively summarized and tabulated. **Analysis of efficacy endpoints:** Best overall response will be listed along with relevant patient/disease characteristics as well as the secondary efficacy endpoints. **Primary analysis:** Analysis of efficacy endpoint will be performed on all patients who received at least one of the recommended dose across Phase I and II part: ORR and a 95% two-sided confidence interval will be computed using Clopper-Pearson method. For recommended dose level, the null hypothesis that the true response rate (ORR) is <10% will be tested using a one-sided exact binomial test with a significance level of 0.025. **Secondary analysis:** The CBR will be analyzed using the same method as the primary efficacy analysis of ORR. DOR, TTP, PFS and OS will be analyzed using Kaplan-Meier methods. **Analysis of the other exploratory endpoints:** The same analysis will be applied in Phase I and Phase II part. The exploratory endpoints and the relationship to clinical outcomes will be analyzed with exploratory manner. **Planned database lock date:** The first cutoff date for the database lock is planned at approximately 4 months after last patient first dosed. The second cutoff date for the database lock is planned at approximately 20 months after last patient first dosed.
DURATION OF STUDY PERIOD (per patient)	The study duration for an individual patient will include a screening period for inclusion of up to 21 days, the treatment period consisting of 28 day cycles and a follow-up period. Treatment with isatuximab may continue until disease progression, unacceptable adverse event or other reason for discontinuation. After study treatment discontinuation, an end of treatment (EoT) visit will be done at 30 days to assess safety and ADA, and at 60 days for ADA. If the ADA is positive or the sample is inconclusive at Day 60 then ADA will be repeated every month (±7 Days) until ADA is negative. Survival status will be collected every 3 months until death or second cutoff date, whichever comes first. Patients with PR or better who come off treatment for reasons other than progression of disease will be followed for disease assessment every 4 weeks until progression or initiation of subsequent therapy, the second analysis cutoff date, whichever comes first. For all patients, any study treatment-related adverse events, and all serious adverse events (regardless of their causal relationship to study treatment) ongoing at the time of study treatment discontinuation will be followed during the follow-up period until resolution or stabilization.

1 FLOW CHARTS

1.1 GRAPHICAL STUDY DESIGN

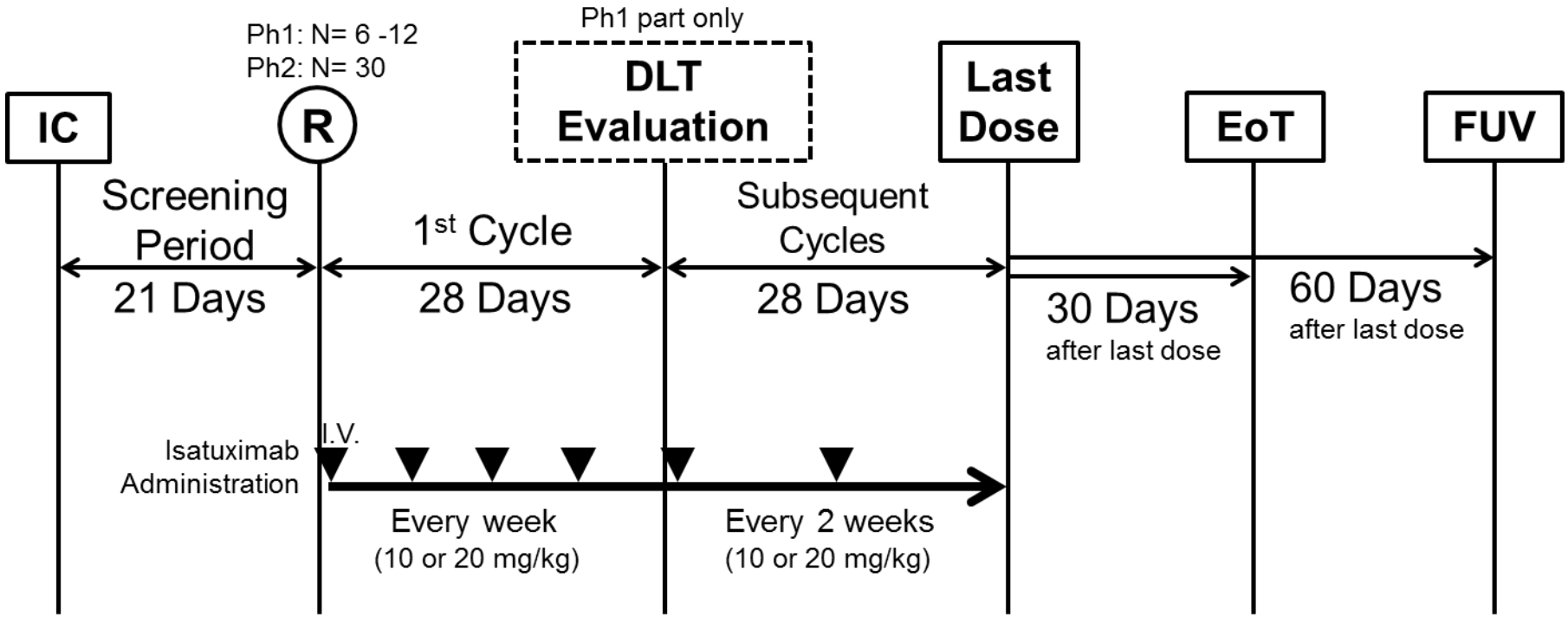
Figure 1 - Study Design of TED14095



(Total N= 36-42 patients)
GRD: Global Recommended Dose

1.2 TREATMENT SCHEMA

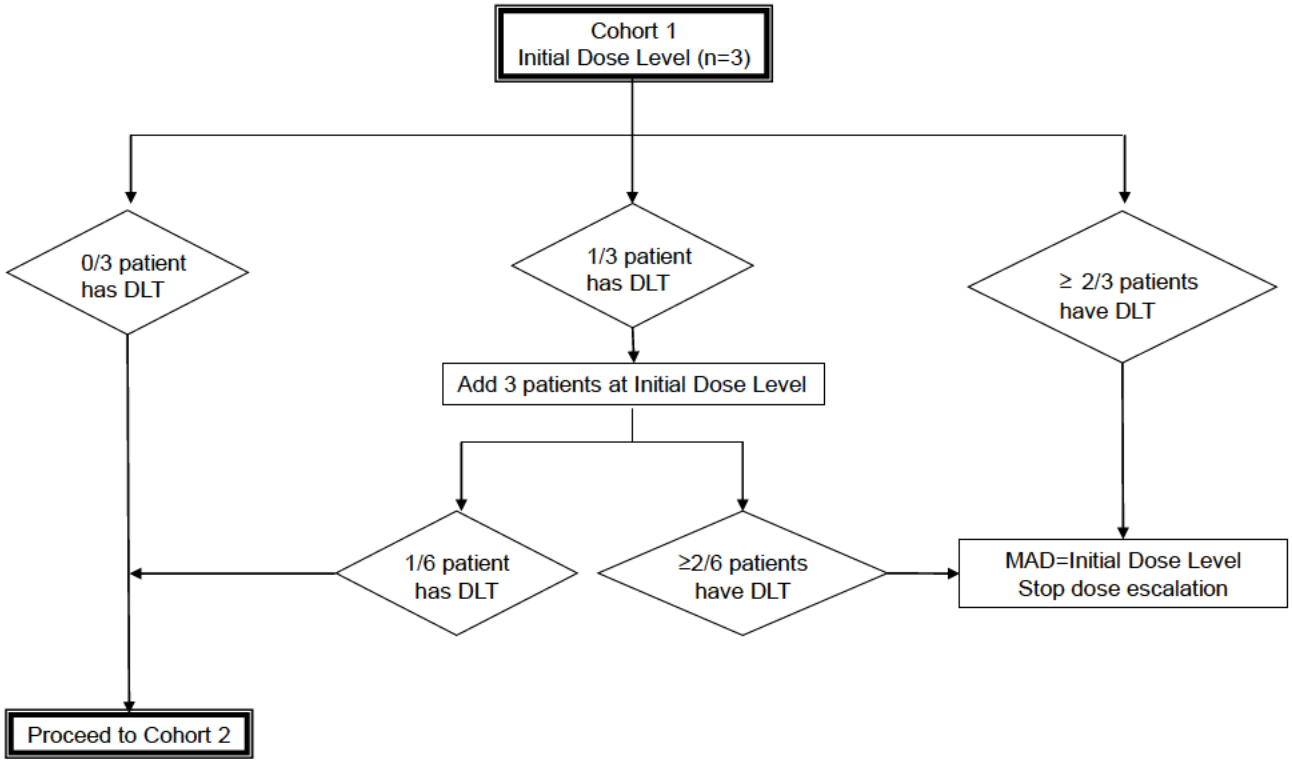
Figure 2 - Treatment schema of TED14095



(IC: Informed Consent form signed, R: Registration, DLT: Dose Limiting Toxicity, EoT: End of Treatment, FUV: Follow-up Visit)

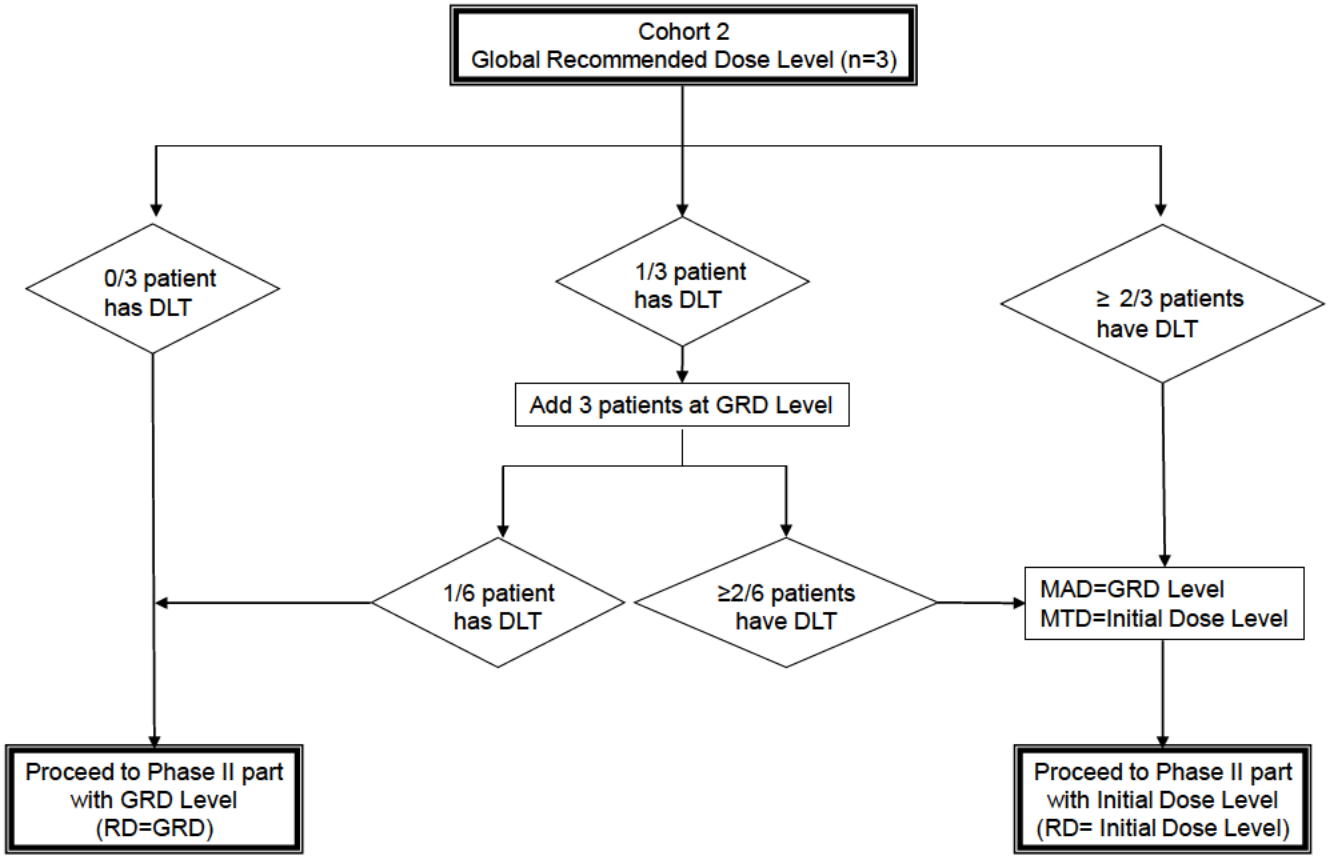
1.3 DESIGN DIAGRAM

Figure 3 - Dose escalation design for Cohort 1 (Initial dose level)



Abbreviations: DLT = Dose-Limiting Toxicity; MAD = Maximum Administered Dose

Figure 4 - Dose escalation design for Cohort 2 (global recommended dose level)



Abbreviations: DLT = Dose-Limiting Toxicity; MAD = Maximum Administered Dose, MTD = Maximum Tolerated Dose
Global Recommended Dose: GRD, Recommended Dose defined in Phase I part: RD

1.4 STUDY FLOWCHART - PHASE I PART

Phase I Part	Screening/ Baseline [2]	Cycle 1 [3]							Subsequent Cycles [3, 36]		End-of-Treatment	Follow-up
Evaluation [1]	D-21 to D-1	D1	D2	D3	D4	D8[4]	D15[4]	D22[4]	D1[4]	D15[4]	30 days (+/- 7 days) after last IMP administration	60 days (+/- 7 days) after last IMP administration and subsequent follow-up
Eligibility criteria & Informed consent[5]	X								Cycle 2 only[5]			
Demography & Medical/surgical & Disease History [6]	X											
Hospitalization [7]		(X)	(X)	(X)	(X)	(X)	(X)					
Patient Registration		X[8]										
Isatuximab Administration		X				X	X	X	X	X		
Isatuximab Safety Labs [9]		(X)				(X)	(X)	(X)	(X)	(X)		
Cytokines		X										
Physical Examination [10]	X	X				X	X	X	X	Cycle 2,3 only	X	
Performance Status (ECOG)	X	X							X		X	
Height	X											
Body weight	X	X				X	X	X	X	X	X	
Vital Signs (HR, Temperature, RR, BP) [11]	X	X				X	X	X	X	X	X	
12-Lead ECG, 2D Echocardiogram or MUGA [12]	X											
Hematology [13]	X	X[14]				X	X	X	X	X	X	
Serum Chemistry [15]	X	X[14]				X	X	X	X	X	X	
Coagulation (PT/INR, aPTT) [16]	X											
Urinalysis [17]	X	X[14]					X		X	X	X	
Pregnancy Test [18] (Within 7 days prior to Day 1)	X								X		X	
HIV-Ab, HBs-Ag, HBc-Ab, HBs-Ab HCV-Ab Tests [19]	X											
Myeloma-specific Lab Tests [21]	X	X[14]							X		X	(X) [23]
Extramedullary Disease [22]	X								(Every 12 weeks)		(X)	(Every 12 weeks)[23]

Phase I Part	**Screening/ Baseline** [2]	**Cycle 1** [3]							**Subsequent Cycles** [3, 36]		**End-of-Treatment**	**Follow-up**
Evaluation [1]	**D-21 to D-1**	**D1**	**D2**	**D3**	**D4**	**D8**[4]	**D15**[4]	**D22**[4]	**D1**[4]	**D15**[4]	**30 days (+/- 7 days) after last IMP administration**	**60 days (+/- 7 days) after last IMP administration and subsequent follow-up**
Skeletal Survey and Chest X-ray [24]	X											
Isatuximab PK plasma samples (See PK flow chart)		X	X	X	X	X	X	X	X	X	X	
Immunogenicity (ADA) [25]		X				X	X	X	X		X	X
Soluble CD38 (PB) [26]		X										
Bone Marrow Aspiration and/or Biopsy [27]	X	(If CR is suspected)										
MRD assessment (BM) [28]	X	(If CR is suspected)										
CD38 Receptor Density (BM) [29]	X											
Cytogenetics/ FISH (BM) [30]	X											
Immune phenotyping (BM) [31]	X											
Immune phenotyping (PB)[32]		X							X (C3 only)		X	
Immune genetic determinants (PB) [33]		X										
Survival Status												X[34]
New Anticancer Therapy												X
AE/ SAE Reporting [35]	Continuously throughout the study period											
Prior/ Concomitant Medication	Continuously throughout the study period											

(PB): Peripheral Blood sample, (BM): Bone Marrow sample

1.5 STUDY FLOWCHART - PHASE II PART

Phase II Part	**Screening/ Baseline [2]**	**Cycle 1 [3]**							**Subsequent Cycles [3, 36]**		**End-of-Treatment**	**Follow-up**
Evaluation [1]	**D-21 to D-1**	**D1**	**D2**	**D3**	**D4**	**D8[4]**	**D15[4]**	**D22[4]**	**D1[4]**	**D15[4]**	**30 days (+/- 7 days) after last IMP administration**	**60 days (+/- 7 days) after last IMP administration and subsequent follow-up**
Eligibility criteria & Informed consent[5]	X											
Demography & Medical/surgical & Disease History [6]	X											
Patient Registration		X[8]										
Isatuximab Administration		X				X	X	X	X	X		
Isatuximab Safety Labs [9]		(X)				(X)	(X)	(X)	(X)	(X)		
Physical Examination [10]	X	X				X	X	X	X	Cycle 2,3 only	X	
Performance Status (ECOG)	X	X							X		X	
Height	X											
Body weight	X	X				X	X	X	X	X	X	
Vital Signs (HR, Temperature, RR, BP) [11]	X	X				X	X	X	X	X	X	
12-Lead ECG, 2D Echocardiogram or MUGA [12]	X											
Hematology [13]	X	X[14]				X	X	X	X	X	X	
Serum Chemistry [15]	X	X[14]				X	X	X	X	X	X	
Coagulation (PT/INR, aPTT) [16]	X											
Urinalysis [17]	X	X[14]					X		X	X	X	
Pregnancy Test [18] (Within 7 days prior to Day 1)	X								X		X	
HIV-Ab, HBs-Ag, HBc-Ab, HBs-Ab HCV-Ab Tests [19]	X								X[20]			
Myeloma-specific Lab Tests [21]	X	X[14]							X		X	(X) [23]
Extramedullary Disease [22]	X								(Every 12 weeks)		(X)	(Every 12 weeks) [23]

Phase II Part	**Screening/ Baseline** [2]	**Cycle 1** [3]							**Subsequent Cycles** [3, 36]		**End-of-Treatment**	**Follow-up**
Evaluation [1]	**D-21 to D-1**	**D1**	**D2**	**D3**	**D4**	**D8**[4]	**D15**[4]	**D22**[4]	**D1**[4]	**D15**[4]	**30 days (+/- 7 days) after last IMP administration**	**60 days (+/- 7 days) after last IMP administration and subsequent follow-up**
Skeletal Survey and Chest X-ray [24]	X											
Isatuximab PK plasma samples (See PK flow chart)		X				X	X	X	X	X	X	
Immunogenicity (ADA) [25]		X				X	X	X	X		X	X
Soluble CD38 [26]		X										
Bone Marrow Aspiration and/or Biopsy [27]	X	(If CR is suspected)										
MRD assessment (BM) [28]	X	(If CR is suspected)										
CD38 Receptor Density (BM) [29]	X											
Cytogenetics/FISH (BM) [30]	X											
Immune phenotyping (BM)[31]	X											
Immune phenotyping (PB) [32]		X							X (C3 only)		X	
Immune genetic determinants (PB) [33]		X										
Survival Status												X[34]
New Anticancer Therapy												X
AE/ SAE Reporting [35]	Continuously throughout the study period											
Prior/ Concomitant Medication	Continuously throughout the study period											

(PB): Peripheral Blood sample, (BM): Bone Marrow sample

1.6 FOOTNOTES FOR STUDY FLOWCHARTS

1. Evaluation: Assessments to be performed prior to study drug administration unless otherwise indicated. Results should be reviewed by the Investigator.
2. If the patient cannot be registered within 21 days of informed consent, the same patient may be re-screened after discussion with the sponsor, provided that there are no persisting safety concerns for patient's study participation. The informed consent form will have to be re-signed by the re-screened patient before starting re-screening procedures. New patient number will be given for the re-screened patients.
3. Cycle: A cycle is 28 days.
4. Allowance for Day 8, Day15 and Day 22 at first cycle is +/- 2 days. Allowance for Day 1 and Day15 at subsequent cycles are +/- 3 days.
5. The ICF should be signed before any study-related procedures or tests are initiated.
   All patients who participated in Phase I part and is going to continue study treatment after completing Cycle 1 must sign a second ICF before commencing IMP administration in Cycle 2 Day1.
6. Demography: Includes date of birth, gender and race.
   Medical/Surgical History: Includes relevant history of previous/associated pathologies other than multiple myeloma.
   Disease History: Includes date of initial diagnosis of symptomatic MM, subtype, stage, previous anti-MM therapy (drug name by line of therapy, start and end date of administration, reason for discontinuation, best response and date of progression/relapse), disease status at inclusion (refractory to last IMiD or PI included therapy). 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. A patient card will be provided to the patient indicating he/she is receiving an anti-CD38 treatment and the site will notify its blood bank that the patient is receiving an anti-CD38 treatment.
7. Hospitalization: Day 1 through the entire day of the 3rd infusion (Day 15) hospitalization is recommended. Hospitalization will be expanded to the entire first cycle of the study treatment (ie. DLT observation period), if the investigator and the study committee judged appropriate.
8. Registration process can be completed in Day -1 however all eligibility criteria should be re-confirmed by investigators in Day 1 before IMP administration.
9. Isatuximab Safety Labs: Should a isatuximab infusion associated reaction of Grade ≥2 occur, additional blood sampling during the AE is required for analysis of markers of potential tumor lysis syndrome (uric acid, lactate dehydrogenase [LDH], BUN, creatinine, potassium, phosphate, ionized or corrected calcium).
10. Physical Examination: Consists of examination of major body systems including neurological, digestive, extramedullary myeloma localizations, respiratory, hepatomegaly, splenomegaly, lymphadenopathy. Only clinically relevant findings will be reported in the electronic case report form (e-CRF) as AEs.
11. Vital Signs: Heart rate (HR), temperature, respiratory rate (RR), blood pressure (BP) to be taken pre-infusion, mid-infusion (when half the volume is administered), and end-infusion on days of investigational medicinal product (IMP) administration. If the infusion rate changes because of an infusion-associated reaction, vital signs should be monitored every hour and at the end of the infusion.
12. 12-Lead ECG, 2-D Echocardiogram or Multigated Acquisition (MUGA): To be performed at screening and then as clinically indicated (the same methods must be used throughout the study). LVEF need to be checked for eligibility.
13. Hematology includes: Hemoglobin, hematocrit, RBC, WBC with differential, Mean Corpuscular Volume (MCV) and platelet counts. To be done at screening, then prior to pre-medication and IMP administration on Day 1, Day 8, Day 15 and Day 22 of Cycle 1 and on Day 1 and Day 15 of every subsequent cycle, at the EoT visit and as clinically indicated. If Grade 4 neutropenia, assess ANC every 2-3 days until ANC $\geq 0.5 \times 10^9$/L and at least weekly thereafter until ANC $\geq 1.0 \times 10^9$/L. Perform direct and indirect coombs tests prior to the first IMP administration.
14. Not required to be repeated prior to Day 1 Cycle 1 if the screening labs were performed within 3 days prior to first IMP administration.

15. Serum chemistry includes: SGOT (AST), SGPT (ALT), bilirubin (total and direct), alkaline phosphatase, lactate dehydrogenase (LDH), fasting glucose, sodium, potassium, magnesium, chloride, calcium, corrected serum calcium, phosphate, uric acid, blood urea nitrogen (BUN), serum creatinine and eGFR (Revised equations for eGFR in Japanese), albumin and total protein. To be done at screening, then prior to pre-medication and IMP administration on Day 1, Day 8, Day 15 and Day 22 of Cycle 1 and on Day 1 and Day 15 of every subsequent cycle, at the EoT visit and as clinically indicated.

16. Coagulation: To be done at screening and then as clinically indicated. Coagulation includes: Prothrombin time (PT) or international normalized ratio (INR) and activated partial thromboplastin time (aPTT).

17. Urinalysis includes: blood, protein, glucose, pH, ketones, bilirubin, leucocytes, nitrites and specific gravity. To be done at baseline, on Day 1 and Day 15 of each cycle, EoT, and if clinically indicated. Quantitative urinalysis will be needed if hematuria is observed or clinically indicated.

18. Pregnancy Test: Women of child bearing potential must have a negative serum pregnancy test result within 7 days prior to first IMP administration and at the EoT visit. Urine test can be used at Day 1 of each subsequent cycle.

19. HBc-Ab, HBs-Ab test: If HBc-Ab and/or HBs-Ab positive at baseline, Hepatitis B Virus (HBV)-DNA test is required prior to registration. If history of HBV infection is suspected, monitoring of HBV-DNA is recommended on Day 1 of each cycle, EoT and if clinically indicated.

20. Once at any time if HBV status unknown before treatment started and to be repeated if clinically indicated.

21. Myeloma-specific Lab Tests: serum electrophoresis, immunoglobulin assay, corrected serum calcium and 24-hour urine collection for Bence Jones protein to be performed at baseline prior to administration, prior to each cycle thereafter and at time of study discontinuation (if last tests were >4 weeks). Serum β2 microglobulin to be performed at baseline prior to administration, EoT and if clinically indicated. Immunofixation and free light chain tests to be performed at baseline prior to administration, EOT, if CR is suspected and if clinically indicated.
    Bone marrow aspiration to be performed to confirm a CR and as clinically indicated. In case of dry-tap, bone marrow biopsy to be performed to confirm CR. Once CR is confirmed at a given time point, a consecutive assessment for immunofixation and free light chain is required.

22. Extramedullary Disease: Baseline to be performed within 21 days prior to study drug administration. If extramedullary disease present at baseline, to be performed approximately every 12 weeks (eg. at Cycle 4, 7, 10). To be performed upon clinical suspicion of progressive disease. This may include computerized tomography (CT) or magnetic resonance imaging (MRI) scan of the abdomen/pelvis, CT or x-ray of the chest, ultrasound of the liver/spleen or abdomen. May be omitted at End of Treatment if conducted within 12 weeks. All imaging will be sent to a central imaging lab.

23. Disease assessments during follow-up period are only required for patients with PR or better who 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 4 weeks for progression during this period. Disease assessments required every 4 weeks is myeloma-specific lab tests. Extramedullary disease assessment is required approximately every 12 weeks or upon clinical suspicion of progressive disease. All imaging will be sent to a central imaging lab. A bone marrow aspiration and/or biopsy, skeletal survey 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.

24. Skeletal survey and chest X-ray: X-ray to be performed at screening on all patients (the same methods must be used throughout the study). Repeat skeletal surveys are only required as clinically indicated. All imaging will be sent to a central imaging lab.
    X-ray skeletal survey should include radiographs of the following: lateral skull; Postero-Anterior (PA) chest; Antero-Posterior(AP) and lateral cervical spine; AP and lateral thoracic spine; AP and lateral lumbar spine; AP pelvis; AP upper extremities, shoulder to elbow, bilateral; and AP lower extremities, hip to knee, bilateral.
    Chest X ray: To be performed at screening for assessment of pulmonary disease condition and then as clinically indicated.

25. ADA (Anti-Drug Antibodies): To be performed on Day 1, Day 8, Day 15, Day 22 of Cycle 1 and Day 1 of cycle up to 10 cycles prior to each IMP administration, at the EoT visit and at 60 days (± 7 days) after last IMP administration. At 60 days, if patient is positive for ADA or the sample is inconclusive, additional ADA samples are required every 30 days (± 7 days) until sample is negative. If ADA is positive at Cycle 10, one additional sampling for ADA evaluation should be collected 3 months later. No further ADA will be collected, even if the 3-month sample is positive.

26. Peripheral blood to be collected on Day 1 of Cycle 1 prior to IMP administration for soluble CD38 analysis.
27. Bone Marrow Aspiration and/or biopsy: Bone marrow aspiration (BMA) to be collected at screening/baseline. In case of dry-tap, bone marrow biopsy to be performed. Repeat bone marrow aspiration and/or biopsy if complete response (CR) is suspected to confirm achievement of response.
28. MRD Assessment: Bone marrow aspiration and/or biopsy to be collected at screening/baseline. Repeat bone marrow aspiration and/or biopsy if CR is suspected.
29. CD38 Receptor Density in bone marrow: Bone marrow aspiration to be performed prior to study drug administration at screening/baseline. See PK flowchart.
30. Cytogenetics/ FISH: Bone marrow aspiration and/or biopsy to be performed prior to study drug administration at screening/ baseline for fluorescence in situ hybridization (FISH) analysis. Probes include those to detect del(17p), t(4;14) and t(14;16).
31. Immune phenotyping (BM): Bone marrow aspiration and/or biopsy to be performed at baseline/screening prior to IMP administration.
32. Immune phenotyping (peripheral blood): To be performed at Day 1 of Cycle 1, Day 1 of Cycle 3 prior to IMP administration and at the EoT visit. Immune phenotyping in bone marrow will be performed by bone marrow sample obtained at the screening/ baseline period.
33. Immune genetic determinants (peripheral blood): includes Killer cell Ig-like receptors (KIR), HLA Typing and FcγR genes. To be performed at Day 1 of Cycle 1 prior to IMP administration.
34. Survival status: Patients will also be followed for survival status approximately every 3 months (± 14 days) from the date of last IMP administration until death or second cutoff date, whichever comes first. 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 obtained immediately. For subsequent survival follow-up, the patient should be contacted 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.
35. Adverse Event/Serious AE Reporting: All AEs, including 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 follow-up all ongoing related AEs, ongoing SAE/AESIs regardless of relationship and new related AE/SAE/AESIs are to be followed to resolution or stabilization.
36. Post second analysis cut-off period, only AE/SAE reporting will be collected

1.7 PK FLOW CHART - PHASE I PART

Cycle	Cycle 1										Cycle 2		
Day	D1				D2	D3	D4	D8 (±2D)	D15 (±2D)	D22 (±2D)	D1 (±3D)		D15 (±3D)
Time (hour)	0H (start infusion)	2H (mid infusion)	EoI	EoI + 4h	24H	48H	72H	0H	0H	0H	0H	EoI	0H
Indicative clock time (example)	8 am	10 am	noon	4 pm	8 am	8 am	8 am	8 am	8 am	8 am	8 am	noon	8 am
IMP administration													
isatuximab Administration	X-	------	-X					X	X	X	X-	-X	X
Samples													
PK sampling	P00[b]	P01[c]	P02[a]	P03	P04	P05	P06	P07[b]	P08[b]	P09[b]	P00[b]	P01[a]	P02[b]
Bone Marrow for CD38 RD	Y00[d]												
ADA	P00[b]							P01[b]	P02[b]	P03[b]	P00[b]		

Cycle	Cycle 3		Cycle 4				Subsequent Cycles[g]		EoT	Follow-up
Day	D1 (±3D)	D15 (±3D)	D1 (±3D)			D15 (±3D)	D1 (±3D)	D15 (±3D)	30 days after last IMP (±7D)	60 days after last IMP (±7D)
Time (hour/minute)	0H	0H	0H	EoI	EoI + 1h	0H	0H	0H		
Indicative clock time (example)	8 am	8 am	8 am	noon	1 pm	8 am	8 am	8 am	8 am	8 am
IMP administration										
isatuximab Administration	X	X	X-	-X		X	X	X		
Samples										
PK sampling	P00[b]	P01[b]	P00[b]	P01[a]	P02	P03[b]	P00[b, f]	P01[b, f]	PF0	
RD in Bone Marrow										
ADA	P00[b]		P00[b]				P00[b, f]		PF0	PF1[e]

EoI = End of Infusion; ADA = Anti-Drug Antibody; RD = CD38 receptor density; IMP = Investigational Medicinal Product; EoT: End of Treatment, P = Plasma, Y= Bone marrow, F = follow up

a Sample collected just before actual end of isatuximab infusion (within -5 min).

b Sample collected just before IMP administration.

c IMP mid-infusion PK sample collected when half of the volume is administered.

d Required at screening/baseline (within 21 days prior to study drug administration).

e At 60 days, if patient is positive for ADA or the sample is inconclusive, additional ADA samples are required every 30 days (± 7 days) until sample is negative (sample ID: PF2, PF3 etc.).

f Sample collected up to 10 cycles. If ADA is positive at Cycle 10, one additional sampling for ADA evaluation should be collected 3 months later. No further ADA will be collected, even if the 3-month sample is positive.

g Post second analysis cut-off period, only ADA samples will be collected.

1.8 PK FLOW CHART - PHASE II PART

Cycle	Cycle 1							Cycle 2		
Day	D1			D8 (±2D)	D15 (±2D)		D22 (±2D)	D1 (±3D)		D15 (±3D)
Time (hour/minute)	0H (start infusion)	EoI	EoI + 1h	0H	0H	EoI	0H	0H	EoI	0H
Indicative clock time (example)	8 am	noon	1 pm	8 am	8 am	noon	8 am	8 am	noon	8 am
IMP administration										
isatuximab Administration	X-	-X		X	X-	-X	X	X-	-X	X
Samples										
PK sampling	P00[b]	P01[a]	P02	P03[b]	P04[b]	P05[a]	P06[b]	P00[b]	P01[a]	P02[b]
RD in Bone Marrow	Y00[c]									
ADA	P00[b]			P01[b]	P02[b]		P03[b]	P00[b]		

Cycle	Cycle 3		Cycle 4				Subsequent Cycles[f]		EoT	Follow-up
Day	D1 (±3D)	D15 (±3D)	D1 (±3D)			D15 (±3D)	D1 (±3D)	D15 (±3D)	30 days after last IMP (±7D)	60 days after last IMP (±7D)
Time (hour/minute)	0H	0H	0H	EoI	EoI + 1h	0H	0H	0H		
Indicative clock time (example)	8 am	8 am	8 am	noon	1 pm	8 am	8 am	8 am	8 am	8 am
IMP administration										
isatuximab Administration	X	X	X-	-X		X	X	X		
Samples										
PK sampling	P00[b]	P01[b]	P00[b]	P01[a]	P02	P03[b]	P00[b,e]	P01[b,e]	PF0	
RD in Bone Marrow										
ADA	P00[b]		P00[b]				P00[b,e]		PF0	PF1[d]

EoI = End of Infusion; ADA = Anti-Drug Antibody; RD = CD38 receptor density; IMP = Investigational Medicinal Product; EoT: End of Treatment, P = Plasma, Y= Bone marrow, F = follow up

a Sample collected just before actual end of isatuximab infusion (within -5 min)

b Sample collected just before IMP administration.

c Required at screening/baseline (within 21 days prior to study drug administration).

d At 60 days, if patient is positive for ADA or the sample is inconclusive, additional ADA samples are required every 30 days (± 7 days) until sample is negative (sample ID: PF2, PF3 etc.).

e Sample collected up to 10 cycles. If ADA is positive at Cycle 10, one additional sampling for ADA evaluation should be collected 3 months later. No further ADA will be collected, even if the 3-month sample is positive.

f Post second analysis cut-off period, only ADA samples will be collected.

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3 LIST OF ABBREVIATIONS

ADA:	anti-drug antibody
ADCC:	anti-body-dependent cell mediated cytotoxicity
ADI:	actual dose intensity
AE:	adverse event
AESI:	adverse event of special interest
ALL:	acute lymphocytic leukemia
ALT:	alanine aminotransferase
ANC:	absolute neutrophil count
ASCT:	autologous stem cell transplantation
AST:	aspartate aminotransferase
BUN:	blood urea nitrogen
CBR:	clinical benefit rate
CD:	cluster of differentiation
CDC:	complement-dependent cytotoxicity
CLL:	chronic lymphocytic leukemia
CR:	complete response
CRF:	case report form
DLTs:	dose limiting toxicities
DOR:	duration of response
DRF:	discrepancy resolution form
ECOG:	eastern cooperative oncology group
eGFR:	estimated glomerular filtration rate
EoT:	end of treatment
FCBP:	female patients of childbearing potential
FcγR:	crystalizable fragment gamma receptor
FISH:	fluorescence in situ hybridization
FLC:	free light chain
GCP:	Good Clinical Practice
G-CSF:	granulocyte colony stimulating factor
HBc-Ab:	Hepatitis B Core Antibody
HBs-Ab:	Hepatitis B Surface Antibody
HBs-Ag:	Hepatitis B Surface Antigen
HBV:	Hepatitis B Virus
HIV:	human immunodeficiency virus
HLA:	human leukocyte antigens
IAC:	independent adjudication committee
IARs:	infusion associated reactions
ICH:	International Conference on Harmonisation
IMiDs:	immunomodulatory drugs
IMP:	investigational medicinal product

IMWG:	international myeloma working group
INR:	international normalized ratio
IRB:	institutional review board
Islands:	Isatuximab singLe agent study in japanese relapsed AND refractory multiple myeloma patientS
IV:	intravenous
kDa:	kilodalton
KIR:	killer cell Ig-like receptors
LDH:	lactate dehydrogenase
mAb:	monoclonal antibody
MAD:	maximum administrated dose
MCV:	mean corpuscular volume
MFC:	multiparametric flow cytometry
MHLW:	Ministry of Health, Labour and Welfare
MM:	multiple myeloma
MR:	minimal response
MRD:	minimal residual disease
MRI:	magnetic resonance imaging
MTD:	maximum tolerated dose
MUGA:	multigated acquisition
NAD:	nicotinamide adenine dinucleotide
NCI CTCAE:	national cancer institute common terminology criteria for adverse events
ORR:	overall response rate
OS:	overall survival
PD:	progressive disease
PFS:	progression free survival
PIs:	proteasome inhibitors
PK:	pharmacokinetic
PR:	partial response
PT:	preferred terms
Q2W:	once every other week
QTc:	QT interval corrected for heart rate
QW:	once every week
RD:	receptor density
RDI:	relative dose intensity
SAE:	serious adverse event
sCR:	stringent complete response
SD:	stable disease
SOC:	system organ class
SUSAR:	suspected unexpected serious adverse reactions
TEAE:	treatment emergent adverse event
TLS:	tumor lysis syndrome
TTP:	time to progression
ULN:	upper limit of normal
VGPR:	very good partial response

4 INTRODUCTION AND RATIONALE

4.1 INTRODUCTION

CD38 is a type II glycosylated 45 kilodalton (kDa) membrane protein that was identified as a lymphocyte marker (1). CD38 has a role in leukocyte homeostasis through modulation of hematopoietic cell survival and differentiation. 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.

Isatuximab (SAR650984) is a naked IgG1 kappa monoclonal antibody (mAb) directed against CD38, a receptor antigen expressed on hematopoietic cells. Isatuximab is produced in a mammalian cell line (Chinese Hamster Ovary) using recombinant DNA technology. The monoclonal anti-body isatuximab has 4 modes of action to kill target cells:

- Anti-body-dependent cell mediated cytotoxicity (ADCC)
- Complement-dependent cytotoxicity (CDC)
- Pro-apoptotic activity
- Inhibition of CD38 enzyme activity (6)

In preclinical tumor models in mice, it was active as a single agent and in combination with reference treatments, on several CD38-positive tumors in multiple hematological malignancies, including multiple myeloma (MM), non-Hodgkin's-lymphoma and leukemia.

4.2 MULTIPLE MYELOMA

MM 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 urinary light chain [paraprotein, M protein or M-component])(7). It is a disease predominantly associated with advancing age with 88.8% of

patients aged 60 years or older and only about 0.4% of cases are diagnosed in individuals under the age of 40. In 2011, there were an estimated 6,860 new cases of MM in Japan, with incidence rates 5.493 cases per 100,000 males and 5.249 cases per 100,000 females, but the incidence of MM for aged 85 years or older was 35.428 cases per 100,000 males and 19.316 cases per 100,000 females. In year 2003-2005, the 5-year survival rate was 32.6% [number of sample: 1,156] (8).

Patients with MM can experience bone pain, bone fractures, fatigue, anemia, infections, hypercalcemia, and kidney problems (9). The disease course for MM varies with the aggressiveness of the disease and related prognostic factors. Median survival is approximately 3 to 5 years; however, some patients can live longer than 10 years (10). Treatment options and survival are based on the patient's disease characteristics including disease stage, b-2 microglobulin level. Patients presenting with symptomatic active disease and in otherwise good physical health can receive consolidation therapy with autologous stem cell transplantation (ASCT) to enhance remission duration. However, all patients with MM will receive some form of induction chemotherapy to achieve cytoreduction, and to induce remission of their disease. The type of induction therapy will vary greatly depending on age, disease status and presence of other comorbidities. The newer agents including bortezomib (Velcade®), and lenalidomide (Revlimid®) are currently used most often as these agents demonstrate higher RRs and lower toxicity (9). Without autologous transplantation, patients typically have remission durations of between 18 and 36 months. Invariably, relapse occurs and additional therapy is needed. Treatment for relapse and/or refractory disease is often referred to as salvage therapy.

At present, the therapeutic options for relapsed and refractory patients, defined as disease that is nonresponsive to salvage therapy or progresses within 60 days of the last therapy in patients who achieved an MR or better to any previous therapy is very limited (11). In view of the lack of effective therapeutic options in relapsed and refractory myeloma patients, additional effective therapies are urgently needed.

TED14095 Study was designed to assess isatuximab monotherapy in Japanese patients with relapsed and refractory multiple myeloma who had exhausted available options, including a PI and an IMiD.

4.3 DESCRIPTION OF INVESTIGATIONAL MEDICINAL PRODUCT

Isatuximab is a naked IgG1 monoclonal antibody directed against CD38, and has 3 modes of action to kill target cells such as ADCC, CDC, pro-apoptotic activity and Inhibition of CD38 enzyme activity.

More detail information on compound description, previous human experience, pharmacology, toxicology and Pharmacokinetic Profile is provided in Investigators Brochure.

4.3.1 Clinical Experience with Single-agent of Isatuximab

Isatuximab is being tested both as a single agent and in combination with MM backbones in late and early lines. The TED10893 study, a first-in-human Phase I/II dose escalation safety and pharmacokinetic (PK) study of multiple IV administrations of isatuximab in patients with selected

CD38+ hematological malignancies including MM is ongoing. The Phase I dose escalation part has been completed back on 2014 and have explored several dose levels ranging from 0.0001 mg/kg up to 20 mg/kg Q2W or weekly. The first results of the Phase I art were presented at ASH2013 and ASCO 2014 (12, 13) and are described in the IB. In the latest part of the Phase I, three cohorts were enrolled sequentially, an expansion cohort of RRMM patients that were treated at 10 mg/kg (N= 19), a high risk cohort (based on clinical GEP and cytogenetics characteristics (n= 18 at 10 mg/kg) and a third cohort of 6 patients treated at 20 mg/kg QW. The ORR for patients treated at 10 mg/kg is 28% (n= 25, 6 from the dose escalation part and 19 from the expansion cohort). Amongst the patients treated in the high risk cohort the ORR was 22%. For the cohort of patients treated at 20 mg/kg QW the observed ORR was 29%.

The Phase II Stage 1 was designed to evaluate 4 cohorts with respectively the following doses and schedules: 3 mg/kg Q2W (N= 23), 10 mg/kg Q2W (N= 24), 10 mg/kg Q2W for 8 weeks followed by Q4W (N= 25), and 20 mg/kg Q2W for 4 weeks followed by Q2W (N= 25) in order to identify the dose and schedule of administration and move forward to the Stage 2. This first stage has been completed and the results are described below.

A summary of the most frequent TEAEs is presented in Table 1. Overall, isatuximab appeared to be well tolerated at all dose levels tested. At doses ≥10mg/kg, preliminary data show no difference in terms of type, incidence and severity of TEAEs. Infusion associated reactions occurred in approximately half of patients and were of Grade 1/2 for all patients except for 2 patients treated at 10mg/kg Q2W.Preliminary efficacy data show a dose response effect between 3 mg/kg Q2W (ORR<10%) and the doses ≥10 mg/kg (ORR ≥20 %). At doses ≥10 mg/kg, response rate was ranging from 20% to 29%, without clear dose response between the 10 mg/kg and the 20 mg/kg arms.

Table 1 - TED10893 – Phase 2 (Stage 1): Summary of TEAEs with an incidence ≥20% by system organ class and preferred term – All treated population (extracted from the database as of 6-Nov-2015)

Primary SOC	3mg/kg Q2W (N=23)		10mg/kg Q2W (N=24)		10mg/kg Q2W/Q4W (N=25)		20mg/kg QW/Q2W (N=25)	
Preferred Term	**All Grades**	**Grade≥3**	**All Grades**	**Grade≥3**	**All Grades**	**Grade≥3**	**All Grades**	**Grade≥3**
Any TEAEs	22 (95.7%)	16 (69.6%)	23 (95.8%)	16 (66.7%)	25 (100%)	14 (56.0%)	24 (96.0%)	11 (44.0%)
Infections and infestations	12 (52.2%)	7 (30.4%)	12 (50.0%)	6 (25.0%)	15 (60.0%)	2 (8.0%)	12 (48.0%)	4 (16.0%)
Upper respiratory tract infection	5 (21.7%)	2 (8.7%)	3 (12.5%)	0	7 (28.0%)	0	3 (12.0%)	0
Blood and lymphatic system disorders	10 (43.5%)	9 (39.1%)	4 (16.7%)	3 (12.5%)	6 (24.0%)	6 (24.0%)	10 (40.0%)	6 (24.0%)
Anemia	9 (39.1%)	8 (34.8%)	2 (8.3%)	1 (4.2%)	5 (20.0%)	5 (20.0%)	7 (28.0%)	4 (16.0%)
Thrombocyto-penia	4 (17.4%)	4 (17.4%)	0	0	0	0	8 (32.0%)	5 (20.0%)
Nervous system disorders	8 (34.8%)	1 (4.3%)	9 (37.5%)	1 (4.2%)	11 (44.0%)	0	7 (28.0%)	1 (4.0%)
Headache	4 (17.4%)	0	3 (12.5%)	0	8 (32.0%)	0	3 (12.0%)	0
Respiratory, thoracic and mediastinal disorders	13 (56.5%)	4 (17.4%)	15 (62.5%)	3 (12.5%)	18 (72.0%)	1 (4.0%)	17 (68.0%)	1 (4.0%)
Dyspnea	7 (30.4%)	1 (4.3%)	5 (20.8%)	1 (4.2%)	7 (28.0%)	1 (4.0%)	6 (24.0%)	0
Cough	3 (13.0%)	1 (4.3%)	8 (33.3%)	0	5 (20.0%)	0	7 (28.0%)	0
Gastrointestinal disorders	14 (60.9%)	2 (8.7%)	11 (45.8%)	0	17 (68.0%)	2 (8.0%)	11 (44.0%)	1 (4.0%)
Nausea	7 (30.4%)	0	8 (33.3%)	0	11 (44.0%)	0	6 (24.0%)	0
Diarrhea	5 (21.7%)	0	5 (20.8%)	0	8 (32.0%)	1 (4.0%)	5 (20.0%)	0
Vomiting	1 (4.3%)	0	3 (12.5%)	0	6 (24.0%)	0	6 (24.0%)	0
Constipation	7 (30.4%)	0	2 (8.3%)	0	2 (8.0%)	0	1 (4.0%)	0

Primary SOC	3mg/kg Q2W (N=23)		10mg/kg Q2W (N=24)		10mg/kg Q2W/Q4W (N=25)		20mg/kg QW/Q2W (N=25)	
Preferred Term	**All Grades**	**Grade≥3**	**All Grades**	**Grade≥3**	**All Grades**	**Grade≥3**	**All Grades**	**Grade≥3**
Musculoskeletal and connective tissue disorders	10 (43.5%)	2 (8.7%)	14 (58.3%)	2 (8.3%)	10 (40.0%)	2 (8.0%)	9 (36.0%)	2 (8.0%)
Back pain	3 (13.0%)	1 (4.3%)	7 (29.2%)	2 (8.3%)	3 (12.0%)	1 (4.0%)	4 (16.0%)	1 (4.0%)
General disorders and administration site conditions	15 (65.2%)	3 (13.0%)	15 (62.5%)	0	17 (68.0%)	2 (8.0%)	16 (64.0%)	1 (4.0%)
Fatigue	5 (21.7%)	0	5 (20.8%)	0	11 (44.0%)	0	8 (32.0%)	0
Chills	4 (17.4%)	0	5 (20.8%)	0	6 (24.0%)	0	3 (12.0%)	0
Chest discomfort	1 (4.3%)	0	4 (16.7%)	0	3 (12.0%)	0	6 (24.0%)	0
Injury, poisoning and procedural complications	10 (43.5%)	0	14 (58.3%)	2 (8.3%)	17 (68.0%)	2 (8.0%)	13 (52.0%)	1 (4.0%)
Infusion related reaction	9 (39.1%)	0	11 (45.8%)	2 (8.3%)	13 (52.0%)	0	13 (52.0%)	0

Only PTs with ≥20% in all grades in at least one group are presented with SOC.

4.4 RATIONALE

4.4.1 Study Rationale

Standard therapy of MM includes proteasome inhibitors (PIs) such as bortezomib, immunomodulatory drugs (IMiDs) such as lenalidomide, pomalidomide and thalidomide, and chemotherapy such as melphalan. While these agents have improved survival in MM, invariably resistance becomes problematic and patients succumb from their illness. Therefore, there is significant unmet medical need for the late line MM.

The CD38 antigen was identified as a negative prognostic marker of clinical importance in some hematological malignancies. As a consequence, monoclonal antibodies to CD38 have the potential to treat a variety of hematological indications including MM, B-cell NHL, chronic lymphocytic leukemia (CLL), acute myeloid leukemia and B-cell ALL. Plasma cells have a high concentration of CD38 receptors and could be an ideal target for this novel therapeutic agent. Myeloma cells have a slower growth fraction than other hematologic malignancies and may be more suitable for antibody therapy.

4.4.2 Study Design Rationale

This is an open-label, single arm, local multi-center study will be conducted in 2 parts, Phase I and Phase II.

The study comprises a Phase I part using traditional “3+3” design and a Phase II part at the recommended dose level. The Phase I part is designed to confirm the safety in Japanese at two doses where isatuximab has been already tested and deemed safe in global study, TED10893. Dose escalation or move to the Phase II part will be confirmed by the study committee after the first cycle of isatuximab of the last patient in the current cohort.

Phase II part will further evaluate the efficacy and safety of isatuximab at the recommended dose level defined in Phase I part. The single-arm design for the Phase II part is suitable for early evaluation of the efficacy and safety isatuximab in consideration of the target patients in this study. Also, since there is limited drug approved in patients with relapsed and refractory multiple myeloma who have previously received an IMiD and a proteasome inhibitor. According to the recent approved drug for the relapsed and refractory patients, an overall response rate target of 20 - 30% is considered to be clinically meaningful. (14)

4.4.3 Rationale of Dose and Regimen

In the dose escalation phase of study TED10893, isatuximab was administered by IV infusion once every 2 weeks at doses initially ranging from 0.0001 to 20 mg/kg and weekly at 10 mg/kg. The dose of 10 mg/kg Q2W was selected to be used for the treatment of the two cohorts described above (standard and high risk cohorts) based on an analysis of safety, PK and efficacy data.

The evaluation of isatuximab PK using both non-compartmental and modeling approaches show that there was a high variability of exposure within a given dose level and isatuximab has a nonlinear PK behavior with dose increases. Furthermore, the analysis of patients enrolled in the standard risk expansion cohort of TED10893 showed that some patients at 10 mg/kg Q2W still presented a biphasic elimination profiles. These data suggest that isatuximab exhibits nonlinear pharmacokinetics with target-mediated clearance dominating the elimination phase at low concentrations (10-20 µg/mL), which leads to low exposure in these patients and overall to a high inter-patient variability at this dose and schedule.

The TED10893 study was subsequently amended in order to explore the administration of isatuximab at 20 mg/kg weekly (in the Phase 1 part) and in a schedule consisting of weekly dosing for 4 weeks followed by every other week (in the Phase 2 part) and subsequently to explore additional doses and schedules of administration. The global recommended dose and schedule (see Section 6.2.1) was determined based on the response rate along with safety, PK, pharmacodynamics and overall efficacy.

A preliminary PK/PD analysis to evaluate the relationship between ORR and PK parameters was performed using an Emax model with pooled Phase 1 and Phase 2 Stage 1 data. This analysis showed that C_{trough} at week 4 (CT4W)) was a significant predictor of ORR. The probability of response to treatment increases as CT4W increases up to a plateau. This plateau was reached for CT4W values following a weekly administrations at 20 mg/kg, indicating that frequent administrations together with a high dose at the first cycle is needed to optimize the response (4 weekly administrations at 20 mg/kg). Based on safety, efficacy and PK/PD modeling and simulation, the selected dose and schedule of administrations for TED10893 Phase II Stage 2 (global recommended dose level) are: 20 mg/kg weekly (QW) for 4 weeks followed by 20 mg/kg every 2 weeks (Q2W).

Therefore, the initial dose level in this study will be 10 mg/kg QW for 4 weeks then 10 mg/kg Q2W which is the half of the global recommended dose (20 mg/kg QW for 4 weeks then Q2W), which is regarded as reasonably safe and well tolerated.

All patients will receive pre-medication (Section 8.3) for prophylaxis of infusion associated reactions (IARs).

5 STUDY OBJECTIVES

5.1 PRIMARY OBJECTIVE(S):

Phase I part

- To evaluate safety and tolerability of isatuximab in Japanese patients with relapsed and refractory multiple myeloma.

Phase II part

- To evaluate efficacy of isatuximab at recommended dose and to further evaluate the overall response rate (ORR) of isatuximab in Japanese patients with relapsed and refractory multiple myeloma.

5.2 SECONDARY OBJECTIVE(S):

- To evaluate the safety including immunogenicity of isatuximab. The severity, frequency and incidence of all adverse events will be assessed.
- To evaluate the pharmacokinetic (PK) profile of isatuximab in the proposed dosing schedule.
- To assess the efficacy using International Myeloma Working Group (IMWG) uniform response criteria.
- To assess the relationship between baseline CD38 receptor density on multiple myeloma cells and efficacy.

5.3 EXPLORATORY OBJECTIVE(S):

- To assess minimal residual disease (MRD) in patients achieving Complete Response (CR) and correlate with clinical outcome.
- To investigate the relationship of soluble CD38 and parameters of PK and clinical response.
- To investigate the relationship between multiple myeloma molecular subtype (as defined by cytogenetics/ FISH) and parameters of clinical response.
- To investigate the relationship between immune genetic determinants, immune phenotype and parameters of clinical response.

6 STUDY DESIGN

6.1 DESCRIPTION OF THE PROTOCOL

This is an open-label, non-randomized, single arm, local multi-center study conducted in 2 parts, Phase I and Phase II.

6.2 STARTING DOSE AND DOSE ESCALATION DESIGN

The rationale for selecting the starting dose and the dose escalation design are described in Section 4.4. Intra patient dose escalation is not permitted.

The dose escalation decision will be made based on dose limiting toxicities (DLTs) observed during Cycle 1 of the study treatment, and deemed to be related to the investigational medicinal product (IMP) in absence of clear evidence to the contrary after validation by the Study Committee, and if not related to a disease progression. Cumulative toxicities observed upon subsequent administrations should also be considered for the dose escalation process and the dose selection decision. The Study Committee role is described in Section 6.9.

The definitions of DLTs are provided in Section 9.1.1.

The Phase II part is to commence after the Cohort 2 of Phase I part has completed enrollment and DLT evaluation. Patients enrolled in Phase II part will be given the recommended dose determined in Phase I part.

6.2.1 Dose Levels

- Phase I part Cohort 1: 1/2 of global maximum administrated dose defined in TED10893 (ie. 10 mg/kg QW in Cycle 1 (4 weeks) followed by 10 mg/kg Q2W in subsequent cycles)
- Phase I part Cohort 2: Global recommended dose defined in TED10893 (ie. 20 mg/kg QW in Cycle 1 (4 weeks) followed by 20 mg/kg Q2W in subsequent cycles)
- Phase II part: Recommended dose level defined in Phase I part (10 mg/kg or 20 mg/kg QW in Cycle 1 (4 weeks) followed by Q2W in subsequent cycles)

No additional or intermediate dose level is planned in this study. Refer to Section 1.2 for the treatment schema.

6.2.2 Dose Escalation

In each cohort of Phase I part, at least 3 and a maximum of 6 patients will be treated and observed for DLT in Cycle 1 (4 weeks). At least 7 calendar days must pass after dosing the first patient before dosing the subsequent patients in Cohort 1. The dose escalation rule is described in Figure 3 and in below:

- If none of the 3 patients experience a DLT, the Cohort 2 or Phase II part starts.

- If 1 of the 3 patients experiences a related DLT, up to 3 additional patients are treated at the same dose level.
- If 2 or more patients experience a related DLT, the maximum administrated dose (MAD) is reached.

The above plan is summarized hereafter.

Table 2 - Dose escalation decision rule

Number of patients with DLT observed at each cohort	Dose escalation decision rule
DLT in 0/3	Proceed to the next cohort or phase
DLT in 1/3	Enroll 3 additional patients at the same dose level : • If 0 out of 3 additional patients experienced DLT (ie.1 DLT/6 patients) → proceed to the next cohort or phase • If 1 or more of 3 additional patients experienced DLT (ie. ≥2 DLTs/6 patients)→ Defines MAD and dose escalation is stopped. (If only 3 patients were treated at Cohort 1 and ≥2 DLTs/6 patients were confirmed in Cohort 2, 3 additional patients may be treated at the Cohort 1 dose level upon recommendation from the study committee.)
DLT in ≥2/3	Defines MAD and dose escalation is stopped. (If only 3 patients were treated at Cohort 1 and ≥2 DLTs/6 patients were confirmed in Cohort 2, 3 additional patients may be treated at the Cohort 1 dose level upon recommendation from the study committee.)
DLT evaluation Period: First cycle	

6.3 MAXIMUM ADMINISTERED DOSE / MAXIMUM TOLERATED DOSE

If a DLT in Phase I part at Cycle 1 is observed in at least 2 out of a maximum of 6 treated patients (≥33%) at a dose level, there will be no further dose escalation and this dose level will constitute the MAD. In this circumstance, the maximum tolerated dose (MTD) is defined as one level lower dose of the MAD.

Although the dose escalation process is guided by the safety evaluation during DLT observation period, cumulative or irreversible toxicities observed in subsequent administrations should also be considered for the dose escalation and dose selection decisions, upon agreement of the study committee.

In absence of MTD, the tested dose in Cohort 2 will be defined as the recommended dose of isatuximab and to be tested in the Phase II part of the study. PK, cumulative safety and efficacy data may be used to review the recommended dose level by the study committee as needed.

Dose and phase escalation algorism are illustrated in Section 1.3.

6.4 RETREATMENT OF PATIENTS

The patient must have recovered to his/her baseline status or Grade ≤1 for any toxicities before initiating the next dose. In those cases of clear clinical benefit, a patient can continue the study treatment until disease progression, unacceptable toxicity, or patient's decision.

6.5 DOSE DELAYS/ MODIFICATIONS

In this study, Cycle 1 consists of 4 isatuximab administrations and consecutive cycles consist of 2 isatuximab administrations.

A dose delay of up to 2 weeks is permitted in order for a patient to recover to their baseline status (see Section 6.4) or to accommodate scheduling issues (eg, holidays, weather, etc.). In case of a delay greater than 2 weeks the patient will be withdrawn from the treatment as per the investigator and the Sponsor decision. Exceptions allowed by the investigator and the Sponsor should be considered only for patients with clear objective clinical benefit.

Intra-patient dose and schedule modifications are not allowed.

6.6 GUIDELINES FOR MANAGEMENT OF ADVERSE EVENTS:

6.6.1 Management of Potential Infusion Associated Reactions (IARs)

Patient(s) should routinely receive pre-medications prior to isatuximab infusion as detailed in Section 8.3 to reduce the risk and severity of IARs commonly observed with monoclonal antibodies. Infusion associated reactions (NCI-CTCAE, version 4.03 term Infusion related reaction), including "allergic/hypersensitivity reactions", or "cytokine release syndrome/acute infusion reaction", are defined as AEs related to isatuximab with onset typically within 24 hours from the start of the infusion.

Refer to Appendix G for diagnoses Table 12 and symptoms typical of an infusion associated reactionTable 13.

General guidelines for the management of IARs are provided in Table 3.

Table 3 - Infusion associated reactions management

NCI CTCAE v. 4.03 criteria definition	Recommendation
Mild Grade 1 Infusion interruption not indicated; intervention not indicated	Continuation of isatuximab infusion is per the judgment of the Investigator following close direct monitoring of the patient's clinical status. Isatuximab infusion may be stopped at any time if deemed necessary. (If stopped, IAR will be classified as a Grade 2 as per NCI-CTCAE)
Moderate Grade 2 Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for <=24 hrs.)	Stop isatuximab infusion; Give additional pre-medication with diphenhydramine 25 mg IV (or equivalent) and/ or IV methylprednisolone 100 mg (or equivalent) as needed. Isatuximab may be resumed[a] only after patient recovery, with slower infusion rate and with close monitoring. (ie. infusion may be restarted at one half of the original infusion rates. 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). Important: Additional blood sampling during the AE is required for analysis of markers of potential TLS (uric acid, lactate dehydrogenase [LDH], BUN, creatinine, potassium, phosphate, ionized or corrected calcium).
Severe or life-threatening Grade 3 or 4 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. Life-threatening, consequences; urgent intervention indicated.	Stop isatuximab infusion; Give additional medication with diphenhydramine 25 mg IV (or equivalent) and/ or IV methylprednisolone 100 mg (or equivalent) and/or epinephrine as needed. Definitive treatment discontinuation. Important: Additional blood sampling during the AE is required for analysis of markers of potential TLS (uric acid, lactate dehydrogenase [LDH], BUN, creatinine, potassium, phosphate, ionized or corrected calcium).

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

6.6.2 Management of Potential Tumor Lysis Syndrome

General guidelines for the management of the tumor lysis syndrome are provided in Table 4.

Table 4 - Tumor lysis syndrome management

Symptom	Recommended Action
Laboratory Tumor Lysis Syndrome (LTLS): • ≥ 2 simultaneous abnormalities within 3 days prior to and up to 7 days after start of treatment • Uric acid >8 mg/dL (>475.8 µmol/L) • Potassium >6.0 mmol/L • Phosphorus >4.5 mg/dL (>1.45 mmol/L) Corrected calcium <7.0 mg/dL (<1.75 mmol/L) or ionized calcium <1.12 mg/dL (<0.3 mmol/L) [a] **Clinical TLS (CTLS)**: meeting criteria for LTLS in addition to one of the following complications, • Acute kidney injury: increase in the serum creatinine level of 0.3 mg/dL (26.5 µmol/L) or the presence of oliguria, defined as an average urine output of <0.5 mL/kg/hr for 6 hrs. • 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 • Dysrhythmia probably or definitely caused by hyperkaliemia	Omit isatuximab until all serum chemistries have resolved Ensure normal hydration; correct laboratory abnormalities, fluid overload, electrolyte or acid-based deviations Monitor TLS complications including renal functions Refer to "serious adverse drug reaction countermeasure manual" for TLS treatment[b]. Reinstitute isatuximab treatment at full doses after resolution

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

b Serious adverse drug reaction countermeasure manual for TLS: http://www.mhlw.go.jp/topics/2006/11/dl/tp1122-1e17.pdf
MHLW site: http://www.mhlw.go.jp/stf/seisakunitsuite/bunya/kenkou_iryou/iyakuhin/topics/tp061122-1.html

6.6.3 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 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-HBc Ab with/without anti-HBs Ab; 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.

6.7 DURATION OF STUDY PARTICIPATION

6.7.1 Duration of Study Participation for Each Patient

The study duration for an individual patient will include a screening period for inclusion of up to 21 days, the treatment period consisting of 28 day cycles and a follow-up period. Treatment with isatuximab may continue until disease progression, unacceptable adverse event or other reason for discontinuation.

After study treatment discontinuation, an end of treatment (EoT) visit will be done at 30 days to assess safety and ADA, and at 60 days for ADA. If the ADA is positive or the sample is inconclusive at Day 60 then ADA will be repeated every month (±7 Days) until ADA is negative. Survival status will be collected approximately every 3 months until death or second cutoff date (refer to Section 6.7.2), whichever comes first.

Patients with PR or better who come off treatment for reasons other than progression of disease will be followed for disease assessment every 4 weeks until progression or initiation of subsequent therapy, the second analysis cutoff date, whichever comes first.

For all patients, any study treatment-related adverse events, and all serious adverse events (regardless of their causal relationship to study treatment) ongoing at the time of study treatment discontinuation will be followed during the follow-up period until resolution or stabilization.

6.7.2 Determination of End of Clinical Trial (all patients)

The first analysis cutoff date for the statistical analysis for ORR will be 4 months after the date of the first dose of the last patient.

Second analysis cutoff date for the updated analysis of ORR and final analysis of time to events data will be 20 months after the date of the first dose of the last patient. Patients still on treatment at time of the second analysis cutoff date and who still continue benefiting from treatment with isatuximab will have the option to continue treatment under this protocol. Study will end after the completion of follow-up for all patients.

6.8 INTERIM ANALYSIS

No interim analysis is planned.

6.9 STUDY COMMITTEE

6.9.1 Study Committee

The Study Committee will be set up to include at least the external medical expert, the Principal Investigator of each participating sites in Phase I part and clinical team members from the Sponsor (Clinical Study Director and/or Medical Advisor), and ad hoc experts when appropriate. The Study Committee will regularly review safety data during the course of the study.

Confirmations to escalate dose or to initiate Phase II part, in accordance with description in the study protocol, will be made with the appropriate data review by the Study Committee at the end of Cohort 1 and Cohort 2 of Phase I part. A tracking form with all TEAEs or adverse event page and DLT page of the e-CRF will be distributed ahead of time and reviewed. Any of these communications will be documented in writing and communicated to all investigators in a timely manner.

6.9.2 Independent Adjudication Committee

The Independent Adjudication Committee (IAC) will be responsible for objectively assessing clinical response as defined by the IMWG response criteria on an ongoing basis in order to independently evaluate the drug effect of isatuximab on disease status.

The IAC will be comprised of multiple independent MM experts. They will be responsible for:

- Objectively assessing clinical response as defined by the IMWG response criteria on an ongoing basis in order to independently evaluate the drug effect of isatuximab on disease status
- The IAC will determine response using:
  - Serum and urine M-protein, free light chains (FLC), bone marrow aspirate/biopsy and corrected calcium
  - Radiologic results for bone lesions and plasmacytoma assessment

Detailed guidelines regarding the structure, function and decision-making mechanisms for this committee are described in the IAC charter.

7 SELECTION OF PATIENTS

7.1 NUMBER OF PATIENTS

Refer to Section 13.1.

7.2 INCLUSION CRITERIA

I 01. Males or females, age 20 years or older.

I 02. Patient must have a known diagnosis of symptomatic multiple myeloma.

I 03. Patients must have received at least 3 prior lines of therapies which must include treatment with an Immunomodulatory Drug (IMiD, eg. Lenalidomide, Pomalidomide or Thalidomide) AND a Proteasome Inhibitor (PI, eg. Bortezomib). The patients must have received an IMiD and a PI for ≥2 cycles or ≥2 months of treatment.
OR
Patients whose disease is double refractory to an IMiD and a PI. For patients who have received more than one type of IMiD and PI, their disease must be refractory to the most recent one. The patients must have received an IMiD and a PI for ≥2 cycles or ≥2 months of treatment.

I 04. Subject must have been responsive (ie. Minimal Response [MR] or better) to at least one prior line of therapy.

I 05. Refractory to the most recently received IMiD or PI included therapy (patient must progress during or within 60 days of completion of treatment with IMiD or PI).

I 06. Patients with measurable disease defined as at least one of the followings:

- IgG Type: Serum M-protein ≥1 g/dL (≥10 g/L)
- IgA Type: Serum M-protein ≥0.5 g/dL (≥5 g/L)
- IgD Type: Serum M-protein ≥0.5 g/dL (≥5 g/L)
- Urine M-protein ≥200 mg/24 hours

I 07. Patients with a Eastern Cooperative Oncology Group (ECOG) performance status ≤2

I 08. Life expectancy of at least 3 months.

I 09. Female patients of childbearing potential (FCBP) and male patients with female partners of childbearing potential who agreed to avoid pregnancy by using an adequate method of contraception for 2 weeks prior to screening, during and 6 months after the last administration of the IMP. Acceptable and effective methods of contraception includes 2 barrier method or 1 barrier method with a spermicide (spermicide is only available for purchase with condoms or diaphragm), oral hormonal contraception, intra-uterine

hormone-releasing system, vasectomy or intrauterine device. Adequate methods of contraception are provided as examples. Other acceptable and effective methods of birth control are also permitted.
A FCBP is a sexually mature woman who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 24 consecutive months.

I 10. Voluntary written informed consent before performance of any study-related procedure not part of routine medical care with the understanding that consent may be withdrawn by the subject at any time without prejudice to future medical care.

I 11. Ability to understand the purpose and risks of the study and provide signed and dated informed consent and authorization to use protected health information (in accordance with national privacy regulations).

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. Patients treated with any anti-CD38 agent.

E 02. Patients with disease measurable only by serum free light chain analysis.

E 03. Diagnosed or treated for another malignancy within 5 years prior to enrollment, with the exception of complete resection of basal cell carcinoma or squamous cell carcinoma of the skin, an in situ malignancy, or low-risk prostate cancer after curative therapy.

E 04. Prior anticancer therapy (chemotherapy, targeted agents, immunotherapy) within 21 days prior to the first drug infusion unless otherwise specified below,

- Alkylating agents (eg, Melphalan) within 28 days prior to the first dose of IMP.
- Steroids treatment (eg, prednisone >10 mg/day orally or equivalent except patients being Treated for adrenal insufficiency/replacement therapy or Treated for inhalation corticosteroids) within 14 days prior to the first dose of IMP.
- Participated in another clinical trial within 30 days prior to the first dose of IMP.

E 05. Patients treated with systemic radiation therapy within 4 weeks prior to the first dose of IMP
OR
Localized radiation therapy within 1 week prior to the first dose of IMP.

E 06. Major surgical procedure within 4 weeks prior to the first dose of IMP.

E 07. Patients with laboratory values of:

- Absolute neutrophil count (ANC) <1,000 cells/µl (1.0 x 10^9/L) (G-CSF cannot be used within the previous 7 days of the laboratory test. Pegylated G-CSF cannot be used within the previous 3 weeks of the laboratory test.).
- Platelet count <50,000/µL (without platelet transfusion during the 7 days previous to the laboratory test).
- Hemoglobin <8.0 g/dL
  (patients may receive red blood cell transfusion).
- AST or ALT >3.0 x upper limit of normal [ULN].
- Total bilirubin >2.0 x ULN.
- Estimating glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2 using revised equation for eGFR in Japanese (see Appendix H).
- Serum calcium (corrected for albumin) level >ULN
  (treatment of hypercalcemia is allowed and subject may be enrolled if hypercalcemia returns to normal with standard treatment).

E 08. Any toxicity Grade ≥2 (excluding alopecia, neutropenia or neuropathy) related to any prior anti-cancer therapy according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03.

E 09. Neuropathy Grade ≥3 or painful peripheral neuropathy Grade ≥2

E 10. History of significant cardiovascular disease unless the disease within the past 6 months is well-controlled.
Significant cardiac diseases include,

- Second/third degree atrioventricular block
- Significant ischemic heart disease
- QTc interval >450 msec at baseline (read by local cardiologist)
- Poorly controlled hypertension
- Congestive heart failure of NYHA Class III or worse (marked limitation of physical activity comfortable at rest, but less than ordinary activity causes fatigue, palpitation, dyspnea or anginal pain)
- LVEF <45%
  Significant ischemic heart disease (eg, angina) and poorly controlled hypertension are defined as medical conditions that, in the opinion of the Investigator or Sponsor, may interfere with patient's participation in the study, affect the interpretation of the study results, or patient's safety.

E 11. Previously received an allogenic stem cell transplant.

E 12. Diagnosed Crow-Fukase (POEMS) syndrome
OR
plasma cell leukemia.

E 13. Patients with known or suspected amyloidosis.

E 14. Patients with Waldenstrom's macroglobulinemia
OR
Multiple myeloma IgM subtype.

E 15. Patients with active infection requiring systemic antibiotics, antivirals or antifungals within 2 weeks prior to the first dose of IMP (except when used for chronic prophylaxis).

E 16. Known human immunodeficiency virus (HIV) or active hepatitis B or C viral infection.

E 17. Serious psychiatric illness, active alcoholism, or drug addiction that may hinder or confuse follow-up evaluation.

E 18. Any medical conditions that, in the Investigator's opinion, would impose excessive risk to the patient (eg, poorly controlled diabetes or poorly controlled hypotension).

E 19. Hypersensitivity or history of intolerance to boron or mannitol, sucrose, histidine (as base and hydrochloride salt) and polysorbate 80 or any of the components of study therapy that are not amenable to pre-medication with steroids and H2 blockers or would prohibit further treatment with these agents.

E 20. Female subjects who are pregnant or lactating.
If a female who stopped lactating before entering in the study, the female must stop lactating from the day of the first IMP administration until 6 months after the last administration of the IMP.

E 21. Any subject who, in the judgment of the Investigator, is likely to be noncompliant during the study, or unable to cooperate because of a language problem or poor mental development.

E 22. Any subject who cannot be contacted in case of emergency.

E 23. Any subject who is the Investigator or any sub-investigator, research assistant, pharmacist, study coordinator, or other staff thereof, directly involved in conducting the study.

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

8 STUDY TREATMENTS

8.1 INVESTIGATIONAL MEDICINAL PRODUCT

8.1.1 Pharmaceutical Form

The drug product (isatuximab) 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 for parenteral administration as a sterile, non-pyrogenic, injectable, colorless, 20 mg/mL concentrate for solution for infusion that may contain white to off-white 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.

The pH of the solution is 6.0 (5.7-6.3). The solution contains the following excipients: water for injection, 10% sucrose, 20 mM histidine (as base and hydrochloride salt) and 0.02% polysorbate 80.

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 period of time that will depend on dose administered and will be based on protein amount given per hour.

8.1.2 Dose of Drug per Administration

Isatuximab will be administered once every week (QW) in Cycle 1 (4 weeks) followed by once every other week (Q2W) in subsequent cycle until unacceptable toxicity, disease progression, withdrawal of consent and/or Investigator's decision (Section 1.2). Cycle N day 1 corresponds to cycle N-1 day 29.
For dose level and schedule, refer to Section 6.2.1.

The initial rate of infusion of isatuximab will be 175 mg/hour.

- First infusion:
  Initiate infusion rate at 175 mg/hour. In the absence of infusion associated reaction after 1 hour of infusion, increase the rate by 50 mg/hour increments every 30 minutes, to a maximum of 400 mg/hour.
- Subsequent infusions:
  Initiate infusion rate at 175 mg/hour. In the absence of infusion associated reaction after 1 hour of infusion, increase the rate by 100 mg/hour increments every 30 minutes, to a maximum of 400 mg/hour.

recovered, the infusion may be restarted at one half of the original infusion rates. 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.

8.1.3 Preparation, Reconstitution and Administration of isatuximab

Isatuximab concentrate for solution 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. Patients with local intolerance after peripheral IV infusion should receive next dose(s) using a central line. 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 dose administered and on the protein amount administered per hour (detailed above). Prior to dosing, each patient's dose will be individually prepared by the hospital pharmacist.

A 0.20 µm in-line filter is required for administration. Therefore for IV infusion, an IV tubing administration set with a 0.20-micron in-line filter will be used for infusion; if an in-line filter is unavailable, a 0.20-micron filter unit may be attached to the administration set before administration.

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

8.1.4 Stability under Light

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

8.1.5 Packaging and Labeling

The Investigational Medicinal Product (IMP) is packaged in 30 mL glass vials fitted with elastomeric closure.

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

8.1.6 Storage Conditions and Shelf Life

The IMP is stored at +2°C to +8°C. Storage of IMP should be in a secure area with restricted access.

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

8.2 METHOD OF REGISTERING PATIENTS TO THE STUDY

At the time of informed consent, the study site will assign each patient a unique patient identification number. After obtained the informed consent from the patient, the site should inform the registration center (pre-registration).

The patient number must be used for patient identification on all study-related documents (e-CRFs, clinic notes, laboratory samples, CT scans, MRIs, etc). After confirmation of all eligibility, the site should inform the registration center (registration).

The site should inform the registration center at the EoT (30 days [+/- 7 days] after last IMP administration) and at the Follow-up (60 days [+/- 7 days] after last IMP administration) as well.

The above mentioned procedures will be applied to both Phase I part and Phase II part.

8.3 PRE-MEDICATION

Patient(s) should routinely receive pre-medications prior to isatuximab infusion to reduce the risk and severity of IARs commonly observed with monoclonal antibodies. The recommended pre-medication is: on the day of isatuximab infusion, 100 mg methylprednisolone (or equivalent) will be administered via intravenous (IV) or oral (PO) route along with diphenhydramine 50 mg IV (or equivalent); ranitidine 50 mg IV (or equivalent) and acetaminophen 650 to 1000 mg PO. The pre-medication regimen should be initiated at least 15 minutes (but no longer than 60 minutes) prior to isatuximab infusion and isatuximab administration is to be initiated as soon as the pre-medication regimen is completed. The order of pre-medications should be acetaminophen, ranitidine, diphenhydramine, and then methylprednisolone when methylprednisolone is administered via IV route. When methylprednisolone is given via PO route, the order of pre-medications will be methylprednisolone (PO), acetaminophen (PO), ranitidine (IV), diphenhydramine (IV). General guidelines for the management of the IARs are provided in Section 6.6.1. If an IAR is observed, patients must also be informed of the potential risk of recurrent IARs.

Patients who do not experience an IAR during the 4 consecutive administrations of isatuximab may have the need for subsequent pre-medication reconsidered at the investigator's discretion in consultation with the Sponsor.

If a subject experiences a Grade 1 to 2 infusion-related AE during infusion, the following can be initiated:

- The methylprednisolone 100 mg IV (or equivalent) and diphenhydramine 25 mg IV (or equivalent) can be given.

8.4 RESPONSIBILITIES

The Investigator, sub-investigator or the hospital pharmacist 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 the regulatory requirements.

The IMP will be dispensed in accordance with the Investigator's or sub-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 the Investigator will supply IMP to a third party, allows the IMP to be used other than as directed by this clinical trial protocol, or disposes of IMP in any other manner.

8.4.1 Treatment Accountability and Compliance

Administration of the IMP will be supervised by the Investigator or sub-investigator.

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.

8.4.2 Return and/or Destruction of IMPs

All used and partially-used IMPs will be destroyed at the study site after an accurate accountability has been performed, signed by the Investigator or the pharmacist, and reconciliated by the Sponsor monitoring team.

All unused IMP will be destroyed on site, after final batch accountability has been validated by the Sponsor monitoring team representative, according to the standard practices of the site and /or to local regulations. The Investigator will not destroy unused IMP unless the Sponsor provides written authorization or according to local procedures.

The destruction is recommended to be performed at site depending on IMP specificities and local requirements but IMP can be returned to the Sponsor for destruction.

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

8.5 CONCOMITANT TREATMENT

All treatments being taken by the patient 7 days prior to first dose of IMP, at any time during the treatment period and up to 30 days after the last dose are regarded as prior and concomitant treatments respectively. These will be reported 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:

- Palliative radiotherapy may be given for control of pain for palliative intents. Sanofi should be notified to obtain approval if palliative radiotherapy is being considered, and prior to resuming therapy on the study. 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 and radiological assessments of the tumor.
- 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.

The following concomitant treatments are not permitted during this study:

- Concurrent treatment with other investigational drugs.
- Concurrent treatment with any other anticancer therapy not specified in this protocol, including immunotherapy, hormonal therapy, targeted therapy, steroid therapy or biological therapies.
- Prophylactic use of hematopoietic growth factors (eg, Pegylated G-CSF) during the DLT observation period (1st Cycle) in Phase I part.

9 ASSESSMENT OF INVESTIGATIONAL MEDICINAL PRODUCT

9.1 SAFETY

The major purpose of the Phase I part is to determine safety and tolerability of isatuximab when administrated as an IV infusion to Japanese patients with relapsed and refractory multiple myeloma. A secondary objective of the Phase II part is to evaluate the safety of isatuximab when administered at recommended dose defined in Phase I part as an IV infusion to Japanese patients with relapsed and refractory multiple myeloma.

The safety profile will be assessed from the findings of physical examination (preferably by the same physician), laboratory tests, etc., and will be based on incidence, severity (as graded by the NCI CTCAE v. 4.03, see Appendix B), and cumulative nature of AEs as defined in Section 10.4.

The NCI CTC AE v 4.03(15) can be accessed through the NCI website at http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf

9.1.1 Dose-limiting Toxicities in Phase I part

For the purposes of dose escalation and determination of tolerability of recommended dose, only DLTs that occur during the first cycle of treatment will be considered for decisions regarding dose escalation and phase transition. The standard duration of DLT evaluation period is 28 days however treatment delay up to 14 days is allowed in the first cycle. The detailed DLT evaluability is defined in Section 13.3.2.

Hematologic DLTs are defined as any of the following, attributed to isatuximab:

- Grade 4 neutropenia lasting for ≥5 days.
- Grade 3 to 4 neutropenia complicated by fever
  OR
  Microbiologically or radiographically documented infection.
- Grade 4 thrombocytopenia lasting for ≥5 days.
- Thrombocytopenia if required platelet transfusion.
- Treatment delay >14 days due to hematologic toxicity.

Non-hematologic DLTs are defined as any of the following, attributed to isatuximab:

- Grade ≥3 non-hematological AE, excluding Grade 3 fatigue, Grade 3 to 4 electrolyte abnormalities, Grade 3 nausea/vomiting/diarrhea if responsive to optimal medical management within 48 hours or allergic reaction/ hypersensitivity attributed to isatuximab.
- AE that requires treatment delay for >14 days.
- Grade 3 neuropathy will not be considered as a DLT if the patient began therapy with Grade 2 neuropathy at baseline.

Any other toxicity that the Investigator and the sponsor deem to be dose limiting, regardless of the grade, may also be considered as DLT.

DLTs will be handled as well as Adverse Event of Special Interest (AESI) (See Section 10.5.5). As such, the investigators will be required to report them to Sanofi within 24 hours of investigator awareness of each event.

Before starting Cohort 2 and Phase II part, all safety data, and the reported potential DLTs will be reviewed to determine their relationship to the IMP. Starting Cohort 2 or Phase II part decisions will be based on the assessment of IMP related DLTs by the Study Committee.

Dose escalation will be stopped if ≥33% (≥2 in up to 6 patients) of patients experienced an IMP related DLT observed during the first cycles of treatment (4 weeks), according to the definition of MAD.

Although the DLT evaluation process is guided by the safety evaluation during the first cycle of treatment, cumulative toxicities observed in subsequent administrations should also be considered for the dose escalation and the dose selection decisions, upon agreement within the Study Committee.

9.1.2 Adverse Events

Safety profile will be based on incidence, severity (as graded by the NCI CTC AE v. 4.03), and cumulative nature of treatment-emergent AEs (TEAEs). TEAEs are defined as AEs that develop, worsen or became serious during the on-treatment period. For this study, the on-treatment period will be defined as the period from the time of first dose of IMP to at least 30 days after last administration of the IMP. Each patient will be assessed preferably by the same physician for AEs and according to the NCI CTC AE v. 4.03 classification.

Adverse events will be coded to “Preferred Term (PT)” and associated primary “System Organ Class (SOC)” using MedDRA (Medical Dictionary for Regulatory Activities). AEs will be summarized with respect to the type, frequency, severity, seriousness, and relatedness.

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 Vital Signs

Please refer to “Study Procedures” Section 12 for assessment timings. Vital signs consist of examination of blood pressure, heart rate, temperature, and respiration rate.

9.1.6 ECG

Please refer to "Study Procedures" Section 12 for assessment timings of the 12-lead ECG and 2-D Echocardiogram/ MUGA.

9.1.7 Chest X-Ray

Please refer to "Study Procedures" Section 12 for assessment timings. Chest X-Ray to be performed for assessment of pulmonary disease condition.

9.1.8 Immunogenicity

Human anti-drug antibodies to isatuximab will be assessed throughout the study. Blood samples will be collected for ADA detection according to the PK flowchart (see Section 1.7 or Section 1.8).

In case of positivity or inconclusive sample at 60 days post last IMP administration, additional assessment of ADA will be performed every month until sample is negative. If ADA is positive at Cycle 10, one additional sampling for ADA evaluation should be collected 3 months later. No further ADA will be collected, even if the 3-month sample is positive.

Detailed instructions for ADA sample preparation and shipping will be provided to the study sites in a separate Laboratory Manual.

9.1.9 Other Clinical Assessments

- Safety laboratory assessments: Please refer to "Study Procedures" Section 12.
- Results of additional procedures (such as karyotype, fluorescence in situ hybridization [FISH], etc.) performed as part of standard of care to assess the current disease status may also be collected.

9.2 PHARMACOKINETIC EVALUATION

9.2.1 Sampling Time and Sample Blood Volume

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

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

The sampling times for blood collection can be found in the PK Flow Chart (Section 1.7 or Section 1.8).

9.2.2 Pharmacokinetic Sample Handling Procedure

Detailed instructions for PK sample preparation and shipping are summarized in Table 5. Further details will be provided to the study sites in a separate Laboratory Manual.

Table 5 - Summary of handling procedures

	PK	ADA
Sample volume:	3 mL of blood	3 mL of blood
Anticoagulant Tube Type:	Blood will be collected into EDTA tube	Blood will be collected into EDTA tube
Handling procedure	Blood with centrifuged at 2000g for 20 min at 4°C within 30 min of sampling time	Blood with centrifuged at 2000g for 20 min at 4°C within 30 min of sampling time
Plasma aliquot split	2 samples, 0.5 mL in aliquot 1 and the remaining in aliquot 2	2 samples, 0.5 mL in aliquot 1 and the remaining in aliquot 2
Plasma storage conditions	Polypropylene tubes with screw caps and frozen promptly (within 1 hour after collection of blood) at (-)80°C.	Polypropylene tubes with screw caps and frozen promptly (within 1 hour after collection of blood) at (-)20°C.
Plasma shipment conditions	Dry ice	Dry ice

9.2.3 Bioanalytical Method

A brief outline of the bioanalytical assay is given in Table 6. Also, see laboratory manual.

Table 6 - Bioanalytical method for isatuximab in plasma

Analyte	isatuximab	ADA
Matrix :	Plasma	Plasma
Analytical technique :	ELISA	Pand A
Lower limit of quantification:	0.5 ng/mL	n.a.
Assay volume:	100 µL	100 µL
Site of bioanalysis:	Sanofi R&D DSAR, [redacted]	Sanofi R&D DSAR, [redacted]

9.2.4 Pharmacokinetic Parameters

Pharmacokinetic analyses will be carried out in the Sponsor Disposition, Safety, and Animal Research department. Pharmacokinetic parameters will be calculated with PKDMS software (Pharsight), using non-compartmental methods from plasma isatuximab concentrations obtained after 1st administration.

The parameters will include, but may not be limited to the following:

Table 7 - List of pharmacokinetic parameters and definitions

Parameters	Drug	Matrix	Definition/calculation
C_{eoi}	isatuximab	Plasma	Concentration observed at the end of infusion
C_{max}	isatuximab	Plasma	Maximum concentration observed
C_{trough}	isatuximab	Plasma	Plasma concentration observed just before treatment administration during repeated dosing
t_{max}	isatuximab	Plasma	First time to reach C_{max}
$AUC_{1\ week}$	isatuximab	Plasma	Area under the plasma concentration versus curve calculated using the trapezoidal method over the dosing interval

Blood concentrations of isatuximab will be also used for population PK analysis by non-linear mixed effects modeling. Additional details of the analysis plan and the results could be provided in a separate document.

9.3 EFFICACY

9.3.1 Criteria for Response

ORR is defined as the proportion of patients with stringent complete response (sCR), complete response (CR), very good partial response (VGPR), and partial response (PR) based on responses as assessed using the International Myeloma Working Group (IMWG) Uniform Response Criteria (see Appendix C). Response evaluation will be performed on a monthly basis. The best overall response for each patient will be determined by independent adjudication committee.

All responses (sCR, CR, VGPR, PR) should be confirmed on 2 consecutive laboratory efficacy parameters assessments according to study flow-chart (approximately 4 weeks interval). Stable disease (SD) does not require confirmation. Disease progression by paraprotein should be confirmed on within the first 4 weeks after last assessment. Disease progression based on imaging, bone marrow plasma cell percentage, or hypercalcemia (not attributable to any other cause) do not need to be confirmed.

Clinical benefit rate (CBR): defined as the proportion of patients with sCR, CR, VGPR, PR or MR according to IMWG criteria.

Duration of response (DOR): defined as the time from the date of the first response to the date of subsequent progressive disease (PD) or death, whichever happens earlier. In the absence of the confirmation of subsequent disease progression or death before the analysis cut-off date, the DOR will be censored at the date of the last valid assessment performed before the analysis cut-off date or date of initiation of new anticancer treatment, whichever is earlier. DOR is determined only for

patients who have achieved a response of ≥PR. DOR will not be calculated for patients that do not achieve a response.

Overall survival (OS): defined as the time interval from the date of first study treatment administration to death due to any cause. In the absence of the confirmation of death before the analysis cutoff date, OS will be censored at the last date the patient is known to be alive or at the study cutoff date, whichever is earlier.

Progression free survival (PFS): defined as the time interval from the date of first study treatment administration to the date of the first assessed disease progression or death due to any cause, whichever comes first. In the absence of disease progression or death before the analysis cutoff date, or the date of initiation of new anticancer treatment, PFS will be censored at the date of the last valid assessment performed before the cutoff date or the date of initiation of new anticancer treatment, whichever is earlier.

Time to progression (TTP): defined as the time interval from the date of first study treatment administration to the date of the first assessed disease progression. In the absence of disease progression before the analysis cutoff date, or the date of initiation of new anticancer treatment, TTP will be censored at the date of the last valid assessment performed before the cutoff date or the date of initiation of new anticancer treatment, whichever is earlier.

Response evaluation will include:

- M-protein quantification (serum and 24 hours urine)
- Serum free light chain (FLC) levels
- Bone marrow aspiration and/or biopsy
- CT/MRI scan of plasmacytoma (medullary and extramedullary)
- Bone skeletal survey
- Corrected serum calcium

9.4 SPECIFIC ASSESSMENTS

9.4.1 CD38 Receptor Density Assessment

Brief instructions for the sample handling and the analytical method are summarized in Table 8. Further details will be provided to the study sites in a separate Laboratory Manual.

Table 8 - Sample handling procedure and Analytical method for CD38 receptor density assessment

Sample handling procedure		Analytical method	
Sample volume:	2 mL of bone marrow	Matrix:	bone marrow
Anticoagulant Tube Type:	Bone marrow will be collected into EDTA tube	Analytical technique:	Flow cytometry
Handling procedure	Refer to operator manual	Lower limit of quantification:	n.a.
Plasma aliquot split	Refer to laboratory manual	Assay volume:	2 mL
Plasma storage conditions	Refer to laboratory manual	Site of bioanalysis:	Sanofi R&D DSAR
Plasma shipment conditions	Ambient temperature		

9.4.2 Minimal Residual Disease Assessment

- Minimal residual disease (MRD) will be assessed by next generation sequencing of leukocyte DNA in bone marrow samples from CR patients and correlated with parameters of clinical response.
  Traditional method to measure MRD include multiparametric 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 aspirate/biopsy samples will be collected at baseline/screening and the time of CR.

9.4.3 Exploratory Biomarker Studies

Please refer to "Study Procedures" Section 12 for assessment timings.

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

- Bone marrow aspirates/biopsy sample will be collected at screening/ baseline. Cytogenetics analyses will be performed and correlated with parameters of clinical response. Suggested FISH probes include, but may not limited to, those for del(17p), t (4, 14) and t(14; 16).
- Correlation of immune genetic determinants (FcγR polymorphisms, HLA and KIR genotypes) with parameters of clinical response. DNA will be extracted from peripheral blood leukocytes. Sequence-specific PCR and Sanger sequencing of selected exomes will be performed. These analyses will not reveal the entire nucleotide sequence of the target gene.
- Correlation of immunophenotype in bone marrow and/or peripheral blood with parameters of clinical response. Immune cell populations (including B-cell, T-cell and NK cell subsets) 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 will be correlated with response to isatuximab.
- Soluble CD38 levels in peripheral blood will be correlated with parameters of PK and clinical response. Other soluble factors in blood may also be analyzed.

Special procedures for processing and shipping of biomarkers samples are described in detail in the laboratory manual.

No sample banking is planned. The samples that are remaining after the testing may be used for potential exploratory research related to the drug action and/or effect of isatuximab pending evolving literature. DNA samples will not be used for broad exploratory unspecified disease or population genetic analysis.

All remaining samples will be discarded within 5 years after the end of the study. The remaining samples will be discarded if the patients withdrew from the study consent.

These samples will remain labelled with the same identifiers than the one used during the study (ie, subject ID). They will be transferred to a Sanofi site (or a subcontractor site) which can be located outside of the country where the study is conducted. The Sponsor has included safeguards for protecting subject confidentiality and personal data.

10 PATIENT SAFETY

10.1 SAFETY ENDPOINTS ASSESSED IN THIS TRIAL

The NCI CTCAE v.4.03 will be used in this study to grade clinical and laboratory AEs.

Please also refer to Section 9.1.

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. For IARs, please refer to Section 6.6.1.

10.3 ADVERSE EVENTS MONITORING

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

10.4 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 dyscrasia, or convulsions) or asymptomatic ALT increase ≥10 ULN that does not result in hospitalization, or development of drug dependency or drug abuse.

10.5 OBLIGATION OF THE INVESTIGATOR REGARDING SAFETY REPORTING

10.5.1 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 e-CRF.

Whenever possible, diagnosis or single syndrome should be reported instead if 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 10.5.5).

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 (see Section 10.5.5).

10.5.2 Serious Adverse Events, Adverse Events of Special Interest, Pregnancy and Symptomatic Overdose

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

- ENTER (within 24 hours) the information related to a SAE, an AESI, a pregnancy report or a symptomatic overdose 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.
- During the Phase I part, the monitoring team will notify the study investigators of the occurrence of DLTs within 24 hours.

10.5.3 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 SAE 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.

10.5.4 Treatment discontinuation due to non-serious adverse event

In the case of a treatment discontinuation due to a non-serious 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 "drug withdrawn", 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.

10.5.5 Adverse Event of Special Interest

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

The following adverse events are considered AESIs:

- Acute infusion associated reactions (IARs; see Appendix G for diagnoses and symptoms typical of an IAR). An IAR is a related adverse event with onset within 24 hours from the start of the infusion. As defined in Section 10.5.1, a main diagnosis and individual symptoms should be reported in the e-CRF. However, only the main diagnosis will be reported as AESI.

- During Phase I part, all protocol–defined potential or IMP related DLTs (as defined in Section 9.1.1) 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 adverse event. The Investigator will attach the DLT-specific CRF page to the DLT/AESI form.

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).

- Symptomatic overdose (serious or non-serious) with IMP
  An overdose (accidental or intentional) with the IMP is an event suspected by the Investigator.

10.5.6 Pregnancy

- Pregnancy will be recorded as an AE in all cases. It will be qualified as a SAE only if it fulfils SAE criteria.
- In the event of pregnancy, IMP should be discontinued and the Sponsor should be informed immediately (within 24 hours), even if the event does not fulfil the criteria for a SAE, using the AE form together with the SAE complementary form to be sent to the representative of the monitoring team whose name, address and fax number appear on page 2 of this protocol.
- 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.

10.5.7 Symptomatic Overdose

In case of accidental or intentional overdose of IMP (at least 30% above the intended administered dose at each cycle expressed in unit per body weight) with any symptoms, 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 e-CRF. Asymptomatic overdose has to be reported as a standard AE.

10.5.8 Laboratory Abnormalities

Laboratory abnormalities should be monitored, documented, and managed according to the related flowchart (see Section 1.4 and Section 1.5). Laboratory values will be reported in the appropriate pages of e-CRF.

Laboratory abnormalities should be reported as AE only in case they lead to an action on study treatment or if there are serious (see Section 10.5.1).

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 [SUSARs]), to the regulatory authorities, Institutional Review Boards (IRBs) as appropriate and to the Investigators.
- All SAEs those are expected and at least reasonably related to the IMPs, AESI (see list in Section 10.5.5) to the regulatory authorities, according to local regulations.
- During Phase I part, when cohorts of more than one patient begin accruing, the monitoring team will notify the study investigators of the occurrence of DLTs and AESI within 24 hours.

Any AE not listed as an expected event in the Investigator's Brochure or in this protocol will be considered as unexpected.

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

Patients are free to withdraw their participation at any time during this clinical trial. The investigator has the right to remove any subject from treatment with study drug or participation in the study. However, the Sponsor requests that the investigator consult with the Sponsor Clinical Study Director before prematurely removing a subject.

Patients, who decide to withdraw from the study, or meet the withdrawal criteria, should undergo an End of Treatment visit. See Section 12.4.

Pregnancy in female subjects 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

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 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).
- 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.
- Sponsor decision to discontinue the study.

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 6.6.3.

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.

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

11.1.3 Temporary Treatment Discontinuation with Investigational Medicinal Product(s)

Temporary treatment discontinuation may be considered by the Investigator because of suspected AEs. Reinitiation of treatment with the IMP will be done under close and appropriate clinical/and or laboratory monitoring once the Investigator has deemed it appropriate according to his/her best medical judgment and considers that the causality of the AE was unlikely related to the IMP(s). The patient must continue to meet the safety related selection criteria (refer to Section 7.2 and Section 7.3).

For all temporary treatment discontinuations, the duration of the discontinuation should be recorded by the Investigator in the appropriate pages of the e-CRF.

11.2 REPLACEMENT OF PATIENTS

During the Phase I 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 6.3.

Patients treated in the Phase II part of the study who are withdrawn from study treatment will not be replaced.

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 and described below. The results of the evaluation will be recorded in the e-CRF pages until the patient is not followed anymore. After the screening/ baseline visit, all eligible patients included in the study will have a visit on site as detailed below. A complete visit will be performed at EoT (30 days +/- 7 days after the last administration of the IMP). The patients will be followed until recovery or consolidation of any SAE or IMP-related AE. Additionally, ADA samples are required (60 days +/- 7 days after last IMP administration).

12.2 BASELINE EVALUATION

The pretreatment examinations are to be performed within 21 days (unless specified otherwise) prior to the first administration of the IMP. The informed consent form will have to be signed by the patient before any procedure specific to the study can be performed. The following assessments are to be performed at this visit.

If the patient cannot be registered within 21 days of informed consent, the same patient may be re-screened after discussion with the sponsor, provided that there are no persisting safety concerns for patient's study participation. The informed consent form will have to be re-signed by the re-screened patient before starting re-screening procedures. New patient number will be given for the re-screened patients.

- Inform to the registration center
- Medical History and Clinical Examinations:
  - Demography: Includes date of birth, gender and race.
  - Medical/Surgical History: includes relevant history of previous/associated pathologies other than multiple myeloma.
  - Disease History: includes date of initial diagnosis of MM, subtype, stage of international stating system (see Appendix F), previous anti-MM therapy (drug name by line of therapy, start and end date of administration, reason for discontinuation, best response and date of progression/relapse), disease status at inclusion (refractory to last IMiD or PI included therapy). In addition, results of additional procedures (such as karyotype, fluorescence in situ hybridization (FISH), etc.) performed as part of standard of care to assess the current disease status may also be collected.
  - Physical Examination: consists of examination of major body systems including neurological, digestive, extramedullary myeloma localizations, respiratory, hepatomegaly, splenomegaly, lymphadenopathy.
  - Weight and Height
  - Vital signs: includes heart rate, temperature, respiratory rate, blood pressure.

  - Performance Status (ECOG)
  - Prior medications given within 7 days prior to first dose.
  - Adverse events/serious adverse events are to be reported from the signing of the informed consent.
- 12-lead ECG
- 2-D Echocardiogram or Multigated Acquisition (MUGA) scan
- Chest X-ray
- Laboratory Assessments:
  - Hematology: includes hemoglobin, hematocrit, RBC, WBC with differential, Mean Corpuscular Volume (MCV) and platelet count.
  - Serum Chemistry: includes SGOT (AST), SGPT (ALT), bilirubin (total and direct), alkaline phosphatase, lactate dehydrogenase (LDH), fasting glucose, sodium, potassium, chloride, magnesium, calcium/ corrected serum calcium, phosphate, uric acid, blood urea nitrogen (BUN), serum creatinine and eGFR (Revised equations for eGFR in Japanese), albumin and total protein.
  - Coagulation: includes PT or INR, and aPTT.
  - Urinalysis: includes blood, protein, glucose, pH, ketones, bilirubin, leucocytes, nitrites and specific gravity.
  - Pregnancy Test: women of child bearing potential must have a negative serum pregnancy test result within 7 days prior to first IMP administration.
  - HBs-Ag, HBc-Ab, HBs-Ab, HCV-Ab tests. If HBc-Ab and/or HBs-Ab positive at baseline, HBV-DNA test is required prior to registration. If history of HBV infection is suspected, monitoring of HBV-DNA is recommended on Day 1 of each cycle.
  - HIV-Ab tests (Testing is not required unless there is a suspicion of virus infection.)
- Disease Assessment:
  - Myeloma-specific Lab Tests:
    - M-protein quantification (serum electrophoresis and immunofixation and 24-hour urine collection for Bence Jones protein with urine electrophoresis and immunofixation)
    - Serum free light chain levels
    - Serum β2-microglobulin
    - Immunoglobulins: IgG, IgA, IgM, IgD and IgE
    - Corrected serum calcium
  - Bone marrow aspiration to be performed.
    In case of dry-tap, bone marrow biopsy to be performed.
    (For subsequent cycle, only required to confirm a CR)
  - Extramedullary Disease: Radiologic imaging (CT/MRI scan) of plasmacytoma.

- Skeletal survey: X-ray.
  X-ray skeletal survey should include radiographs of the following: lateral skull; Postero-Anterior (PA) chest; Antero-Posterior(AP) and lateral cervical spine; AP and lateral thoracic spine; AP and lateral lumbar spine; AP pelvis; AP upper extremities, shoulder to elbow, bilateral; and AP lower extremities, hip to knee, bilateral.

- Biomarker/ Exploratory Studies:
  - CD38 Receptor Density in bone marrow.
  - Cytogenetics/FISH in screening/ baseline bone marrow sample. Probes for fluorescence in situ hybridization (FISH) analysis may include t(4;14), t(14;16) and del(17p).
  - Immune phenotyping (bone marrow).
  - MRD assessment in bone marrow: baseline sample will be used as reference to determine major disease clone(s).
    (For subsequent cycle, only required to confirm a CR)

All patients who signed the study informed consent form will be assigned a patient number. Each patient will receive an incremental identification number corresponding to his/her order of enrollment in the study. Those patients, who meet all the inclusion criteria and none of the exclusion criteria, will be eligible for registration in the study. A written confirmation of each eligible patient identification and treatment dose level will be forwarded to the Investigator.

12.3 DURING THE TREATMENT PERIOD

See flow charts in Section 1.4 and Section 1.5

12.3.1 Day 1 of Each Cycle

All patients who are going to continue study treatment after completing Cycle 1 must sign a second ICF before commencing IMP administration. (Phase I part Cycle 2 only)

The evaluations below are to be performed prior to first IMP administration on Day 1 of each cycle unless otherwise indicated.

- Inform to the registration center (Cycle 1 only)
- Patient Registration (Cycle 1 only)
- Clinical Examinations:
  - Physical Examination
  - Performance Status (ECOG)
  - Weight
  - Vital signs
    (to be taken pre-infusion, mid-infusion (when half the volume is administered), and end-infusion on days of IMP administration. If the infusion rate changes because of an

infusion-associated reaction, vital signs should be monitored every hour and at the end of the infusion.)

- AE/ SAE assessment
- Concomitant Medications

- Laboratory Assessments:
  - Hematology
    (not required to be repeated at Cycle 1 Day 1 if screening labs were performed within 3 days prior to first IMP administration)
    Perform direct and indirect coombs tests prior to the first IMP administration.
  - Serum Chemistry
    (not required to be repeated at Cycle 1 Day 1 if screening labs were performed within 3 days prior to first IMP administration)
  - If history of HBV infection is suspected, perform HBV-DNA test on Day 1 of each cycle.
  - Urinalysis: Quantitative urinalysis will be needed if hematuria is observed or clinically indicated.
    (not required to be repeated at Cycle 1 Day 1 if screening labs were performed within 3 days prior to first IMP administration)
  - Pregnancy Test: Not required at Cycle 1 Day 1 if a negative serum pregnancy test result available within 7 days prior to first IMP administration. Urine test can be used at Day 1 of each subsequent cycle.
  - 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 (Phase II part, Subsequent Cycles only).
- Disease Assessment:
  - Myeloma-specific Lab Tests:
    (not required to be repeated at Cycle 1 if screening labs were performed within 3 days prior to first IMP administration)
    - M-protein quantification (serum and 24-hours urine)
    - Serum β2-microglobulin to be performed if clinically indicated
    - Immunoglobulins: IgG, IgA and IgM (IgD or IgE test to be performed if positive at baseline)
    - Corrected serum calcium
    - Serum and urine immunofixation and free light chain tests to be performed to confirm a CR and as clinically indicated.

- Extramedullary Disease (approximately every 12 weeks, eg. Cycle 4, 7, 10): Required if positive at screening/ baseline as determined by Independent Adjudication Committee.
- Skeletal survey (Cycle ≥2): only required if clinically indicated or to confirm response according to IMWG criteria. CT/MRI scans can also be performed if clinically indicated or to confirm response according to IMWG criteria.

- PK (up to 10 cycles) and ADA (refer to Section 1.7 and Section 1.8)
- Biomarker/ Exploratory Studies:
  - Immune genetic determinants in peripheral blood: including Killer cell Ig-like receptors (KIR), HLA Typing and FcγR genes (Cycle 1 only).
  - Peripheral blood for soluble CD38 (Cycle 1 only).
  - Peripheral blood for Immune phenotyping (Cycle 1 and 3 only).

Administration of isatuximab

Isatuximab Safety Labs:
Should a isatuximab infusion associated reaction of Grade ≥2 occur, additional blood sampling during the AE is required for analysis of markers of potential tumor lysis syndrome (uric acid, lactate dehydrogenase [LDH], BUN, creatinine, potassium, phosphate, ionized or corrected calcium).

Bone marrow aspirates/biopsy will be collected in CR suspected patients for MRD analysis.

12.3.2 Day 2, 3, 4 of Cycle 1 of Phase I part

- PK (refer to Section 1.7)

12.3.3 Day 8 and Day 22 of Cycle 1

The evaluations below are to be performed prior to IMP administration on Day 8 and 22 of Cycles 1 only.

- Clinical Examinations:
  - Physical Examination
  - Weight
  - Vital signs
    (to be taken pre-infusion, mid-infusion (when half the volume is administered), and end-infusion on days of IMP administration. If the infusion rate changes because of an infusion-associated reaction, vital signs should be monitored every hour and at the end of the infusion.)
  - AE/ SAE assessment
  - Concomitant Medications

- Laboratory Assessments:
  - Hematology
  - Serum Chemistry
- PK and ADA (refer to Section 1.7 and Section 1.8)

Administration of isatuximab

Isatuximab Safety Labs (if ≥Grade 2 infusion associated reaction)

12.3.4 Day 15 of Each Cycle

The evaluations below are to be performed prior to IMP administration on Day 15 of each cycle unless otherwise indicated.

- Clinical Examinations:
  - Physical Examination (Cycle 1, 2, 3 only)
  - Weight
  - Vital signs
    (to be taken pre-infusion, mid-infusion (when half the volume is administered), and end-infusion on days of IMP administration. If the infusion rate changes because of an infusion-associated reaction, vital signs should be monitored every hour and at the end of the infusion.)
  - AE/ SAE assessment
  - Concomitant Medications
- Laboratory Assessments:
  - Hematology
  - Serum Chemistry
  - Urinalysis: Quantitative urinalysis will be needed if hematuria is observed or clinically indicated.
  - 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 (Phase II part, Subsequent Cycles only).
- PK (refer to Section 1.7 and Section 1.8, up to 10 cycles)
- ADA (Cycle 1 only)

Administration of isatuximab

Isatuximab Safety Labs

12.4 END OF TREATMENT VISIT (TO BE PERFORMED 30 DAYS (+/- 7 DAYS) AFTER THE LAST ADMINISTRATION OF THE INVESTIGATION MEDICINAL PRODUCT)

- Inform to the registration center
- Clinical Examinations:
  - Physical Examination
  - Performance Status (ECOG)
  - Weight
  - Vital signs
  - AE/ SAE assessment
  - Concomitant Medications
- Laboratory Assessments:
  - Hematology
  - Serum Chemistry
  - If history of HBV infection is suspected, perform HBV-DNA test.
  - Urinalysis: Quantitative urinalysis will be needed if hematuria is observed or clinically indicated.
  - Serum Pregnancy Test
- Disease Assessment:
  - Myeloma-specific Lab Tests:
    - M-protein quantification (serum electrophoresis and immunofixation and 24-hour urine collection for Bence Jones protein with urine electrophoresis and immunofixation)
    - Serum free light chain levels
    - Serum β2-microglobulin
    - Immunoglobulins: IgG, IgA, IgM, IgD and IgE
    - Corrected serum calcium
  - Extramedullary Disease (approximately every 12 weeks, eg. Cycle 4, 7, 10): Required if positive at screening/ baseline as determined by Independent Adjudication Committee. May be omitted at End of Treatment if conducted within 12 weeks.
- PK and ADA (refer to Section 1.7 and Section 1.8)
- Biomarker/ Exploratory Studies:
  - Immune phenotyping (peripheral blood sample)

12.5 FOLLOW-UP VISIT (TO BE PERFORMED 60 DAYS (+/- 7 DAYS) AFTER THE LAST ADMINISTRATION OF THE INVESTIGATION MEDICINAL PRODUCT)

- Inform to the registration center.
- Clinical Examinations:
  - AE/SAE Assessment (all ongoing related AE, ongoing SAE/AESIs, and new related AE/SAE/AESIs are to be followed up to resolution or stabilization)
  - Concomitant Medication (if for related AE, ongoing SAE/AESIs, and new related AE/SAE/AESIs)
  - The first new anticancer therapy after the last IMP administration.
- Disease Assessment:
  Disease assessments during follow-up period are only required for patients with PR or better who have discontinued study treatment for reasons other than disease progression and have not yet started treatment with another anti-cancer therapy. Disease assessments will be done up to PD, initiation of further anti-cancer therapy or second cut-off date, whichever comes first. Patients will be followed every 4 weeks for progression during this period. Disease assessments required every 4 weeks is myeloma-specific lab tests. Extramedullary disease assessment is required approximately every 12 weeks or upon clinical suspicion of progressive disease. All imaging will be sent to a central imaging lab. A bone marrow aspiration and/or biopsy, skeletal survey are only required if clinically indicated to confirm response or progression according to IMWG criteria.
  - Myeloma-specific Lab Tests:
    - M-protein quantification (serum and 24-hours urine)
    - Serum β2-microglobulin to be performed if clinically indicated
    - Immunoglobulins: IgG, IgA, IgM (IgD or IgE test to be performed if positive at baseline)
    - Corrected serum calcium
    - Serum and urine immunofixation and free light chain tests to be performed to confirm a CR and as clinically indicated.
  - Extramedullary Disease: Required if positive at screening/ baseline as determined by Independent Adjudication Committee.
- ADA (refer to Section 1.7 and Section 1.8): if patient is positive for ADA or the sample is inconclusive, additional ADA samples are required every month (± 7 days) until sample is negative.

12.6 PERIOD POST 60 DAYS FOLLOW-UP PERIOD

- Clinical Examinations:
  - New anticancer therapy
  - AE/SAE Assessment (all ongoing related AE, ongoing SAE, and new related AE/SAEs are to be followed up to resolution or stabilization)
  - Concomitant Medication (if for related AE, ongoing SAE, and new related AE/SAEs)
- Survival Status:
  Patients will also be followed for survival status approximately every 3 months from the date of last IMP administration until death or second cut-off date, whichever comes first. 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 obtained immediately. For subsequent survival follow-up, the patient should be contacted 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.
- Disease Assessment:
  Disease assessments during follow-up period are only required for patients with PR or better who 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 4 weeks for progression during this period. Disease assessments required every 4 weeks is myeloma-specific lab tests. Extramedullary disease assessment is required approximately every 12 weeks or upon clinical suspicion of progressive disease. All imaging will be sent to a central imaging lab. A bone marrow aspiration and/or biopsy, skeletal survey 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.
  - Myeloma-specific Lab Tests:
    (For patients with PR or better who have discontinued study treatment for reasons other than disease progression and have not yet started treatment with another anti-cancer therapy only)
    - M-protein quantification (serum and 24-hours urine)
    - Serum β2-microglobulin to be performed if clinically indicated
    - Immunoglobulins: IgG, IgA and IgM (IgD or IgE test to be performed if positive at baseline)
    - Corrected serum calcium
    - Serum and urine immunofixation and free light chain to be performed to confirm a CR and as clinically indicated.
  - Extramedullary Disease: Required if positive at screening/ baseline as determined by Independent Adjudication Committee.

- ADA:
  If patient is positive for ADA or the sample is inconclusive, additional ADA samples are required every month (± 7 days) until sample is negative.

12.7 POST SECOND ANALYSIS CUT-OFF PERIOD

If a patient continues to benefit from the treatment after the second analysis cut-off date, the patient can continue study treatment. Such patients will be followed until 60 days after the last administration of the IMP and will continue to undergo select study assessments. The following information will be collected: IMP(s) administration, IMP-related AEs, and any SAEs.

Procedures and data collection for patients still receiving isatuximab at the time of the second analysis cutoff date will be as follows:

- Clinical Examinations:
  - Ongoing related AE(s) and ongoing SAE(s), up to stabilization or resolution,
  - New SAE(s), new related AE(s),
  - Reason for end of treatment upon isatuximab discontinuation
- ADA:
  If patient is positive for ADA or the sample is inconclusive, additional ADA samples are required every month (± 7 days) until sample is negative.
- Administration of isatuximab

Patients with ongoing related AE(s) and ongoing SAE(s) after treatment discontinuation will be followed until stabilization or resolution of the AE/SAE.

13 STATISTICAL CONSIDERATIONS

13.1 DETERMINATION OF SAMPLE SIZE

Phase I part:

The Phase I part of this study aims to determine the safety and tolerability of isatuximab. It is anticipated that up to 6 to 12 evaluable patients will be enrolled. Patient(s) not evaluable for DLT will be replaced.

Phase II part:

The Phase II part of the study aims to evaluate 33-36 subjects which include the subjects in Phase I part at the recommended dose level. Given an assumed true ORR of 28%, the null hypothesis ORR ≤10% will be rejected using an exact binomial test at a one-sided alpha of 0.025 with at least 80% power, if the observed ORR is greater than or equal to 24.2% (ie, 8 responders). The sample size calculation was performed using SAS ver. 9.4 SAS/STAT 13.2, power procedure.

13.2 PATIENT DESCRIPTION

13.2.1 Disposition of Patients

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 all treated/safety population.

13.2.2 Protocol Deviations

All critical or major deviations potentially impacting evaluation of the MTD (Phase I part only), efficacy analyses, as well as drug-dispensing irregularities and other major or critical deviations will be summarized in tables giving numbers and percentages of patients with deviations, or only the listing will be provided.

13.3 ANALYSIS POPULATIONS

13.3.1 All-treated/safety Population

For both Phase I and Phase II parts of the study, the all treated/safety population will include all patients who have given their informed consent and who have received at least one dose (even incomplete) of isatuximab.

This population is the primary population for the analyses of efficacy and safety parameters. All analyses using this population will be based on the treatment actually received.

13.3.2 Patients Evaluable for DLT Assessment

The DLT evaluable population is only applicable to the Phase I part of the study.

The DLT evaluable population is the subset of patients from the all treated population who have completed the first cycle which consists of 4 administrations of the IMP, or they discontinued the IMP before completion of the first cycle for a DLT. In practice, a "Dose-Limiting Toxicities" form should have been filled in at the end of Cycle 1. If there are missing or incomplete data that influence the evaluation of DLT, the patient will not be evaluable for DLT. Patients excluded from this population will be replaced.

13.3.3 Pharmacokinetic Population

The PK and CD38 receptor density analysis will be performed on the all treated/safety population who have a PK parameter.

13.3.4 Activity/efficacy Population

The exploratory analysis will be performed on the all treated/safety population who have evaluable data.

13.4 STATISTICAL METHODS

The statistical methods defined in this section will be used for the analysis of the data from the Phase I and Phase II parts, unless otherwise specified. Data from each phase will be analyzed and reported separately except efficacy evaluation in Phase II part (see Section 6.7.2). Summary tables will be presented by dose levels (when appropriate) and overall in Phase I part, unless otherwise noted.

Unless otherwise specified, analyses will be descriptive and performed based on the all treated population.

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

13.4.1 Demographics and Baseline Characteristics

The demographic and baseline characteristics (including age, race, gender, ECOG performance status), medical history, cancer diagnosis will be collected at baseline.

13.4.2 Extent of Investigational Medicinal Product Exposure

The extent of investigational product exposure will be assessed and summarized within the all treated population.

The following dose information will be summarized descriptively (N, Mean, Standard deviation, Median, Min, and Max).

- Duration of study treatment exposure: defined as day 1 of last cycle date – first dose date + 28 days, regardless of unplanned intermittent discontinuations.
- Cumulative dose: The cumulative dose is the sum of all doses from first dose to last isatuximab administration.
- Actual dose intensity (ADI): defined as the cumulative dose divided by the number of weeks on study (duration of study treatment exposure divided by 7).
- 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.

The number and its percentage of people who correspond to the following condition will be calculated.

- Infusion delay: Within Cycle 1, an infusion is deemed to be delayed if start date of the current administration – start date of previous administration is >9 days. For subsequent cycles (≥Cycle 2), an infusion is deemed to be delayed if the time interval between 2 infusions is >17 days (ie. >3 days compared to the theoretical duration between 2 infusions).
- Dose interruption: administration of isatuximab treatment is temporarily stopped during the infusion.

13.4.3 Prior/concomitant Medication/therapy

The following parameters regarding prior anticancer will be summarized:

- Prior anticancer treatments: number of prior lines, main anticancer treatments, time from completion of last line of treatment to first isatuximab administration (months), best response to last line, duration of last line of therapy
- Prior transplant: number (%) of patients with transplant, number of transplants by patients
- Prior surgery: number (%) of patients with any prior surgery related to cancer, type of surgery and time from last surgery to first isatuximab administration (months)
- Prior radiotherapy: number (%) of patients with any prior radiotherapy related to cancer, intent, location and time from last radiotherapy to first study treatment infusion (months)

Medications will be summarized by dose level of IMP 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. In that summarization, patients will be counted once in each ATC categories (anatomic or therapeutic) linked to the medication.

Medications of specific interest such as antibiotics and hematopoietic growth factors (G-CSF and red blood cells transfusion) will be summarized and listed by dose level. Further treatment of interest for the analysis and given to the patient after withdrawal from IMP will be listed.

13.4.4 Analyses of Safety Data

Analyses of data will be based on the all treated/safety population except DLT evaluation.

13.4.4.1 Dose-limiting toxicities

For the Phase I part of the study, DLTs will be summarized by dose level using DLT evaluable population. Details will be provided (characteristics of DLTs) by patient.

13.4.4.2 Analyses of adverse events

Adverse events will be assessed according to NCI-CTCAE ver. 4.03 from the time of informed consent is signed until at least 30 days after the last IMP administration. AEs will be classified by System Organ Class/preferred term according to the latest available version of MedDRA dictionary.

Definitions

- Period of observation: The observation period will be divided into three segments: pre-treatment, on-treatment and post-treatment.
- The pre-treatment period is defined as the time from when the patients give informed consent to the start of IMP.
- The on-treatment period is defined as the time from the first dose of IMP up to 30 days after the last dose of IMP.
- The post-treatment period is defined as the time starting 31 days after the last dose of IMP to the study closure.

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

Treatment-emergent AEs (TEAEs) are defined as AEs that developed, worsened (according to the Investigator’s opinion) or became serious during the on-treatment phase.

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

The grade and cycle will be taken into account in the summary. For patients with multiple occurrences of the same PT, the maximum grade is used. The denominator used for the summary by cycle is the total number of cycles administered in dose level. For a given PT, a patient contributes 1 to the numerator for each cycle in which an episode occurred.

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

Adverse event incidence tables will present for each dose level, the number (n) and percentage (%) of patients experiencing an AE. Multiple occurrences of the same event in the same patient will be counted only once in the tables within a treatment phase. The denominator for computation of percentages is the number of patients in the all treated population.

The table of all TEAEs presented by system organ class (SOC) and preferred terms (PT) sorted by internationally agreed order in SOC and descending order of that frequency in the pooled dose in PT (in case of the same frequency, then alphabet order) unless otherwise specified.

The following TEAE summaries will be generated:

Overview of TEAEs, summarizing number (%) of patients with any

- TEAEs
- Any Grade 3-4 TEAEs
- Drug-related TEAEs
- Drug-related TEAEs of Grade 3-4
- Serious TEAEs
- TEAEs with a fatal outcome
- TEAEs leading to discontinuation
- DLT
- AESI
- AESI of Grade 3-4

The following frequency distribution of AEs (incidence tables) will be provided for the safety population:

- All TEAEs by SOC and PT and worst NCI-CTCAE grade.

The same analysis will be performed for drug-related TEAEs, TEAEs leading to discontinuation, serious TEAEs, TEAEs with a fatal outcome, and drug-related SAEs occurred during the post treatment dosing period.

13.4.4.3 Deaths

A listing of deaths will be provided.

13.4.4.4 Clinical laboratory evaluations

For patients with multiple occurrences of the same laboratory variable during the on treatment period, the maximum grade (worst) per patient and/or per cycle will be used. The denominator

used for the summary by cycle is the total number of cycles administered. For a given laboratory variable, a patient contributes 1 to the numerator for each cycle in which an episode occurred. An episode occurs during a cycle, if the date of sampling is on or after the first day of the cycle, but prior to the first day of the next cycle. Hematological and clinical biochemistry toxicities will be assessed from laboratory test parameters. Each test result will be graded by NCI-CTCAE ver. 4.03. The number of patients with abnormal lab tests at baseline will be presented by grade. The frequency of patients and/or cycles in each grade of lab tests during on-treatment will be summarized (similar analysis will be performed based on data recorded at Cycle 1). When appropriate, the summary table will present the frequency of patients and/or cycles with any grade of abnormal laboratory tests and with Grade 3-4 of abnormal laboratory tests.

13.4.4.5 Vital signs

The descriptive statistics (including mean, median, SD, minimum and maximum) of all vital signs' variables (raw data and changes from baseline) will be calculated for each visit or study endpoint (baseline, each post baseline time point, last on treatment value and/or worst value) by dosing levels.

13.4.4.6 Analyses of other safety variables

Not applicable.

13.4.5 Analyses of Pharmacokinetic Variables

Pharmacokinetic parameters of isatuximab will be summarized by descriptive statistics (such as mean, geometric mean, median, standard deviation, SEM, CV, minimum, and maximum) under the responsibility of Drug Disposition, Disposition, Safety and Animal Research, Sanofi.

Individual plasma concentrations and PK parameters of isatuximab will be tabulated with standard descriptive statistics. Individual and mean profiles will be presented graphically.

The relationship between dose and exposure will be investigated, using analysis of variance.

13.4.6 Analysis of Anti-drug Antibody

The ADA will be summarized by study visits.

13.4.7 Analysis of CD38 Receptor Density

The CD38 receptor density will be summarized by study visits for Phase I and Phase II.

13.4.8 Analyses of Efficacy Variables

All efficacy analyses will be performed using the all treated/safety population. (see Section 9.3.1)

13.4.8.1 Efficacy endpoints for Phase I part of the study

Best overall response, OS, PFS, TTP, and DOR will be listed along with relevant patient/disease characteristics.

13.4.8.2 Analysis of primary efficacy endpoint for Phase I (Recommended dose level) and Phase II part of the study

Analysis of efficacy endpoint will be performed on all patients who received at least one dose of recommended dose across Phase I and II part:

ORR and the 95% two-sided confidence interval will be computed using Clopper-Pearson method. The null hypothesis that the true response rate (ORR) is <10% will be tested using a one-sided exact binomial test with a significance level of 0.025.

13.4.8.3 Analysis of secondary efficacy endpoint for Phase II part of the study

The CBR will be analyzed using the same method as the primary efficacy analysis of ORR. The DOR, TTP, 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 will also be computed. The Kaplan-Meier curves will be plotted.

13.4.8.4 Analysis of the other exploratory endpoints

The same analysis will be applied in Phase I and Phase II part. The exploratory endpoints and the relationship to clinical outcomes will be analyzed with exploratory manner.

13.5 INTERIM ANALYSIS

No interim analysis is planned.

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 the principles laid down by the 18th World Medical Assembly (Helsinki, 1964) and all applicable amendments laid down by the World Medical Assemblies, 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 IRB. 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 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 IRB for approval/favorable opinion.

The Investigator, or a person designated by the Investigator, should fully inform the patient of all pertinent aspects of the clinical trial. All participants should be informed to the fullest extent possible about the study in terms they are able to understand.

14.3 INSTITUTIONAL REVIEW BOARD

As required by local regulation, the Investigator must submit this clinical trial protocol to the appropriate IRB, 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 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, Investigator's CV, etc.) and the date of the review should be clearly stated on the written IRB 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 IRB before implementation, unless the change is necessary to eliminate an immediate hazard to the patients, in which case the IRB should be informed as soon as possible. It should also be informed of any event likely to affect the safety of patients or the continued conduct of the clinical trial, in particular any change in safety. All updates to the Investigator's Brochure will be sent to the IRB.

A progress report will be sent to the IRB 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 pre-identified 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 IRB, 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 is expressly permitted, the IRB 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.

Subject race or ethnicity ("Asian/Oriental, others") will be collected in this study because these data are required by the PMDA.

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 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 is 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 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.

When the data from all investigational sites have been fully analyzed by the Sponsor, the latter will communicate the results of the clinical trial to the Investigator(s).

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 of an amendment, 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 prior to its implementation, unless there are overriding safety reasons.

In some instances, an amendment may require a change to the informed consent form. The Investigator must receive an IRB 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 ECOG Performance Status Scale

Performance Status	Description
0	Normal, fully functional
1	Fatigue without significant decrease in daily activity
2	Fatigue with significant impairment of daily activities or bedrest <50% of waking hours
3	Bedrest/sitting>50% of waking hours
4	Bedridden or unable to care for self

Appendix B National Cancer Institute Common Terminology Criteria for Adverse Events

Refer to NCI CTC AE v.4.03 (15) in the Study Reference Manual, or online at the following NCI website: http://ctep.cancer.gov/reporting/ctc.html

- Toxicity grade should reflect the most severe degree occurring during the evaluated period, not an average.
- When 2 criteria are available for similar toxicities, the one resulting in the more severe grade should be used.
- The evaluator must attempt to discriminate between disease/treatment and related signs/symptoms.
- An accurate baseline prior to therapy is essential.

Appendix C IMWG Response Criteria

Disease response will be assessed using the updated International Myeloma Working Group Response Criteria (IMWG)(10).

A confirmation assessment within 4 weeks (±3 days) for disease response evaluation assessments is required in this protocol, including MR.

Table 9 - International Myeloma Working Group Response Criteria

Response	IMWG criteria
sCR	CR as defined below plus: • Normal FLC ratio and • Absence of clonal cells in bone marrow by immunohistochemistry or 2 – 4 color flow cytometry
CR	• Negative immunofixation on the serum and urine and • Disappearance of any soft tissue plasmacytomas and • <5% plasma cells in bone marrow. • In patients with only FLC disease, a normal FLC ratio of 0.26–1.65 is required.
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. • In patients with only FLC disease, >90% decrease in the difference between involved and uninvolved FLC levels is required.
PR	• ≥50% reduction of serum M-protein and reduction in 24 hours urinary M protein by ≥90% or to <200 mg/24 h • If the 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 not measurable, and serum free light assay is also not measureable, ≥ 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 of soft tissue plasmacytomas is also required
SD	• Not meeting criteria for CR, VGPR, PR or progressive disease
PD	Increase of ≥25% from lowest response value in any one of the following: • Serum M-component (the absolute increase must be ≥0.5 g/dL) and/or • Urine M-component (the absolute increase must be ≥200 mg/24 h) and/or • Only in patients without measurable serum and urine M-protein, the difference between involved and uninvolved FLC levels. The absolute increase must be >10 mg/dL • Only in patients without measurable serum and urine M-protein and without measurable disease by FLC levels, bone marrow plasma cell percentage (absolute % must be ≥10%) • Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas • Development of hypercalcemia (corrected serum calcium >11.5 mg/dL) that can be attributed solely to the plasma cell proliferative disorder

All response categories (CR, sCR, VGPR, PR and PD) require two consecutive assessments made at any time before the institution of any new therapy; complete response and PR and SD categories also require no known evidence of progressive or new bone lesions if radiographic studies were performed. VGPR and CR categories require serum and urine studies regardless of whether disease at baseline was measurable in serum, urine both or either. Radiographic studies

are not required to satisfy these response requirements. Bone marrow assessments need not be confirmed. For progressive disease, serum M-component increases of ≥1 g/dL are sufficient to define response if starting M-component is ≥5 g/dL.

IMWG clarification for coding PD: Clarified that Bone marrow criteria for PD are to be used only in patients without measurable disease by M protein and by FLC levels. Clarified that 25% increase refers to M protein, FLC, and bone marrow results and does not refer to bone lesions, soft tissue plasmacytomas or hypercalcemia. Note the lowest response value does not need to be a confirmed value.

Table 10 - Additional response criteria for specific disease states

Minor/ minimal response(MR) in patients with relapsed and refractory myeloma adapted from the EMBT criteria	≥25% but ≤49% reduction of serum M protein and reduction in 24 hour urine M protein by 50 – 89%, which still exceeds 200 mg/24 hrs. In addition to above; if present at baseline, 25-49% reduction in the size of soft tissue plasmacytomas is also required. No increase in size or number of lytic bone lesions (development of compression fractures does not exclude response).
Immunophenotypic CR	Stringent CR plus Absence of phenotypic aberrant PC (clonal) in bone marrow with a minimum of one million of total BM cells analyzed by miltiparamtric flow cytometry (with ≥4 colors)
Molecular CR	Stringent CR plus negative ASO-PCR (sensitivity 10^{-5})

Appendix D Definition of Line of Therapy

A line of therapy is defined as one or more cycles of a planned treatment program. This may consist of one or more planned cycles of single-agent therapy or combination therapy, as well as a sequence of treatments administered in a planned manner. For example, a planned treatment approach of induction therapy followed by autologous stem cell transplantation, followed by maintenance is considered one line of therapy. A new line of therapy starts when a planned course of therapy is modified to include other treatment agents (alone or in combination) as a result of disease progression, relapse, or toxicity. A new line of therapy also starts when a planned period of observation off therapy is interrupted by a need for additional treatment for the disease. (11)

Appendix E Definition of Relapsed and Refractory Myeloma

Refractory Myeloma:

Refractory myeloma is defined as disease that is non-responsive (failure to achieve minimal response or develop 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. (11)

Appendix F Staging Criteria

Table 11 - Staging criteria for multiple myeloma

STAGE	Criteria
I	Serum β2 – microglobulin < 3.5 mg/L Serum albumin ≥ 3.5 g/dL
II	Not stage I or III*
III	Serum β2 – microglobulin ≥ 5.5 mg/L

* There are two categories for Stage II,

- Serum β_2 – microglobulin <3.5 mg/L and serum albumin <3.5 g/dL.
- Serum β_2 – microglobulin 3.5 mg/L to <5.5 mg/L irrespective of the serum albumin.

Appendix G Definitions of Infusion Associated Reactions (IARs)

Table 12 - Types of infusion associated reactions[a]

Anaphylaxis
Acute coronary syndrome
Cytokine release syndrome
Drug hypersensitivity
Infusion related reaction

a This list is not intended to be exhaustive

Table 13 - Symptoms typically associated with infusion associated reactions[a]

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

a This list is not intended to be exhaustive

Appendix H Revised equations for estimated GFR in Japanese

eGFR (mL/min/1.73 m^2) = 194 x Serum $creatinine^{-1.094}$ x $Age^{-0.287}$ x 0.739 (if female). (16)

Web site of Japan Association of Chronic Kidney Disease Initiative:
http://j-ckdi.jp/ckd/check.html

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]—President
[redacted]—Chief Executive Officer
Re: Mitigating the Anti-CD38 Interference with Serologic Testing

Summary

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

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

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

Background

CD38 monoclonal antibodies are a new treatment for multiple myeloma

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

CD38 monoclonal antibodies interfere with blood bank serologic tests

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

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

Other notes on anti-CD38 serologic interference:

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

Anti-CD38 interference can cause delays in issuing RBCs
If the transfusion service is unaware that a patient has received anti-CD38, the following scenario may occur when the patient's sample is tested:

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

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

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

BEFORE a patient begins taking anti-CD38:

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

AFTER a patient begins taking anti-CD38:

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

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

Crossmatch

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

Future/alternative approaches to mitigating the anti-CD38 interference

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

References

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

9. Schmidt AE, Kirkley S, Patel N, et al. An alternative method to dithiothreitol treatment for antibody screening in patients receiving daratumumab (abstract). Transfusion 2015;55(3S):2292-3.

Appendix J Protocol amendment history

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

AMENDED PROTOCOL 04 (14-Dec-2018)

OVERALL RATIONALE FOR THE AMENDMENT

The purpose of the second analysis is to obtain PFS and OS by monotherapy from mature data in Japanese patients. However, it was found only two events of OS in phase 2 at the first analysis, so 12 months would not be enough to observe median of OS. That median of OS in 20mg/kg arm in TED10893 P2S1 was 18.1 months. Therefore, second cut-off will be postponed from approximately 12 months to approximately 20 months.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
NAMES AND ADDRESSES OF	To delete information	These information are provided in CTP attachment.
CLINICAL TRIAL SUMMARY, 6.7.1 Duration of Study Participation for Each Patient	DURATION OF STUDY PERIOD (per patient) To add as follow; Patients with PR or better who come off treatment for reasons other than progression of disease will be followed for disease assessment every 4 weeks until progression or initiation of subsequent therapy, the second analysis cutoff date, whichever comes first.	To clarify follow-up assessment.
CLINICAL TRIAL SUMMARY, 6.7.2 Determination of End of Clinical Trial (all patients)	STATISTICAL CONSIDERATIONS Planned database lock - the second cutoff date: 20 months	To get enough period for observation of median of OS.
1.4 STUDY FLOWCHART - PHASE I PART	To add a new footnote as follow; Subsequent Cycles [3, 35]	To clarify assesment items post second analysis cut-off period.
1.5 STUDY FLOWCHART - PHASE II PART	To add a new footnote as follow; Subsequent Cycles [3, 35]	To clarify assesment items post second analysis cut-off period.
1.6 FOOTNOTES FOR STUDY FLOWCHARTS	33 To add as follow;“or second cut-off date, whichever comes first.”	To clarify study duration.
	To add as follow; 35. Post second analysis cut-off period, only AE/SAE reporting will be collected	To clarify assesment items post second analysis cut-off period.
1.7 PK FLOW CHART - PHASE I PART	To add a new footnote as follow; Subsequent Cycles[9]	To clarify assesment items post second analysis cut-off period.

Section # and Name	Description of Change	Brief Rationale
	To add as follow; g Post second analysis cut-off period, only ADA samples will be collected.	To clarify assesment items post second analysis cut-off period.
1.8 PK FLOW CHART - PHASE II PART	To add a new footnote as follow; Subsequent Cycles[f]	To clarify assesment items post second analysis cut-off period.
	To add as follow; f Post second analysis cut-off period, only ADA samples will be collected.	To clarify assesment items post second analysis cut-off period.
12.5 FOLLOW-UP VISIT (TO BE PERFORMED 60 DAYS (+/- 7 DAYS) AFTER THE LAST ADMINISTRATION OF THE INVESTIGATION MEDICINAL PRODUCT)	To add disease assessment section with the sentence as follow; Disease assessments during follow-up period are only required for patients with PR or better who have discontinued study treatment for reasons other than disease progression and have not yet started treatment with another anti-cancer therapy. Disease assessments will be done up to PD, initiation of further anti cancer therapy or second cut-off date, whichever comes first. To delete ~~Disease assessments not required once patient starts treatment with another anti-cancer therapy~~	To clarify disease assesment on follow-up visit.
12.6 PERIOD POST 60 DAYS FOLLOW-UP PERIOD	Patients will also be followed for survival status approximately every 3 months from the date of last IMP administration until death or second cutoff date, whichever comes first.	To clarify study duration.
12.7 POST SECOND ANALYSIS CUT-OFF PERIOD	To delete as follow; ~~-Laboratory Assessments:~~ ~~-Urine Pregnancy Test~~ ~~-Disease Assessment:~~ ~~-Myeloma-specific Lab Tests:~~ ~~-M-protein quantification (serum and 24-hours urine)~~ ~~-Serum β2-microglobulin to be performed if clinically indicated~~ ~~-Immunoglobulins: IgG, IgA and IgM (IgD or IgE test to be performed if positive at baseline)~~ ~~-Corrected serum calcium~~ ~~-Serum and urine immunofixation and free light chain to be performed to confirm a CR and as clinically indicated.~~ ~~-Extramedullary Disease (approximately every 12 weeks): only required if~~	In post second analysis cut-off period, it is modified to do only safety observation.

Section # and Name	Description of Change	Brief Rationale
	~~clinically indicated. No need to send images to the committee.~~ ~~-Skeletal survey: only required if clinically indicated.~~	
Appendix J Protocol amendment history	Added an Appendix with details of past protocol amendment changes as per the new template requirements	Added this Appendix as per the new template requirements

Amended Clinical Trial Protocol 3 based on Protocol Amendment 03: [12-Oct-2017]

Rationale for the amendment (03)

Section # and Name	Description of Change	Brief Rationale
CLINICAL TRIAL SUMMARY, 1.4 STUDY FLOWCHART - PHASE I PART, 1.5 STUDY FLOWCHART - PHASE II PART, 1.6 FOOTNOTES FOR STUDY FLOWCHARTS: 9 and 10, 1.7, 1.8, 3 LIST OF ABBREVIATIONS, 6.6.1 Management of Potential Infusion Associated Reactions (IARs) , 9.1.9 Other Clinical Assessments, 12.3.1 Day 1 of Each Cycle,	Removed cytokines from safety evaluation	Following isatuximab administration (TED10893, phase 1), higher cytokine levels for IL-1, IL-6, TNF-α, and IFN γ were noted as compared to baseline: the median peak values (defined as the highest value during the on-treatment period) of IFN-γ, IL-1β, IL-6, and TNF-α were 0.44, 0.34, 6.48, and 24.66 pg/mL, respectively, with median relative change from baseline ranging from 6% to 184% across the 4 cytokines with no evident dose dependency. For each cytokine, the median of the peak value was overall similar for patients who never experienced an IAR during the on-treatment and those who developed at least one IAR during the on-treatment period. Therefore, no association between the transient cytokine increases and the occurrence of IARs could be demonstrated.
CLINICAL TRIAL SUMMARY, 1.6 FOOTNOTES FOR STUDY FLOWCHARTS: 9 , 6.6.1 Management of Potential Infusion Associated Reactions (IARs), 12.3.1 Day 1 of Each Cycle	Removed markers of complement and serum tryptase from safety evaluation	Regarding complement activation (C3a, C4, CH50) and serum tryptase measurement, the samples are collected only in case of IARs do not allow to perform any interpretation and reach a conclusive outcome.
CLINICAL TRIAL SUMMARY, 7.3 EXCLUSION CRITERIA	E 18. Any medical conditions that, in the Investigator's opinion, would impose excessive risk to the patient (eg, poorly controlled diabetes ~~requiring insulin treatment~~ or poorly controlled hypotension).	To clarify exclusion criteria.
1.6 FOOTNOTES FOR STUDY FLOWCHARTS,	ADA (Anti-Drug Antibodies) is performed on Day 1 of cycle up to 10 cycles. If ADA is positive at	To modify according to Amendment of the global studies.

Section # and Name	Description of Change	Brief Rationale
1.7 PK FLOW CHART-PHASE I PART, 1.8 PK FLOW CHART- PHASE II PART, 9.1.8 Immunogenicity, 12.3.1 Day 1 of Each Cycle	Cycle 10, one additional sampling for ADA evaluation should be collected 3 months later. No further ADA will be collected, even if the 3-month sample is positive.	
8.3 PRE-MEDICATION	Patients who do not experience an IAR during the ~~first~~ 4 consecutive administrations of isatuximab may have the need for subsequent pre-medication reconsidered at the investigator's discretion in consultation with the Sponsor.	To clarify the condition for reconsideration of pe-medication.
In addition, other minor changes were made in the document.		

Amended Clinical Trial Protocol 02 based on Protocol Amendment 02 [27-Jan-2017]

Overall Rationale for the Amendment

Rationale for the amendment (02)

Section # and Name	Description of Change	Brief Rationale
CLINICAL TRIAL SUMMARY, 8.1.1 Pharmaceutical Form, 8.1.3 Preparation, Reconstitution and Administration of isatuximab	Addition to the dose preparation method of the IMP as "5% dextrose solution".	To harmonize the dose preparation method of the IMP with most current pharmacy manual. The data of 5% dextrose as an IV diluent become available.
6.6.1 Management of Potential Infusion Associated Reactions (IARs)	Patient(s) should routinely receive pre-medications prior to isatuximab infusion as detailed in Section 8.3 to reduce the risk and severity of IARs commonly observed with monoclonal antibodies. Infusion associated reactions (NCI-CTCAE, version 4.03 term Infusion related reaction), including "allergic/hypersensitivity reactions", or "cytokine release syndrome/acute infusion reaction", are defined as AEs related to isatuximab with onset typically within 24 hours from the start of the infusion.	To clarify the definition of infusion associated reaction.
Appendix I CD38 blood test interference guideline AABB2016	To add information letter.	To inform that CD38 monoclonal antibodies interferers with blood bank serologic tests.
In addition, other minor changes were made in the document.		

Amended Clinical Trial Protocol 01 based on Protocol Amendment01: [13-May-2016]

Rationale for the amendment (01)

Section # and Name	Description of Change	Brief Rationale
CLINICAL TRIAL SUMMARY; 5.3 Exploratory Objectives, 9.4.3 Exploratory Biomarker Studies.	Exploratory objective change due to deletion of tumor cell genomics testing	The analysis of tumor cell genomics is terminated worldwide due to difficult sample collection from bone marrow and deprioritization of CD38 expression as predictive biomarker. Preliminary analysis in TED10893 Phase 2 Stage 1 did not show clear predictive value of CD38 mRNA.
CLINICAL TRIAL SUMMARY, 7.2 Inclusion Criteria	Change in inclusion criteria #9 due to comply with the comments from the local regulatory authority (PMDA) regarding contraceptive measures and contraception period in the protocol Added examples of contraceptive measures which are available in Japan. Deleted uncertain contraceptive measures such as “abstinence”. Prolonged the contraception period from 12 weeks to 6 months.	To comply with PMDA suggestions arose during the review period of initial Clinical Trial Notification (CTN). • PMDA suggested to clarify the contraceptive measures which are available in Japan. • PMDA suggested to delete uncertain method of contraception such as “abstinence”. • PMDA requested to prolong the contraception period based on the PK data such as half live of isatuximab.
CLINICAL TRIAL SUMMARY, 7.3 Exclusion Criteria	Change in exclusion criteria # 20 due to comply with the comment from PMDA regarding lactating patients. Added when female subjects who stopped lactating can re-start.	To comply with PMDA suggestions arose during the review period of initial CTN. PMDA suggested to articulate the eligibility for female subjects who stopped lactating and the washout period allowing re-start of lactating.
CLINICAL TRIAL SUMMARY, 1.6 Footnotes for Study Flowcharts #9, #10, 6.6.1. Management of Potential Infusion Associated Reactions (IARs), 12 Study Procedures.	Change in test items of cytokines assessment. Added new test item IL-4 as a new test item for cytokines assessment.	To harmonize standard method of cytokines assessment across the ongoing studies.
CLINICAL TRIAL SUMMARY, 9.1.1 Dose-limiting Toxicities in Phase I part	Change in DLT criteria regarding platelet transfusion.	Due to comply with the comment from PMDA.
CLINICAL TRIAL SUMMARY, 9.2.3 Bioanalytical Method	Replaced bioanalytical method of ADA from “Bridge ELISA” to “P and A”.	To harmonize standard bioanalytical method across the ongoing studies.
1.6 Footnotes for Study Flowcharts #6, #14	Addition of anti-CD38 interference with serologic testing. Added how to deal with anti-CD38 interference with serologic testing.	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. The AABB Clinical Transfusion

Section # and Name	Description of Change	Brief Rationale
		Medicine Committee has developed a bulletin (# 16-02) to provide background information and guidance to members regarding anti-CD38 interference with serologic testing. This bulletin will be provided to the investigators as a protocol supplemental document. The patients treated in the study will receive a patient card indicating the treatment with a CD38 agent. The protocol also requested to the study site to notify its blood bank that the patient is receiving an anti- CD38 treatment. Direct and indirect coombs tests prior to first IMP administration was recommended by potential principal investigator of JP red cross medical center on April 14th, 2016.
1.4 Study Flowchart - Phase I part, 1.6 Footnotes for Study Flowcharts #7	Change in recommended hospitalization period. The end date of the recommended hospitalization during the DLT observation period was changed from “Day 8” to “the entire day of the 3rd infusion”.	To comply with PMDA suggestions arose during the review period of initial Clinical Trial Notification (CTN). PMDA suggested to refer the local guideline: “Guideline of clinical evaluation method for anti-cancer drugs” and consider hospitalization during the entire DLT period. PMDA accepted to shorten the recommended hospitalization period to the end of the 3rd infusion which may cover all infusion associated reactions (IARs) based on the IARs data as of Nov. 6th, 2015 (presentation of TED10893 at ASH 2015, page 10).
1.4 Study Flowchart - Phase I part, 1.5 Study Flowchart - Phase II part, 1.6 Footnotes for Study Flowcharts #20.	Change in Hepatitis B Virus (HBV) test. Added HBc-Ab and HBs-Ab test in screening/ baseline and monthly HBV-DNA test if history of HBV is suspected.	To comply with PMDA suggestions arose during the review period of initial CTN. Need to amend the protocol in accordance with the local guideline of “hepatitis B caused by immunosuppressive drug or chemo therapy” which recommends monthly HBV-DNA if history of HBV infection is suspected.
1.6 Footnotes for Study Flowcharts #21, 22, 12. Study Procedures	Change in disease assessment procedures to comply with IMWG The disease assessment procedures are detailed and frequency of the assessments is adjusted based on IMWG criteria.	To clarify the procedure requiring for efficacy evaluation and adjusted the frequency of the assessments.
4.1 Introduction	Change in introduction of isatuximab Added the information of isatuximab is produced in CHO cells and using recombinant DNA technology.	To comply with PMDA suggestions arose during the review period of initial CTN. PMDA suggested adding information on cell line and using recombinant DNA technology.
Other additional minor changes and edits were included in this amendment for the sake of clarity.		

Signature Page for VV-CLIN-0514516 v5.0
ted14095-16-1-1-amended-protocol05