NCT02812706

16.1.9 Statistical analysis plan

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STATISTICAL ANALYSIS PLAN

A Phase I/ II Study of Isatuximab (Anti-CD38 mAb) administered as a single agent in Japanese Patients With Relapsed AND Refractory Multiple Myeloma

SAR650984-TED14095 (Phase 1)

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ADA:	anti-drug antibody
ADI:	actual dose intensity
AESI:	adverse events of special interest
ATC:	anatomical therapeutic chemical
BOR:	best overall response
CR:	complete response
CT:	computed tomography
DLT:	dose limiting toxicity
DOR:	duration of response
ECOG:	eastern cooperative oncology group
FISH:	fluorescence in situ hybridization
FLC:	free light chain
HLGT:	high level group term
HLT:	high level term
IAC:	independent adjudication committee
IAR:	infusion associated reaction
IMP:	investigational medicinal product
IMWG:	international myeloma working group
ISS:	international staging system
IV:	intravenous
MM:	multiple myeloma
MR:	minimal response
MRD:	minimal residual disease
MRI:	magnetic resonance imaging
MUGA:	multigated acquisition
NCI-CTCAE:	national cancer institute common terminology criteria for adverse event
OS:	overall survival
PCSA:	Potentially Clinically Significant Abnormalities
PFS:	progression free survival
PK:	pharmacokinetic
PR:	partial response
PS:	performance status
PT:	preferred term
Q2W:	once every other week
QW:	once every week
RD:	receptor density
RDI:	relative dose intensity
SAP:	statistical analysis plan
SD:	stable disease
SOC:	system organ class

TEAE:	treatment-emergent adverse event
TTR:	time to response
VGPR:	very good partial response

1 OVERVIEW AND INVESTIGATIONAL PLAN

This is an open-label, single arm, local multi-center study conducted in 2 parts, phase 1 and phase 2. This statistical analysis plan (SAP) describes the statistical methods to be used for the analyses of data collected during the phase 1 part of the study. For the phase 2 part, the SAP is described separately. This SAP should be read in conjunction with the study protocol and electronic case report form (e-CRF).

1.1 STUDY DESIGN AND RANDOMIZATION

The phase 1 part of TED14095 is a standard 3+3 dose-escalation study of isatuximab administered as a single agent as an intravenous (IV) infusion every week (QW) during cycle 1 followed by every 2 weeks (Q2W) during subsequent cycles to adult patients with relapsed and refractory multiple myeloma (MM).

In this study, a cycle is basically 28 days. Treatment with isatuximab is to be continued until unacceptable adverse event, disease progression, death, withdrawal of patient, or investigator's decision. Dose has two levels, 10 mg/kg and 20 mg/kg.

1.2 OBJECTIVES

1.2.1 Primary objectives

The primary objective of the phase 1 part of this study is to evaluate safety and tolerability of isatuximab in Japanese patients with relapsed and refractory MM.

1.2.2 Secondary objectives

Secondary objectives of the phase 1 part of the study are:

- 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 MM cells and efficacy.

1.2.3 Exploratory objectives

The following exploratory objectives will be investigated in the end of phase 2 part of the study.

- 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/ fluorescence in situ hybridization (FISH)) and parameters of clinical response.
- To investigate the relationship between immune genetic determinants, immune phenotype and parameters of clinical response.

1.3 DETERMINATION OF SAMPLE SIZE

The phase 1 part of this study aims to determine the safety of isatuximab at the global recommended dose. It is anticipated that up to 6 to 12 evaluable patients will be enrolled, depending on the toxicity occurrence. Patient(s) not evaluable for Dose Limiting Toxicity (DLT) will be replaced.

1.4 STUDY PLAN

Safety evaluations are performed continuously throughout the study and included the following:

- DLTs evaluations
- AEs according to the National Cancer Institute Common Toxicity Criteria for Adverse Event (NCI-CTCAE) v. 4.03 grading scale
- Vital signs
- Eastern Cooperative Oncology Group Performance Status (ECOG PS)
- 12 lead electrocardiogram (ECG) or 2-D echocardiogram or Multigated Acquisition (MUGA) scan
- Chest X-ray
- Laboratory tests in blood and urine
- Level of human anti-drug antibodies (ADA)
- Cytokines (tumor necrosis factor alpha [TNF-α], interleukin [IL]-1-β, IL-4, IL-6, interferon-gamma [IFN-γ]), complement activators and tryptase

Disease response evaluation for patients is performed every 4 weeks, unless otherwise stated, including:

- M-protein quantification (serum and/or 24-hour urine, protein electrophoresis and immunoelectrophoresis), serum free light chain (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

The following additional evaluation is also performed:

- CD38 RD on bone marrow samples

PK samples are collected in all patients receiving isatuximab as depicted in the PK study flowcharts included in the protocol.

1.5 MODIFICATIONS TO THE STATISTICAL SECTION OF THE PROTOCOL

This section summarizes major changes to the protocol statistical section with emphasis on changes after study start (after the first patient was enrolled). The protocol history table below gives the timing, rationale, and key details of major changes to the protocol statistical section.

Table 1 – protocol amendment statistical changes

Amendment Number	Date Approved	Rationale	Description of statistical chnages
1	13-May-2016	To harmonize the other global studies	Summary of prior anti-cancer therapy
1	13-May-2016	To harmonize the other global studies	Overview of TEAEs
1	13-May-2016	To harmonize the other global studies	Deletion of the description in “Analyses of Pharmacokinetic variables”

1.6 STATISTICAL MODIFICATIONS MADE IN THE STATISTICAL ANALYSIS PLAN

This statistical analysis plan history table below gives the timing, rationale, and key details for major changes to the statistical analysis features in the statistical analysis plan. Changes also incorporated in a protocol amendment are cross-referenced to Table 1.

The first patient was enrolled on September 2016. There were no planned interim analyses.

Table 2 – Statistical analysis plan statistical changes

SAP version number	Date approved	Rationale	Description of statistical changes
2	This version	To harmonize the other global studies	MM characteristics at study entry
2	This version	To harmonize the other global studies	Refractory status in prior anticancer therapies
2	This version	To harmonize the other global studies	Analyses for infusion associated reaction
2	This version	To harmonize the other global studies	Summary for extent of exposure and dose modification
2	This version	To harmonize the other global studies	Summary of ADA

2 STATISTICAL AND ANALYTICAL PROCEDURES

2.1 ANALYSIS ENDPOINTS

2.1.1 Demographic and baseline characteristics

Unless otherwise specified, the baseline value is defined as the last available value before the first isatuximab administration.

All baseline safety and efficacy parameters (apart from those listed below) are presented along with the on-treatment summary statistics in the safety and efficacy sections (Section 2.4.5 and Section 2.4.4).

Demographic characteristics

Demographic variables are gender (Male, Female), ethnicity (Hispanic or Latino , Not Hispanic or Latino, Not reported, and Unknown), race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Not reported, Unknown), age in years (quantitative and qualitative variable : < 65, [65 - 75) and ≥ 75 years), weight (kg), and ECOG PS at baseline.

Medical or surgical history

Medical or surgical history other than MM will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version in effect at Sanofi (or the data management vendor) at the time of the data base lock.

MM characteristics at initial diagnosis

The following MM characteristics at initial diagnosis will be described: time from initial diagnosis to first isatuximab administration (in years) and by category (<5 years and ≥5 years), International Staging System (ISS) stage, and MM subtype (as collected in the e-CRF).

MM characteristics at study entry

The following MM characteristics at study entry will be displayed: derived ISS stage (Table 3), measurable paraprotein at baseline (Table 4), plasmacytoma in bone marrow (quantitative results and by category: 0, (0 - 5%), [5 - 20%), [20 - 50%), and ≥ 50%), patients with plasmacytomas, patients with bone lesions, serum β2-microglobulin level in mg/L (quantitative results and by category: < 3.5 mg/L, [3.5 - 5.5 mg/L), ≥ 5.5 mg/L), serum albumin in g/L (quantitative results and by category: < 35 g/L and ≥ 35 g/L).

Table 3 – ISS staging definition

Stage	Definition
Stage I	Serum β2-microglobulin <3.5 mg/L and serum albumin ≥ 35 g/L
Stage II	serum β2-microglobulin <3.5 mg/L and serum albumin <35 g/L or serum β2-microglobulin 3.5 - <5.5 mg/L regardless of serum albumin levels
Stage III	Serum β2-microglobulin ≥5.5 mg/L regardless of serum albumin levels

Table 4 – Derivation of measurable paraprotein at study entry

Measurable paraprotein	Criteria
Serum M-Protein	Serum M-Protein ≥ 0.5 g/dL and urine M-Protein < 200 mg/24hours or missing
Urine M-Protein	Serum M-Protein < 0.5 g/dL or missing and urine M-Protein ≥ 200 mg/24hours
Serum M-Protein and Urine M-Protein	Serum M-Protein ≥ 0.5 g/dL and urine M-Protein ≥ 200 mg/24hours

Molecular subtype at initial diagnosis

Molecular subtype included cytogenetics analysis by FISH (as collected in the e-CRF).

Molecular subtype at study entry

Molecular subtype included cytogenetics analysis by FISH which are 17p deletion, t (4, 14), and t (14; 16). High risk group is defined as patients with at least one chromosomal abnormality.

Prior anticancer therapies

- Prior anticancer treatments: number of prior lines (2, 3, 4, 5, 6, 7 and ≥ 8 and as a quantitative variable), main category of drug (i.e., alkylating agent, anthracycline, proteasome inhibitor, immunomodulatory drugs others), drug name (i.e., melphalan, cyclophosphamide, doxorubicin, lenalidomide, pomalidomide, thalidomide, bortezomib, carfilzomib, ixazomib, elotuzumab, and panobinostat), time from completion of last line of treatment to first Investigational Medicinal Product (IMP) administration (months), best response to last line, duration of last line of therapy.

In addition, the refractory status to each anticancer treatment will be derived. A patient is considered to be refractory if any of the following conditions are met:

- Progression date and anticancer treatment end date are complete and progression date is within (≤) 60 days of anticancer treatment end date (progression date – anticancer treatment end date ≤ 60 days). If only the day is missing for either date or both dates, and the progression date and anticancer treatment end date corresponds to two consecutive months within the same year, then, the patient will be considered refractory, otherwise they will be considered not refractory.
- Best overall response is SD or PD.
- Reason for treatment discontinuation is "disease progression"

- Prior transplant: number (%) of patients with transplant, number (%) of transplant by patient (1, 2 and ≥3)
- Prior surgery: number (%) of patients with any prior surgery and time from last surgery to first IMP administration (months)
- Prior radiotherapy: number (%) of patients with any prior radiotherapy, intent (curative and palliative), type (systemic, internal beam, and external beam), and time from last radiotherapy to first IMP administration (months)

Any technical details related to computation, dates, and imputation for missing dates, are described in Section 2.5.

2.1.2 Prior or concomitant medications (other than anticancer therapies)

All medications taken within 7 days prior to first dose of IMP, at any time during the treatment period, and up to 30 days after the last isatuximab administration are reported in the e-CRF.

All medications will be coded using the World Health Organization-Drug Dictionary (WHO-DD) version in effect at Sanofi (or the data management vendor) at the time of the data base lock.

- Prior medications are those the patient used prior to first isatuximab administration. Prior medications can be discontinued before first administration or can be ongoing during treatment phase.
- Concomitant medications are any treatments received by the patient concomitantly to isatuximab, from first dose to the date of last administration + 30 days. A given medication can be classified both as a prior medication and as a concomitant medication. Concomitant medications do not include medications started during the post treatment period (as defined in the observation period in Section 2.1.4).
- Post treatment medications (excluding post anticancer treatments) are those the patient took from 31 days after last isatuximab administration up to the end of the study.

Pre-medication

Patients are to routinely receive pre-medications prior to isatuximab infusion to reduce the incidence and severity of hypersensitivity reactions. Pre-medications were defined in the protocol as non-IMP(s). The recommended pre-medication agents were: diphenhydramine 25-50 mg IV (or equivalent), methylprednisolone 100 mg IV (or equivalent), ranitidine 50 mg IV (or equivalent), and acetaminophen 650-1000 mg po 15-30 minutes (but no longer than 60 minutes) prior to isatuximab infusion. Analysis of pre-medications will focus on antihistamine, corticosteroids, h2 blocker, and acetaminophen given (start and stop dates) on the days of isatuximab administrations.

Any technical details related to computation, dates, imputation for missing dates are described in Section 2.5.

2.1.3 Efficacy endpoints

All efficacy endpoints are defined as secondary objectives.

Disease assessments are performed every cycle by the Independent Adjudication Committee (IAC) using the IMWG criteria. The assessment of "Progressive disease" by the site doctor (collected in e-CRF) will not be used for phase 1 in efficacy analysis.

The following efficacy endpoints will be derived for the phase 1 part of the study.

Best overall response (BOR): defined as the best sequential response in every cycle's assessment from the start of treatment through the entire study excluding any time point following the start of other treatment for MM. The ordering of evaluations from best to worse is: stringent complete response (sCR), complete response (CR), very good partial response (VGPR), partial response (PR), minimal response (MR), stable disease (SD), progressive disease (PD), not evaluable (NE). Confirmation of response is needed.

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, death before the analysis cutoff date or death before the date of initiation of new anticancer treatment, PFS will be censored at the earliest of the date of the last valid assessment not showing disease progression performed before initiation of new anticancer treatment or the analysis cutoff date, whichever is earlier.

Duration of response (DOR): DOR is defined as the time from first response that is subsequently confirmed to the first documented tumor progression or death. If progression or death is not observed, the date of the last valid disease assessment performed before cutoff date or initiation of

a new anticancer treatment will be used. DOR is determined only for patients who have achieved a response of ≥ PR and will not be calculated for patients who did not achieve a response.

Time to response (TTR): TTR is defined as the time from first dose to first response (PR or better) that is subsequently confirmed.

2.1.4 Safety endpoints

The safety analysis will be based on the reported adverse events and other safety information, such as clinical laboratory data, vital signs, ECG, etc.

Observation period

The observation period will be divided into 3 periods: pre-treatment, on-treatment and post-treatment.

- The **pre-treatment period** is defined as the time from when the patients give informed consent and the start of isatuximab.
- The **on-treatment period** is defined as the time from first dose of isatuximab up to 30 days after the last dose of isatuximab.
- The **post-treatment period** is defined as the time from 31 days after the last dose of isatuximab to the study closure.

2.1.4.1 Adverse events variables

All adverse events occurring from informed consent signature until at least 30 days after the last isatuximab administration and new adverse events related to isatuximab on the post-treatment period will be collected in the e-CRF. The severity of AEs will be assessed according to NCI-CTCAE version 4.03.

All adverse events (including serious adverse events [SAEs]) will be coded to a lower-level term (LLT), preferred term (PT), high-level term (HLT), high-level group term (HLGT), and associated primary system organ class (SOC) using the version of Medical Dictionary for Regulatory Activities (MedDRA) in effect at Sanofi (or the data management vendor) at the time of the data base lock.

Adverse event observation period

- Pretreatment adverse events are adverse events that developed or worsened or became serious during the pre-treatment period.
- Treatment-emergent adverse events are adverse events that developed or worsened or became serious during the on-treatment period.
- Post-treatment adverse events are adverse events that developed or worsened or became serious during the post-treatment period.

Adverse events of special interest

The following AEs are considered adverse events of special interest (AESIs):

- Acute infusion associated reactions (IARs)
- DLTs
- Symptomatic overdose
- Pregnancy occurring in a female patient or in a female partner of a male patient

Infusion associated reactions

Infusion associated reactions, commonly observed with monoclonal antibodies, include AEs with onset date typically within 24 hours from the start of each isatuximab infusion (See Section 6.6 of the protocol for guidelines for IARs management). As described above, IARs are considered to be AESI.

Two analyses of IARs will be performed. The first one will be based on the investigator's reporting of IARs (i.e., as AESIs). For each IAR-AESI, the sites were instructed to report a generic term (infusion related reaction) and each individual symptom. For IAR analyses based on the generic term, a customized MedDRA query (CMQ) including the single preferred term of infusion related reaction will be used.

The second analysis of IAR will include TEAEs occurring within 24 hours (one table including causally related TEAEs, one table including all TEAEs regardless of causal relationship) from the start of each isatuximab infusion (i.e., TEAEs with onset on the same calendar day of the isatuximab infusion or on the following day).

Respiratory AEs

Analysis of respiratory TEAEs will focus particularly on the groupings by CMQ.

Hematological analyses

Neutropenic complications will focus particular on the groupings by CMQ.

2.1.4.2 Deaths

The deaths observation period are based on the observation periods defined in Section 2.1.4.

- Death on-treatment: deaths occurring during the on-treatment period
- Death post-treatment: deaths occurring during the post-treatment period

2.1.4.3 Laboratory safety variables

Clinical laboratory data consists of blood analysis, including hematology, clinical chemistry, and urinalysis. Clinical laboratory values will be converted into standard international units and international units that will be used in all listings and tables.

Blood samples for clinical laboratories will be taken as defined in the study flow charts and as clinically indicated. The laboratory parameters will be classified as follows:

- Hematology
  - **Red blood cells and platelets and coagulation:** hemoglobin, hematocrit, mean corpuscular volume, red blood cell count, platelet count, prothrombin time (expressed as international normalized ratio), activated partial thromboplastin time
  - **White blood cells:** white blood cell count, neutrophils, lymphocytes, monocytes, basophils, eosinophils
- Clinical chemistry
  - **Metabolism:** glucose, total protein, albumin
  - **Electrolytes:** sodium, potassium, chloride, calcium, corrected serum calcium, phosphate, magnesium
  - **Renal function:** creatinine, blood urea nitrogen, uric acid, e-GFR (revised equations for e-GFR in Japanese)
  - **Liver function:** alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, lactate dehydrogenase, total and conjugated (direct) bilirubin
  - **Pregnancy test:** serum β-human chorionic gonadotropin (all female patients)
  - **Hepatitis screen:** hepatitis B surface antigen (HBs-Ag, HBc-Ab, and HBs-Ab), HBV-DNA, anti-hepatitis-C antibody (HCV-Ab)

Urine samples will be collected as follows:

- **Urinalysis –** quantitative: pH, leukocytes, erythrocytes and specific gravity
- **Urinalysis –** qualitative: blood, ketones, bilirubin, leucocytes, nitrites, proteins and glucose

2.1.4.4 Vital signs variables

Vital signs include: heart rate, respiratory rate, temperature, body weight, and systolic/diastolic blood pressure.

2.1.4.5 Electrocardiogram variables

Electrocardiogram variable include: 12 leads electrocardiogram and 2-D echocardiogram or MUGA scan.

2.1.4.6 Other safety endpoints

Other safety endpoints include:

- Cytokines
  - TNF-α,IL-4, IL-6, IL-1-β, IFN-γ
- IAR laboratory test
  - Complement (C3a, C4, CH50)
  - Serum tryptase
- Chest X-ray at baseline and as clinically indicated
- Tumor lysis syndrome (TLS)

2.1.5 Pharmacokinetic variables

The PK sampling times were provided in the study flowcharts.

Isatuximab concentrations will be analyzed with the PKDMS software (Pharsight) using non-compartmental methods for all cohorts. The following PK parameters will be calculated following the first administration:

- Concentration observed at the end of an IV infusion (C_{eoi})
- Maximum observed concentration (C_{max})
- Time to reach C_{max} (t_{max})
- Concentrations just before drug infusion (C_{trough})
- AUC over the dosing interval (AUC_{1week})

C_{trough} are defined as sample collected before dosing of all cycles, and in a time window of 6 to 8 days after the previous start of infusion for the QW administration.

2.1.6 CD38 Receptor density

CD38 RD will be assessed from bone marrow aspirates at baseline.

2.1.7 Immune response

Human ADA status to isatuximab was assessed during the study as defined in the protocol.

Observation period

The observation period will be divided into 2 periods: ADA pre-treatment and ADA on-study observation.

- ADA pre-treatment period: The ADA pre-treatment period is defined as the time from signed informed consent to the first isatuximab administration.

- ADA on-study observation period: the ADA on-study observation period is defined as the time from first isatuximab administration until Cycle 10.

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

ADA attributes:

- Pre-existing ADA is defined as ADA that was present in samples drawn during the ADA pretreatment period.
- Treatment boosted ADA is defined as preexisting ADA with an increase in titer value between pre-treatment and post-treatment samples of at least two titer steps during the ADA on-study observation period. With a 2-fold serial dilution, this means that the posttreatment sample titer value is at least (≥) 4 fold of pretreatment titer value.
- Treatment-induced ADA is defined as ADA that developed at any time during the ADA on-study observation period in patients without pre-existing ADA, including patients without pretreatment samples.
- Transient ADA response is defined by:
  - Treatment induced ADA detected only at one sampling time point during the ADA on study observation period (excluding the last sampling time point), OR
  - Treatment induced ADA detected at two or more sampling time points during ADA on-study observation period, where the first and last ADA-positive samples (irrespective of any negative samples in between) are separated by a period less than 16 weeks, and the patient's last sampling time point is ADA negative.
- A persistent ADA response is defined by:
  - Treatment induced ADA detected at two or more sampling time points during the ADA on-study observation period, where the first and last ADA-positive on study samples are separated by at least 16 weeks (irrespective of any negative samples in between), OR
- Indeterminate ADA response is defined by:
  - Treatment induced ADA detected only at the last sampling time point with all previous samples being negative, OR
  - The last two samples being ADA-positive and separated by a period of less than 16 weeks.

ADA response endpoints:

- An **ADA positive patient** is defined as a patient with at least one treatment-induced or treatment-boosted ADA positive sample at any time during the on-study observation period
- **ADA incidence** is defined as the number of ADA positive patients among evaluable patients divided by the number of evaluable patients.

- **ADA prevalence** is defined as the sum of the number of patients with preexisting ADA and the number of patients with treatment induced ADAs, divided by the number of evaluable patients

2.1.8 Pharmacodynamic/genomics endpoints

Not applicable.

2.1.9 Quality-of-life endpoints

Not applicable.

2.1.10 Health economic endpoints

Not applicable.

2.1.11 Exploratory endpoints

Exploratory endpoints are FISH, MRD, immune genetic determinants, immune phenotyping bone marrow/blood, and soluble CD38.

2.1.12 Further therapy after discontinuation of investigational medicinal product administration during the study

Further therapies after discontinuation of IMP will be assessed.

2.2 DISPOSITION OF PATIENTS

This section describes patient disposition for both patient study status and the patient analysis populations.

Screened patients are defined as any patients who signed the informed consent. A listing of screening failure patients (screened patients who were not treated with isatuximab) and reason for screening failure will be provided.

The number and percentage (when applicable) of patients in each of the following analysis population will be provided:

- All treated/safety population
- DLT evaluable population
- Pharmacokinetics population
- ADA evaluable population

For all above categories (except for the all treated population) percentages will be calculated using the number of patients in the all treated population. For the all treated population, no percentages will be calculated.

For patient study status, the number and percentage of patients in each of the following categories will be provided using the all treated/safety population:

- Patients off treatment and reasons for treatment discontinuation
- Patients on treatment at time of the analysis cut-off date

Major deviation potentially impacting efficacy/safety analyses include:

- No prior treatment with IMiD and PI (for 2 cycles or 2 months of treatment)
- Was not refractory to the most recently received both IMiD and PI included therapy
- Did not achieve an MR or better to all prior lines of therapy.

All critical or major deviations will be summarized in a table giving numbers and percentages of patients with deviations. Protocol deviation will also be listed.

2.2.1 Randomization and drug dispensing irregularities

Not applicable, as this is a non-randomized study.

2.3 ANALYSIS POPULATIONS

2.3.1 All treated/safety populations

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.

2.3.2 DLT evaluable population

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.

2.3.3 Pharmacokinetic population

The PK parameter analysis will be performed on the all treated/safety population who have a concentration data.

2.3.4 ADA population

The ADA evaluable population will include all treated patients with at least one ADA assessment with a reportable during the ADA on-study observation periods.

2.4 STATISTICAL METHODS

2.4.1 Demographics and baseline characteristics

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

Parameters described in Section 2.1.1 will be summarized by dose level cohort and overall group using descriptive statistics.

Past medical or surgical history other than multiple myeloma will be summarized by SOC (sorted by internationally agreed order) and PT (sorted by descending frequency in overall group and alphabetical order) for the all treated population.

2.4.2 Prior or concomitant medications (other than anticancer therapies)

Prior and concomitant medications will be presented for the all treated population.

Medications will be summarized according to the WHO-DD dictionary, considering the first digit of the anatomical therapeutic chemical (ATC) class (anatomical category) and the first 3 digits of the ATC class (therapeutic category). All ATC codes corresponding to a medication will be summarized, and patients will be counted once in each ATC category (anatomical or therapeutic) linked to the medication. Therefore, patients may be counted several times for the same medication.

The table for prior and concomitant medications will be sorted by decreasing frequency of ATC followed by all other therapeutic classes based on the overall incidence across all dose levels (i.e., the all patients column). In case of equal frequency regarding ATCs, alphabetical order will be used.

Pre-medications

Number (%) of patients with pre-medications (antihistamine, corticosteroids, h2 blocker, and acetaminophen) will be summarized by each administration until 7 and more than 7.

2.4.3 Extent of investigational medicinal product exposure and compliance

The extent of IMP exposure will be assessed and summarized by dose level cohort within the all treated population (Section 2.3.1).

The dose information will be assessed by the following variables.

- Number of cycles started
- Duration of isatuximab exposure (or time on-treatment) in weeks: defined as {min(date of last dose of isatuximab + X days, date of death) – first dose date} / 7 (X equals to 7 in cycle 1 and 14 in the subsequent cycle). The theoretical duration of a cycle is 28 days
- Actual dose in mg/kg: for a given cycle and day of administration, the actual dose in mg/kg corresponds to the actual dose in mg administered at this time point divided by the actual body weight as measured at each time point
- Cumulative dose in mg/kg: the cumulative dose is the sum of all actual doses of isatuximab, expressed in mg/kg, given from first to last administration
- Actual dose intensity (ADI) in mg/kg/week: defined as the cumulative dose (in mg/kg) divided the duration of isatuximab exposure (in weeks)
- Relative dose intensity (RDI) in %: 100 × ADI (mg/kg/week) / Planned Dose Intensity (mg/kg/week)

Planned dose intensities corresponds to the planned dose (mg/kg) received at Day 1 of cycle 1, multiplied by the theoretical total number of doses during the started cycles (count 2 for Q2W and 4 for QW), divided by the theoretical cycle duration expressed in weeks (i.e., 4 weeks), regardless of dose/schedule changes (as defined in the protocol section 6.5). ADI and RDI will be calculated separately in cycle 1 and subsequent cycles respectively, due to the difference of administration interval.

Total number of cycles started, number of cycles started by patients as a quantitative variable and by category (i.e., number [%] of patients receiving at least 1 cycle, at least 2 cycles…), duration of isatuximab exposure, cumulative dose, ADI, RDI, and RDI by category (< 80%, [80 - 105%), ≥105%) will be summarized by descriptive statistics.

The following variables will be computed to describe dose delays and interruption:

- Cycle delayed is defined as follows:
  - A cycle is deemed as delayed if the start date of the current cycle - 28 - start date of the previous cycle is >3 days. Cycle delay is not defined for the first cycle.
- Infusion delay: within cycle 1, an infusion is deemed to be delayed if start date of the current administration – start date of previous administration – the theoretical duration (which is 7 days) is ≥3 days. For subsequent cycles (≥cycle 2), an infusion is deemed to be delayed if start date of the current administration – start date of previous administration – the theoretical duration (which is 14 days) is ≥4 days
- Dose interruption: A dose will be considered to be interrupted if the isatuximab administration is temporarily stopped during an infusion and then restarted (typically in case of Grade 2 IARs).
- Dose reduction: although not allowed in the study protocol, potential dose reductions will be screened and reported in the clinical study report. The first administration will not be counted as a dose reduction. For the second and subsequent isatuximab administrations,

dose reduction will be determined using the dose level intervals provided in Table 5, by comparing the current dose level to the previous dose level. If the current dose level is not within the same dose level interval as the previous dose level, then the current dose level is considered reduced.

Table 5 – Dose reduction criteria

Actual dose level	Dose level interval
Dose level 1 (10 mg/kg)	>0 mg/kg and ≤15 mg/kg
Dose level 2 (20 mg/kg)	>15 mg/kg and ≤25 mg/kg

- Infusion not completed: patients who received less than 90% of the planned dose at an infusion.

Dose modification will be analyzed at the patient, cycle, and total number of isatuximab administration levels as follows:

- Patient level
  - Number of patients
  - Number (%) of patients with at least 1 dose reduction
  - Number (%) of patients with at least 1 infusion interrupted
  - Number (%) of patients with at least 2 infusion interrupted
  - Number of patients who could have a cycle delayed (patients who received ≥2 cycles, used for % calculation in this section):
    - Number (%) of patients with at least 1 cycle delayed
      - Number (%) of patients with a maximum cycle delayed between 4 and 7 days
      - Number (%) of patients with a maximum cycle delayed > 7 days
    - Number of patients who could have an infusion delay (patients who received ≥2 infusions, used for % calculation in this section).
      - Number (%) of patients with at least 1 infusion delay.
- Cycle level
  - Number of cycles administered (used for % calculation for this level)
  - Number (%) of cycles delayed
    - Number (%) of cycles with delay between 4 and 7 days
    - Number (%) of cycles with delay on > 7 days
- Total number of isatuximab administration level
  - Total number of isatuximab administration (used for % calculation for this level)
    - Number (%) of isatuximab administration interrupted

- Number (%) of isatuximab infusions interrupted more than once

- Number of infusion interrupted at (with % calculated using the total number of infusions interrupted): 1st infusion, 2nd infusion, subsequent infusions.
  - Time from infusion start to first interruption in minutes (quantitative (descriptive statistics) and qualitative: 5<, 5-10, 11-30, 31-40, 41-50, 51-60, 61-90, 91-120, >120), missing.
- Number (%) of infusions not completed (patients who received less than 90% of the planned dose)

Duration of infusion is defined as the time from the start (date/time) of infusion to the end (date/time) of infusion. It will be summarized with descriptive statistics for first and subsequent infusions. A listing of dosing data will be provided and include the following variables, number of cycles started, cycle-day, start date, cycle delayed, actual dose in mg/kg, dose interruption, dose reduced and dose not complete.

2.4.4 Analyses of efficacy endpoints

BOR will be summarized.

A listing of best percent change in % plasma cell in bone marrow biopsy will be provided and will include the following variables: measurable paraprotein at baseline, best percent change in paraprotein, BOR, baseline plasma cells count, best post baseline percent change in plasma cells count (only for CR confirmation) and MRD.

2.4.5 Analyses of safety data

The summary of safety results will be presented by dose level cohort.

General common rules

All safety analyses will be performed on the safety population as defined in Section 2.3.1. Unless otherwise specified, the baseline value is defined as the last available value before the first isatuximab administration.

2.4.5.1 Analyses of adverse events

Generalities

The primary focus of adverse event reporting will be on treatment-emergent adverse events. Pre-treatment and post-treatment adverse events will be described separately.

If an adverse event date/time of onset (occurrence, worsening, or becoming serious) is incomplete, the adverse event will be classified as pre-treatment, treatment-emergent, or post-treatment, according to the cycle number or visit of onset. The algorithm for imputing date of onset will be conservative and will classify an AE as treatment emergent unless there is definitive information to determine it is pretreatment or post-treatment. Details on classification of adverse events with missing or partial onset dates are provided in Section 2.5.

The grade will be taken into account in the summary. For patients with multiple occurrences of the same event during the observation period, the maximum grade is used.

Sorting within tables ensures the same presentation for the set of all adverse events within the observation period (pre-treatment, treatment-emergent, and post-treatment). For that purpose, the table of all treatment-emergent adverse events presented by SOC and PT sorted by the internationally agreed SOC order and decreasing frequency of PTs within SOCs in the highest dose level cohort will define the presentation order for all other tables unless otherwise specified.

The following treatment-emergent adverse event summaries will be generated by dose level for the safety population.

- Overview of treatment-emergent adverse events, summarizing number (%) of patients with any
  - Treatment-emergent adverse event (TEAE)
  - Grade 3-5 TEAE
  - Drug-related TEAE
  - Grade 3-5 drug-related TEAE
  - Serious TEAE
  - Drug-related serious TEAE
  - TEAE leading to death
  - TEAE leading to permanent treatment discontinuation
  - Dose limiting toxicity
  - Infusion associated reaction (excluding symptoms)
  - Grade 3-5 infusion associated reaction (excluding symptoms)
- All TEAEs by primary SOC, HLGT, HLT and PT, showing number (%) of patients with at least 1 treatment-emergent adverse event sorted by the SOC internationally agreed order. The other levels (HLGT, HLT and PT) will be presented in alphabetical order.
- All TEAEs by grade, primary SOC, and PT, showing the number (%) of patients with at least 1 treatment-emergent adverse event by grade (i.e., all grade, ≥ grade 3).
- All serious TEAEs by primary SOC and PT, showing the number (%) of patients with at least 1 serious treatment-emergent adverse event.

- All TEAEs related to isatuximab, by primary SOC and PT, showing the number (%) of patients with at least 1 treatment-emergent adverse event related to isatuximab.
- All serious TEAEs related to isatuximab, by primary SOC and PT, showing the number (%) of patients with at least 1 treatment-emergent serious adverse event related to isatuximab.
- All TEAEs leading to treatment discontinuation, by primary SOC and PT, showing the number (%) of patients.
- All TEAEs leading to dose delay or interrupted, by primary SOC and PT, showing the number (%) of patients.
- All TEAEs with a fatal outcome, by primary SOC and PT, showing the number (%) of patients.
- All treatment-emergent DLT by primary SOC and PT, showing the number (%) of patients.
- All treatment-emergent IAR by primary SOC and PT, showing the number (%) of patients.
- IAR-AESI (using the CMQ corresponding to the generic term of infusion related reaction reported by investigator as an AESI):
  - Analysis by patient: number of patients (used as denominator), worst grade by patient, number of episodes by patient (only 1 episode, ≥1 episode, ≥2 episodes, …. – an episode corresponds to a unique AE reference ID), first occurrence of IARs, patients with IAR at the first and/or subsequent isatuximab infusion, and number (%) of patients with at least 2 episodes of IARs at the same infusion
  - Analysis by infusion: number of infusions (used as denominator), worst grade by infusion (a patient can have several IAR episodes at the same infusion).
  - Analysis by episode: number of episode (used as denominator), proportion of IARs occurring at each infusion, IAR duration, and day of onset
- IAR-AESI including symptoms as reported by investigator
  - Summary of IAR-AESI by SOC and PT
  - Listing of IAR-AESI

All AEs, AEs related to isatuximab, DLTs, IARs, respiratory AE, neutropenic complications, SAEs, and AEs leading to permanent treatment discontinuation are listed separately.

2.4.5.2 Deaths

Number (%) of patients who died by study period (on-treatment and post-treatment) and within 60 days from first dose of study treatment, and cause of death will be summarized. All deaths with relevant information (which are study period, cause of death, death date, etc.) will be listed.

2.4.5.3 Analyses of laboratory variables

The summary statistics (including number, mean, median, standard deviation, minimum, and maximum) of all laboratory tests will be calculated for each planned visit (for cycle 1 to cycle 3) by dose level cohort.

Each laboratory test result will be graded by NCI CTCAE (version 4.03), when applicable. Sponsor generic ranges are used for the grading of laboratory results, otherwise site ranges are used. For patients with multiple occurrences of the same laboratory variable during the on-treatment period, the maximum grade (worst) per patient will be used. The number (%) of patients with abnormal laboratory tests at baseline and during the on-treatment period will be presented by all grades and each grade. At baseline, the last available value before or on the date of first study treatment administration (excluding repeated tests) will be used.

All laboratory variables will be listed.

2.4.5.4 Analyses of vital sign variables

The summary statistics (including number, mean, median, standard deviation, minimum, and maximum) of all vital signs variables will be calculated for each planned visit (pre-infusion, mid-infusion and end-infusion for cycle 1 to cycle 3) by dose level cohort.

The incidence of potentially clinically significant abnormalities (PCSAs) at any time during the on-treatment period will be summarized by dose level cohort.

The PCSA values are defined as abnormal values considered medically important by the Sponsor according to predefined criteria/thresholds based on literature review and defined by the Sponsor for vital signs. PCSA criteria will determine which patients had at least 1 PCSA during the on-treatment period, taking into account all evaluations performed during the on-treatment period, including nonscheduled or repeated evaluations (Appendix A).

A listing of vital signs will be provided.

2.4.5.5 Analyses of electrocardiogram variables

Results of ECG will be listed.

2.4.5.6 Analyses of other safety endpoints

ECOG PS and results of chest X-ray will be listed.

The patients with TLS reported under the TLS standard MedDRA query (SMQ) will be listed.

2.4.6 Analyses of pharmacokinetic, CD38 receptor density and immune response

2.4.6.1 Pharmacokinetic variables

All individual concentrations and all pharmacokinetic parameters if isatuximab will be tabulated using descriptive statistics: arithmetic and geometric mean, median, standard deviation, standard error of the mean (SEM) (optional), coefficient of variation (CV), minimum, maximum and number of available observations, using PKDMS.

Individual and mean plasma concentration over time (Day) and individual and mean PK parameters will be represented graphically after 1st administration by dose level cohort.

Individual and mean C_{trough} of isatuximab will be represented graphically as function of actual sampling time (Day) over study period by dose level cohort.

2.4.6.2 CD38 receptor density

CD38 RD will be summarized with descriptive statistics by dose level cohort and listed with BOR.

2.4.6.3 Immune response

Using the ADA evaluable population, the number (%) of patients will be provided for the following if at least one positive observed:

- Pre-existing ADA
- ADA negative at baseline
- On study ADA
  - Treatment-induced ADA
  - Persistent ADA
  - Transient ADA
  - Treatment boosted ADA
  - Indeterminate ADA
  - Last sample positive
- ADA prevalence
- ADA incidence

Data listing of each ADA sample results for patients evaluable for ADA will be listed.

2.4.7 Analyses of quality of life/health economics variables

Not applicable.

2.4.8 Analyses of exploratory variables

CD38 RD and soluble CD38 will be summarized with descriptive statistics for responder/non-responder. A responder is a patient with IAC assessment response ≥ PR. In addition, summary of BOR will be provided by CD38 RD level and immune generic determinants, and a graph showing responder/non-responder rate (in y-axis) by CD38 RD level, soluble CD38 and immune phenotyping will be provided. All variables are listed.

2.4.9 Further therapy after discontinuation of investigational medicinal product administration during the study

Further therapy for MM will be listed and not summary table will be provided.

2.5 DATA HANDLING CONVENTIONS

2.5.1 General conventions

For the data censored at detection limits, its value will be substituted by DL/2.

2.5.2 Data handling conventions for secondary efficacy variables

Not applicable.

2.5.3 Missing data

For categorical variables, patients with missing data are not included in calculations of percentages unless otherwise specified. When relevant, the number of patients with missing data is presented.

Handling of disease characteristics missing/partial dates

- If the day is missing, it will be estimated by 1.
- If the month is missing, it will be estimated by 1 (only for medical history variables).
- If the year is missing, no estimation will be performed.

Handling of medication missing/partial dates

No imputation of medication start/end dates or times will be performed. If a medication date or time is missing or partially missing and it cannot be determined whether it was taken prior or concomitantly, it will be considered a prior, concomitant, and post-treatment medication.

For post anticancer treatments, if the anticancer treatment start date is missing, it will be imputed as follows:

1. If the anticancer treatment start day is missing and the anticancer treatment start month and year are the same as the study treatment end month and year, the anticancer treatment start day will be set equal to the date of last study treatment administration + 1.
2. If the anticancer treatment start day is missing and the anticancer treatment start month is not missing and the anticancer treatment start year is after the study treatment end year, the anticancer treatment start day will be set to 01.
3. If the anticancer treatment start day is missing and the anticancer treatment start month is after the study treatment end month and the anticancer treatment start year is the same as treatment end year, the anticancer treatment start day will be set to 01.
4. If the anticancer treatment start day and month are missing and the anticancer treatment start year is the same as study treatment end year, the anticancer treatment start date will be set equal to the date of last study treatment administration + 1.
5. If the anticancer treatment start day and month are missing and the anticancer treatment start year is after the study treatment end year, the anticancer treatment start day and month will each be set to 01.
6. If the anticancer treatment start day is missing and anticancer treatment start month is before the study treatment end month and the anticancer treatment start year is the same as treatment end year, the anticancer treatment start day will be set to 01.
7. If the anticancer treatment start day, start month and start year is missing, the anticancer treatment start date will be set equal to the treatment end date + 1.

Handling of adverse events with missing/partial dates

Missing or partial adverse event onset dates and times will be imputed so that if the partial adverse event onset date/time information or cycle/visit number does not indicate that the adverse event started prior to treatment or after the treatment-emergent adverse event period, the adverse event will be classified as treatment-emergent. No imputation of adverse event end dates/times will be performed. These data imputations are for categorization purpose only and will not be used in listings. No imputation is planned for date/time of adverse event resolution.

Handing of adverse events with missing grade

Missing grades, if any, will be included in the “all grade” category.

Handling of missing assessment of relationship of adverse events to investigational medicinal product

If the assessment of the relationship to isatuximab is missing, then the relationship to isatuximab has to be assumed and the adverse event considered as such in the frequency tables of possibly related adverse events, but no imputation should be done at the data level.

Handling of potentially clinically significant abnormalities

If a patient has a missing baseline he will be grouped in the category "normal/missing at baseline."

For PCSAs with 2 conditions, one based on a change from baseline value or a normal range and the other on a threshold value, with the first condition being missing, the PCSA will be based only on the second condition.

Measurements flagged as invalid by the laboratory will not be summarized or taken into account in the computation of PCSA values.

2.5.4 Windows for time points

An episode occurred during a cycle if the date of sampling is equal to or after (≥) the first date of the cycle, but prior to the first day of the next cycle.

2.5.5 Unscheduled visits

Unscheduled visit measurements of laboratory data and vital signs will be used for only computation of worst values and/or grades.

2.5.6 Pooling of centers for statistical analyses

Data from all sites will be pooled together for analysis.

2.5.7 Statistical technical issues

Not applicable.

3 INTERIM ANALYSIS

Not applicable.

4 DATABASE LOCK

The database lock is planned to be locked twice after phase 2. The first is at approximately 4 months after last patient first dosed. The second is at approximately 12 months after last patient first dosed.

5 SOFTWARE DOCUMENTATION

All summaries and statistical analyses will be generated using SAS version 9.2 or higher.

6 REFERENCES

Not applicable.

7 LIST OF APPENDICES

Appendix A: Potentially clinically significant abnormalities (PCSA) criteria

Appendix B: Sponsor generic ranges

Appendix A Potentially clinically significant abnormalities criteria

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES

Parameter	PCSA	Comments
Vital signs		
HR	≤50 bpm and decrease from baseline ≥20 bpm ≥120 bpm and increase from baseline≥20 bpm	To be applied for all positions (including missing) except STANDING.
SBP	≤95 mmHg and decrease from baseline ≥20mmHg ≥160 mmHg and increase from baseline ≥20 mmHg	To be applied for all positions (including missing) except STANDING.
DBP	≤45 mmHg and decrease from baseline ≥10 mmHg ≥110 mmHg and increase from baseline ≥10 mmHg	To be applied for all positions (including missing) except STANDING.
Weight	≥5% increase from baseline ≥5% decrease from baseline	FDA Feb 2007.

Appendix B Sponsor generic ranges

Table 6 – Hematological parameters

LBTESTCD	LBTEST	GENDER	LBSTRESU	LBGNNRLO
HGB	Hemoglobin	F	g/L	120
HGB	Hemoglobin	M	g/L	135
LYM	Lymphocytes		10^9/L	1
NEUT	Neutrophils		10^9/L	1,8
PLAT	Platelets		10^9/L	150
WBC	Leukocytes		10^9/L	4,5
EOS	Eosinophils		10^9/L	0
BASO	Basophils		10^9/L	0
MONO	Monocytes		10^9/L	0,18
HCT	Hematocrit	M	%	0,41
HCT	Hematocrit	F	%	0,36
RBC	Erythrocytes	F	10^12/L	4
RBC	Erythrocytes	M	10^12/L	4,5

Table 7 – Biochemistry parameters

LBTEST	LBSTRESU	LBGNNRLO - LBGNNRHI
Albumin	g/L	35 - 55
Blood Urea Nitrogen (BUN)	mmol/L	NA-17
Calcium	mmol/L	2,2 - 2,6
Chloride	mmol/L	80 - 115
Glucose	mmol/L	3,9 - 7
Bicarbonate (HCO3)	mmol/L	22 - 29
Potassium	mmol/L	3,5 - 5
Magnesium	mmol/L	0,8 - 1,2
Sodium	mmol/L	129 - 160
Phosphate	mmol/L	1 - 1,4
Protein	g/L	55 - 80
Urea	mmol/L	3,6 - 7,1

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm)
[redacted]	Clinical Approval	[redacted]
[redacted]	Clinical Approval	[redacted]

STATISTICAL ANALYSIS PLAN

A Phase I/ II Study of Isatuximab (Anti-CD38 mAb) administered as a single agent in Japanese Patients With Relapsed AND Refractory Multiple Myeloma

SAR650984-TED14095 (Phase 2)

STATISTICIAN: [redacted]

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ADA:	anti-drug antibodies
AESI:	adverse events of special interest
CT:	computed tomography
DFU:	duration of follow-up
ECG:	electrocardiogram
ECOG:	Eastern Cooperative Oncology Group
e-CRF:	electronic case report form
FISH:	fluorescence in situ hybridization
FLC:	free light chain
IAC:	independent adjudication committee
IAR:	infusion associated reaction
IFN-γ:	interferon-gamma
IL:	interleukin
IV:	intravenous
MM:	multiple myeloma
MRD:	minimal residual disease
MRI:	magnetic resonance imaging
MTD:	maximum tolerated dose
MUGA:	multigated acquisition
NCI-CTCAE:	National Cancer Institute Common Toxicity Criteria for Adverse Event
ORR:	overall response rate
OS:	overall survival
PFS:	progression free survival
PK:	pharmacokinetic
PS:	Performance Status
RD:	receptor density
RRMM:	relapsed and refractory multiple myeloma
SAP:	statistical analysis plan
TNF-α:	tumor necrosis factor alpha

1 OVERVIEW AND INVESTIGATIONAL PLAN

This is an open-label, single arm, local, multi-center study conducted in 2 parts, phase 1 and phase 2. This statistical analysis plan (SAP) describes the statistical methods to be used for the analyses of data collected during the phase 2 part of the study. For the phase 1 part, the SAP is described separately. This SAP should be read in conjunction with the study protocol and electronic case report form (e-CRF).

1.1 STUDY DESIGN AND RANDOMIZATION

The phase 2 part of TED14095 is a study of isatuximab administered as a single agent as an intravenous (IV) infusion every week (QW) during cycle 1 followed by every 2 weeks (Q2W) during subsequent cycles to adult patients with relapsed and refractory multiple myeloma (MM).

1.2 OBJECTIVES

1.2.1 Primary objectives

The primary objective of the phase 2 part of this study is to evaluate efficacy of isatuximab at the recommended dose determined in phase 1 part as assessed by overall response rate (ORR) in Japanese patients with relapsed and refractory multiple myeloma (RRMM).

1.2.2 Secondary objectives

Secondary objectives of the phase 2 part of the study are:

- 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 relationship between baseline CD38 receptor density (RD) on MM cells and efficacy.

1.2.3 Exploratory objectives

The following exploratory objectives will be investigated in the end of phase 2 part of the study.

- To assess minimal residual disease (MRD) in patients achieving 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/ fluorescence in situ hybridization (FISH)) and parameters of clinical response.
- To investigate the relationship between immune genetic determinants, immune phenotype and parameters of clinical response.

1.3 DETERMINATION OF SAMPLE SIZE

The phase 2 part of the study aims to evaluate 33-36 subjects which include the subjects in Phase 1 part at the dose level determined as MTD/recommended dose. Given an assumed true ORR of 28%, the null hypothesis ORR $\leq$ 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% (i.e., 8 responders). The sample size calculation was performed using SAS ver. 9.4 SAS/STAT 13.2, power procedure.

1.4 STUDY PLAN

Safety evaluations are performed continuously throughout the study and included the following:

- AEs according to the National Cancer Institute Common Toxicity Criteria for Adverse Event (NCI-CTCAE) v. 4.03 grading scale
- Vital signs
- Eastern Cooperative Oncology Group Performance Status (ECOG PS)
- 12 lead electrocardiogram (ECG) or 2-D echocardiogram or Multigated Acquisition (MUGA) scan
- Chest X-ray
- Laboratory tests in blood and urine
- Level of human anti-drug antibodies (ADA)
- Cytokines (tumor necrosis factor alpha [TNF-α], interleukin [IL]-1-β, IL-4, IL-6, interferon-gamma [IFN-γ]), complement activators and tryptase

Disease response evaluations are performed every 4 weeks, unless otherwise stated, including:

- M-protein quantification (serum and/or 24-hour urine, protein electrophoresis and immunoelectrophoresis), serum free light chain (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

The following additional evaluation is also performed:

- CD38 RD on bone marrow samples

PK samples are collected in all patients receiving isatuximab as depicted in the PK study flowcharts included in the protocol.

1.5 MODIFICATIONS TO THE STATISTICAL SECTION OF THE PROTOCOL

This section summarizes major changes to the protocol statistical section with emphasis on changes after study start (after the first patient was enrolled). The protocol history table below gives the timing, rationale, and key details of major changes to the protocol statistical section.

Table 1 – Protocol amendment statistical changes

Amendment Number	Date Approved	Rationale	Description of statistical changes
1	13-May-2016	To harmonize the other global studies	Summary of prior anti-cancer therapy
1	13-May-2016	To harmonize the other global studies	Overview of TEAEs
1	13-May-2016	To harmonize the other global studies	Deletion of the description in “Analyses of Pharmacokinetic variables”

1.6 STATISTICAL MODIFICATIONS MADE IN THE STATISTICAL ANALYSIS PLAN

Not applicable as this is the 1st version of the SAP.

2 STATISTICAL AND ANALYTICAL PROCEDURES

2.1 ANALYSIS ENDPOINTS

2.1.1 Demographic and baseline characteristics

The baseline value is defined as the last available value before the first isatuximab administration, unless otherwise specified.

All baseline safety and efficacy parameters (apart from those listed below) are presented along with the on-treatment summary statistics in the safety and efficacy sections (Section 2.4.5 and Section 2.4.4).

Demographic characteristics

Demographic variables are gender (Male, Female), ethnicity (Hispanic or Latino , Not Hispanic or Latino, Not reported, and Unknown), race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Not reported, Unknown), age in years (quantitative and qualitative variable : < 65, [65 - 75) and ≥ 75 years), weight (kg), and ECOG PS at baseline.

Medical or surgical history

Medical or surgical history other than MM will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version in effect at Sanofi (or the data management vender) at the time of the data base lock.

Disease characteristics at initial diagnosis

The following MM characteristics at initial diagnosis will be described: time from initial diagnosis to first isatuximab administration (in years) and by category (<5 years and ≥ 5 years), International Staging System (ISS) stage, and MM subtype (as collected in the e-CRF).

Disease characteristics at study entry

The following MM characteristics at study entry will be displayed: derived ISS stage (Table 2), measurable paraprotein at baseline (Table 3), percent of plasma cells in bone marrow (quantitative results and by category: 0, (0 - 5%), [5 - 20%), [20 - 50%) and ≥ 50%), patients with plasmacytomas, patients with bone lesions, serum β2-microglobulin level in mg/L (quantitative results and by category: < 3.5 mg/L, [3.5 - 5.5 mg/L) and ≥ 5.5 mg/L), serum albumin in g/L (quantitative results and by category: < 35 g/L and ≥ 35 g/L).

Table 2 – ISS staging definition

Stage	Definition
Stage I	Serum β2-microglobulin <3.5 mg/L and serum albumin ≥ 35 g/L
Stage II	serum β2-microglobulin <3.5 mg/L and serum albumin <35 g/L or serum β2-microglobulin 3.5 - <5.5 mg/L regardless of serum albumin levels
Stage III	Serum β2-microglobulin ≥5.5 mg/L regardless of serum albumin levels

Table 3 – Derivation of measurable paraprotein at study entry

Measurable paraprotein	Criteria
Serum M-Protein	Serum M-protein ≥ 0.5 g/dL and urine M-Protein < 200 mg/24hours or missing
Urine M-Protein	Serum M-protein < 0.5 g/dL or missing and urine M-protein ≥ 200 mg/24hours
Serum M-Protein and Urine M-Protein	Serum M-protein ≥ 0.5 g/dL and urine M-protein ≥ 200 mg/24 hours

Molecular subtype at initial diagnosis

Molecular subtype included cytogenetics analysis by FISH (as collected in the e-CRF).

Molecular subtype at study entry

Molecular subtype included cytogenetics analysis by FISH which are 17p deletion, t (4, 14), and t (14; 16). High risk group is defined as patients with at least one chromosomal abnormality. Considering many missing is observed, two kinds of summaries will be provided with imputation from results at initial diagnosis and no imputation (used results at study entry only).

Prior anticancer therapies

- Prior anticancer treatments: number of prior lines (2, 3, 4, 5, 6, 7 and ≥ 8 and as a quantitative variable), main category of drug (i.e., alkylating agent, anthracycline, proteasome inhibitor, immunomodulatory drugs and others), drug name (i.e., melphalan, cyclophosphamide, doxorubicin, lenalidomide, pomalidomide, thalidomide, bortezomib, carfilzomib, ixazomib, elotuzumab, and panobinostat), time from completion of last line of

treatment to first Investigational Medicinal Product (IMP) administration (months), best response to last line, duration of last line of therapy.
In addition, the refractory status to each anticancer treatment will be derived. A patient is considered to be refractory if any of the following conditions are met:

- Progression date and anticancer treatment end date are complete and progression date is within (≤) 60 days of anticancer treatment end date (progression date – anticancer treatment end date ≤ 60 days). If only the day is missing for either date or both dates, and the progression date and anticancer treatment end date corresponds to two consecutive months within the same year, then, the patient will be considered refractory, otherwise they will be considered not refractory.
- Best overall response is SD or PD.
- Reason for treatment discontinuation is "disease progression".

- Prior transplant: number (%) of patients with transplant, number (%) of transplant by patient (1, 2 and ≥3)
- Prior surgery: number (%) of patients with any prior surgery and time from last surgery to first IMP administration (months)
- Prior radiotherapy: number (%) of patients with any prior radiotherapy, intent (curative and palliative), type (systemic, internal beam, and external beam), and time from last radiotherapy to first IMP administration (months)

Any technical details related to computation, dates, and imputation for missing dates are described in Section 2.5

2.1.2 Prior or concomitant medications (other than anticancer therapies)

All medications taken within 7 days prior to first dose of IMP, at any time during the treatment period, and up to 30 days after the last isatuximab administration are reported in the e-CRF.

All medications will be coded using the World Health Organization-Drug Dictionary (WHO-DD) version in effect at Sanofi (or the data management vender) at the time of the data base lock.

- Prior medications are those the patient used prior to first isatuximab administration. Prior medications can be discontinued before first administration or can be ongoing during treatment phase.
- Concomitant medications are any treatments received by the patient concomitantly to isatuximab, from first dose to the date of last administration + 30 days. A given medication can be classified both as a prior medication and as a concomitant medication. Concomitant medications do not include medications started during the post treatment period (as defined in the observation period in Section 2.1.4).
- Post treatment medications (excluding post anticancer treatments) are those the patient took from 31 days after last isatuximab administration up to the end of the study.

Pre-medication

Patients are to routinely receive pre-medications prior to isatuximab infusion to reduce the incidence and severity of hypersensitivity reactions. Pre-medications were defined in the protocol as non-IMP(s). The recommended pre-medication agents were: diphenhydramine 25-50 mg IV (or equivalent), methylprednisolone 100 mg IV (or equivalent), ranitidine 50 mg IV (or equivalent), and acetaminophen 650-1000 mg po 15-30 minutes (but no longer than 60 minutes) prior to isatuximab infusion. Analysis of pre-medications will focus on antihistamine, corticosteroids, h2 blocker, and acetaminophen given (start and stop dates) on the days of isatuximab administrations.

Any technical details related to computation, dates, imputation for missing dates are described in Section 2.5.

2.1.3 Efficacy endpoints

Response assessments were to be performed on a monthly basis using IMWG criteria (Rajkumar. 2011) and included:

- M-protein quantification (serum and 24-hr urine)
- Serum free light chain levels
- Corrected serum calcium

In case of plasmacytoma at baseline, radiological evaluations were to be performed every 3 cycles or when clinically indicated (i.e., to confirm a progression).

In case of bone lesions at baseline, bone lesion evaluations were to be performed when clinically indicated or to confirm a response or progression. Bone marrow biopsy/aspiration was to be performed to confirm a sCR or CR.

An independent adjudication committee (IAC) independently assessed clinical response using the IMWG response criteria.

Biological responses (≥PR) and progression were to be confirmed on 2 consecutive biological (serum and/or urine M protein) disease assessments. No confirmation was required for radiological assessment.

2.1.3.1 Primary efficacy endpoint(s)

The primary efficacy endpoint is ORR, defined as the proportion of patients with sCR, CR, VGPR or PR as best overall response (BOR) as assessed by the IAC. The BOR will be derived using disease assessments performed from the start of treatment through the entire study excluding any assessments performed after the cutoff date or following the start of further therapies for MM.

The ordering of evaluations from best to worse is: sCR, CR, VGPR, PR, MR, stable disease (SD), progressive disease (PD), not evaluable (NE). BOR for patients without response assessment by the IAC will be ‘Not evaluable’.

Subgroup analyses of BOR using IAC assessment will be performed for the variables listed in Table 4.

Table 4 – List of variables for subgroup analyses

Variable	Description
Age	<70 vs. ≥70
Number of previous lines of therapy	≤6 vs. >6
Gender	Male vs. Female
ECOG PS	0-1 vs. 2
ISS staging at study entry	I vs. II vs. III
High risk cytogenetic	Yes vs. No
Baseline creatinine clearance	<60 ml/min/1.73m^2 vs. ≥60 ml/min/1.73m^2
With plasmacytomas at screening	Yes vs. No

2.1.3.2 Secondary efficacy endpoint(s)

Secondary efficacy endpoints are defined below.

- Duration of Response (DOR) (in weeks): DOR is defined as the time from the date of the first IAC determined response (≥ PR) that is subsequently confirmed, to the date of first IAC determined PD or death, whichever happens earlier (if reported before the analysis cut-off date or the date of initiation of a new anticancer treatment). If progression and death are not observed before the analysis cut-off date or the date of initiation of new anticancer treatment, DOR will be censored at the earliest of the date of the last valid disease assessment not showing disease progression performed prior to initiation of a further anticancer treatment or the analysis cut-off date. DOR is determined only for patients who have achieved a confirmed response of ≥PR.
- Clinical benefit rate (CBR): defined as the proportion of patients with sCR, CR, VGPR, PR or MR as BOR according to IMWG criteria, as determined by the IAC.
- Progression free survival (PFS) (in months): defined as the time interval from the date of first isatuximab administration to the date of the first IAC-confirmed disease progression or the date of death due to any cause, whichever comes first. For patients who did not experience IAC-confirmed disease progression and death before the analysis cut-off date of or the date of initiation of new anticancer treatment, PFS will be censored at the date of the last valid disease assessment not showing disease progression performed prior to initiation of a further anticancer treatment or the analysis cut-off date, whichever comes first.
- Overall survival (OS) (in months): defined as the time interval from the date of first isatuximab administration to death from any cause. In the absence of the confirmation of death before the cut-off date, OS will be censored at the cut-off date or at the last date the patient is known to be alive, whichever comes first.

- Time to response (TTR) (in weeks): TTR is defined as the time from first dose to first IAC response (PR or better) that is subsequently confirmed.
- Duration of follow-up (DFU) (in weeks): DFU is defined as the time from first dose to last response disease assessment before start of other therapy or cut-off date, whichever comes first.
- Best percent change in paraprotein: best percent change in paraprotein will be calculated for the measurable paraprotein parameter defined at baseline excluding anytime point following the start of other anticancer therapy.

2.1.4 Safety endpoints

The safety analysis will be based on the reported adverse events and other safety information, such as clinical laboratory data, vital signs, ECG.

Observation period

The observation period will be divided into 3 periods: pre-treatment, on-treatment and post-treatment.

- The **pre-treatment period** is defined as the time from when the patients give informed consent and the start of isatuximab.
- The **on-treatment period** is defined as the time from the first dose of isatuximab up to 30 days after the last dose of isatuximab.
- The **post-treatment period** is defined as the time from 31days after the last dose of isatuximab to the study closure.

2.1.4.1 Adverse events variables

Adverse events occurring from signature of informed consent form up to 30 days after the last isatuximab administration were to be recorded in the eCRF.

All isatuximab related AEs and SAEs ongoing at time of study treatment discontinuation were to be followed during the follow-up period until resolution or stabilization.

All AEs (including SAEs) will be coded to a lower-level term (LLT), preferred term (PT), high-level term (HLT), high-level group term (HLGT), and associated primary system organ class (SOC) using the version of MedDRA in effect at Sanofi at the time of database lock.

The severity of AEs was assessed according to NCI-CTCAE version 4.03.

Adverse event observation period

- Pre-treatment adverse events are adverse events that developed or worsened or became serious during pre-treatment period
- Treatment-emergent adverse events are adverse events that developed or worsened or became serious during the on-treatment period

- Post-treatment adverse events are adverse events that developed or worsened or became serious during the post-treatment period

Other significant adverse events

Other significant adverse events will include adverse events of special interest (AESIs), respiratory AEs, and specific hematological analyses.

Adverse events of special interest

The following AEs are considered adverse events of special interest:

- Acute infusion associated reactions (IARs)
- Symptomatic overdose
- Pregnancy occurring in a female patient or in a female partner of a male patient

Infusion associated reactions

Infusion associated reactions, commonly observed with monoclonal antibodies, include AEs with onset date typically within 24 hours from the start of each isatuximab infusion (See Section 6.6 of the protocol for guidelines for IARs management). As described above, IARs are considered to be AESI.

Two analyses of IARs will be performed. The first one will be based on the investigator's reporting of IARs (i.e., as AESIs). For each IAR-AESI, the sites were instructed to report a generic term (infusion related reaction) and each individual symptom. For IAR analyses based on the generic term, a customized MedDRA query (CMQ) including the single preferred term of infusion related reaction will be used.

The second analysis of IAR will include TEAEs occurring within 24 hours (one table including causally related TEAEs, one table including all TEAEs regardless of causal relationship) from the start of each isatuximab infusion (i.e., TEAEs with onset on the same calendar day of the isatuximab infusion or on the following day).

Respiratory AEs

Analysis of respiratory TEAEs will focus particularly on the groupings by CMQ.

The respiratory AEs with onset during the post-treatment period will be analyzed separately, according to the same methods above.

Hematological analyses (including both AE and laboratory neutropenia)

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

2.1.4.2 Deaths

The deaths observation period are per the observation periods defined in Section 2.1.4.

- Death on-treatment: deaths occurring during the on-treatment period
- Death post-treatment: deaths occurring during the post-treatment period

2.1.4.3 Laboratory safety variables

Clinical laboratory data consists of blood analysis, including hematology, clinical chemistry, and urinalysis. Clinical laboratory values after conversion will be analyzed into standard international units and international units will be used in all listings and tables.

Blood samples for clinical laboratories will be taken as defined in the study flow charts and as clinically indicated. The laboratory parameters will be classified as follows:

- Hematology
  - **Red blood cells, platelets and coagulation:** hemoglobin, hematocrit, mean corpuscular volume, red blood cell count, platelet count, prothrombin time (expressed as international normalized ratio), activated partial thromboplastin time
  - **White blood cells:** white blood cell count, neutrophils, lymphocytes, monocytes, basophils, eosinophils
- Clinical chemistry
  - **Metabolism:** glucose, total protein, albumin
  - **Electrolytes:** sodium, potassium, chloride, calcium, corrected serum calcium, phosphate, magnesium
  - **Renal function:** creatinine, blood urea nitrogen, uric acid, e-GFR (revised equations for e-GFR in Japanese)
  - **Liver parameters:** alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, lactate dehydrogenase, total and conjugated (direct) bilirubin
  - **Pregnancy test:** serum β-human chorionic gonadotropin (all female patients)
  - **Hepatitis screen:** hepatitis B surface antigen (HBs-Ag, HBc-Ab and HBs-Ab), HBV-DNA, anti-hepatitis-C antibody (HCV-Ab)

Urine samples will be collected as follows:

- **Urinalysis** – quantitative: pH and specific gravity
- **Urinalysis** – qualitative: blood, ketones, bilirubin, leucocytes, nitrites, proteins and glucose

Technical formulas are described in Section 2.5.1.

2.1.4.4 Vital signs variables

Vital signs include: heart rate, respiratory rate, temperature, body weight, and systolic/diastolic blood pressure.

2.1.4.5 Electrocardiogram variables

Electrocardiogram variable include: 12 leads electrocardiogram and 2-D echocardiogram or MUGA scan. ECG was to be performed at screening and if clinically indicated.

2.1.4.6 Other safety endpoints

Other safety endpoints include:

- Cytokines
  - TNF-α, IL-4, IL-6, IL-1-β, IFN-γ
- IAR laboratory test
  - Complement (C3a, C4, CH50)
  - Serum tryptase
- Chest X-ray at baseline and as clinically indicated.
- Tumor lysis syndrome (TLS)

2.1.5 Pharmacokinetic variables

Isatuximab plasma concentrations will be summarized and the following PK individual parameters will be calculated:

- Cumulative AUC over a 1, 2 or 4 week interval (AUC1W, AUC2W, AUC4W)
- C_{trough} (pre-dose concentration) at 1, 2, 4 weeks
- C_{max} at Cycle 1 Day 1, Cycle 2 Day 1 and Cycle 4 Day 1
- Clearance (CL)
- Accumulation ratios (AUCss/AUC1W). AUCss is AUC at steady state.

2.1.6 Immunogenicity

Human ADA to isatuximab was assessed during the study as defined in the protocol.

Observation period

The observation period will be divided into 2 periods: ADA pre-treatment and ADA on-study observation.

- ADA pre-treatment period: The ADA pre-treatment period is defined as the time from signed informed consent to the first isatuximab administration.
- ADA on-study observation period: the ADA on-study observation period is defined as the time from first isatuximab administration until Cycle 10.

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

ADA attributes:

- **Pre-existing ADA** is defined as ADA that was present in samples drawn during the ADA pretreatment period.
- **Treatment boosted ADA** is defined as preexisting ADA with an increase in titer value between pre-treatment and post-treatment samples of at least two titer steps during the ADA on-study observation period. With a 2-fold serial dilution, this means that the post-treatment sample titer value is at least (≥) 4 fold of pretreatment titer value.
- **Treatment-induced ADA** is defined as ADA that developed at any time during the ADA on-study observation period in patients without pre-existing ADA, including patients without pretreatment samples.
- **Transient ADA response** is defined by:
  - Treatment induced ADA detected only at one sampling time point during the ADA on study observation period (excluding the last sampling time point), OR
  - Treatment induced ADA detected at two or more sampling time points during ADA on-study observation period, where the first and last ADA-positive samples (irrespective of any negative samples in between) are separated by a period less than 16 weeks, and the patient's last sampling time point is ADA negative.
- **A persistent ADA response** is defined by:
  - Treatment induced ADA detected at two or more sampling time points during the ADA on-study observation period, where the first and last ADA-positive on study samples are separated by at least 16 weeks (irrespective of any negative samples in between), OR
  - Treatment induced ADA detected in the last two sampling time points (both are positive), irrespective of the time period in between.
  - Indeterminate ADA is defined by treatment induced ADA detected only at the last sampling time point with all previous samples being negative

ADA response endpoints:

- An **ADA positive patient** is defined as a patient with at least one treatment-induced or treatment-boosted ADA positive sample at any time during the on-study observation period

- **ADA incidence** is defined as the number of ADA positive patients among evaluable patients divided by the number of evaluable patients.
- **ADA prevalence** is defined as the sum of the number of patients with preexisting ADA and the number of patients with treatment induced ADAs, divided by the number of evaluable patients.

2.1.7 Biomarker endpoints

2.1.7.1 Receptor density

CD38 RD will be assessed from bone marrow aspirates at the screening.

2.1.7.2 Immune genetic determinants

Immune genetic determinants in peripheral blood plasma samples will be assessed at Cycle 1 Day 1.

2.1.7.3 Immune phenotyping

Immune phenotyping in bone marrow (screening) and/or peripheral blood (Cycle 1 Day 1 and Cycle 3 Day 1) will be assessed.

2.1.7.4 Soluble CD38

Soluble CD38 levels in peripheral blood plasma samples will be assessed at Cycle 1 Day 1.

2.1.8 Quality-of-life endpoints

Not applicable

2.1.9 Health economic endpoints

Not applicable

2.1.10 Further therapy after discontinuation of investigational medicinal product administration during the study

Further therapies after discontinuation of IMP will be assessed.

2.2 DISPOSITION OF PATIENTS

This section describes patient disposition for both patient study status and the patient analysis populations.

Screened patients are defined as any patients who signed the informed consent. A listing of screening failure patients (screened patients who were not treated with isatuximab) and reason for screening failure (when available) will be provided.

The number and percentage (when applicable) of patients in each of the following analysis population will be provided:

- All treated/safety population
- Pharmacokinetics population
- ADA evaluable population

For all above categories (except for the all treated population) percentages will be calculated using the number of patients in the all treated population. For the all treated population, no percentages will be calculated.

For patient study status, the number and percentage of patients in each of the following categories will be provided using the all treated/safety population:

- Patients off treatment and reasons for treatment discontinuation
- Patients on treatment at time of the analysis cut-off date

Major deviations potentially impacting efficacy/safety analyses include:

- No prior treatment with IMiD and PI (for ≥2 cycles or ≥2 months of treatment)
- Was not refractory to the most recently received both IMiD and PI included therapy
- Did not achieve an MR or better to all prior lines of therapy

All critical or major deviations will be summarized in a table giving numbers and percentages of patients with deviations. Protocol deviation will also be listed.

2.2.1 Randomization and drug dispensing irregularities

Not applicable, as this is non-randomized study.

2.3 ANALYSIS POPULATIONS

2.3.1 All treated/safety population

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.

2.3.2 Pharmacokinetic population

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

2.3.3 ADA evaluable population

The ADA evaluable population will include all treated patients with at least one ADA assessment with a reportable during the ADA on-study observation periods

2.4 STATISTICAL METHODS

2.4.1 Demographics and baseline characteristics

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

Parameters described in Section 2.1.1 will be summarized using descriptive statistics.

Past medical or surgical history other than multiple myeloma will be summarized by SOC (sorted by internationally agreed order) and PT (sorted by alphabetical order) for the all treated population.

2.4.2 Prior or concomitant medications (other than anticancer therapies)

Prior and concomitant medications will be presented for the all treated population.

Medications will be summarized according to the WHO-DD, considering the first digit of the anatomical therapeutic chemical (ATC) class (anatomical category) and the first 3 digits of the ATC class (therapeutic category). All ATC codes corresponding to a medication will be summarized, and patients will be counted once in each ATC category (anatomical or therapeutic) linked to the medication. Therefore, patients may be counted several times for the same medication.

The table for prior and concomitant medications will be sorted by decreasing frequency of ATC followed by all other therapeutic classes. In case of equal frequency regarding ATCs, alphabetical order will be used.

Pre-medications

Number (%) of patients with pre-medications (antihistamine, corticosteroids, h2 blocker, and acetaminophen) will be summarized by each administration in cycle 1.

2.4.3 Extent of investigational medicinal product exposure and compliance

The extent of IMP exposure will be assessed and summarized within the all treated population (Section 2.3.1).

The dose information will be assessed by the following variables.

- Number of cycles started
- Duration of isatuximab exposure (or time on-treatment) in weeks is defined depending on the isatuximab administration schedule as follows:
  - If treatment is discontinued at a cycle with QW isatuximab administration: [date of last dose of isatuximab + 7 days – date of first dose of isatuximab] / 7.
  - If treatment is discontinued at a cycle with Q2W isatuximab administration: [date of last dose of isatuximab + 14 days – date of first dose of isatuximab] / 7.
- Actual dose in mg/kg: for a given cycle and day of administration, the actual dose in mg/kg corresponds to the actual dose in mg administered at this time point divided by the actual body weight as measured at each time point
- Cumulative dose in mg/kg: the cumulative dose is the sum of all actual doses of isatuximab, expressed in mg/kg, given from first to last administration
- Actual dose intensity (ADI) in mg/kg/week: defined as the cumulative dose (in mg/kg) divided the duration of isatuximab exposure (in weeks)
- Relative dose intensity (RDI) in %: 100 × ADI (mg/kg/week) / Planned Dose Intensity (mg/kg/week)

Planned dose intensities corresponds to the planned dose (mg/kg) received at Day 1 of cycle 1, multiplied by the theoretical total number of doses during the started cycles (count 2 for Q2W and 4 for QW), divided by the theoretical cycle duration expressed in weeks (i.e., 4 weeks), regardless of dose/schedule changes (as defined in the protocol section 6.5). ADI and RDI will be calculated separately in cycle 1 and subsequent cycles respectively, due to the difference of administration interval.

Total number of cycles started, number of cycles started by patients as a quantitative variable and by category (i.e., number [%] of patients receiving at least 1 cycle, at least 2 cycles…), duration of isatuximab exposure, cumulative dose, ADI, RDI, and RDI by category (< 80%, [80 - 105%), ≥105%) will be summarized by descriptive statistics.

The following variables will be computed to describe dose delays and interruption:

- Cycle delayed is defined as follows:
  - A cycle is deemed as delayed if the start date of the current cycle - 28 - start date of the previous cycle is >3 days. Cycle delay is not defined for the first cycle.
- Infusion delay (within a cycle, excluding day 1): within cycle 1, an infusion is deemed to be delayed if start date of the current administration – start date of previous administration – the theoretical duration (which is 7 days) is ≥3 days. For subsequent cycles (≥cycle 2),

an infusion is deemed to be delayed if start date of the current administration – start date of previous administration – the theoretical duration (which is 14 days) is ≥4 days

- Dose interruption: A dose will be considered to be interrupted if the isatuximab administration is temporarily stopped during an infusion and then restarted (typically in case of Grade 2 IARs).
- Dose reduction: Although not allowed in the study protocol, potential dose reductions will be screened and reported in the clinical study report. The first administration will not be counted as a dose reduction. For the second and subsequent isatuximab administrations, dose reduction will be determined using the dose level intervals provided in Table 5, by comparing the current dose level to the previous dose level. If the current dose level is not within the same dose level interval as the previous dose level, then the current dose level is considered reduced.

Table 5 - Dose reduction criteria

Actual dose level	Dose level interval
Dose level 1 (10 mg/kg)	>0 mg/kg and ≤15 mg/kg
Dose level 2 (20 mg/kg)	>15 mg/kg and ≤25 mg/kg

- Infusions not completed: patients who received less than 90% of the planned dose at an infusion.

Dose delay and interruption will be analyzed at the patient, cycle, and total number of isatuximab administration levels as follows:

- Patient level
  - Number of patients
  - Number (%) of patients with at least 1 dose reduction
  - Number (%) of patients with at least 1 dose interruption
  - Number (%) of patients with at least 2 infusions interrupted
  - Number of patients who could have a cycle delayed (patients who received ≥2 cycles, used for % calculation in this section):
    - Number (%) of patients with at least 1 cycle delayed
      - Number (%) of patients with a maximum cycle delayed between 4 and 7 days
      - Number (%) of patients with a maximum cycle delayed > 7 days
    - Number of patients who could have an infusion delay (patients who received ≥2 infusions, used for % calculation in this section).
      - Number (%) of patients with at least 1 infusion delay.
- Cycle level
  - Number of cycles administered (used for % calculation for this level)

- Number (%) of cycles delayed
  - Number (%) of cycles delayed with a maximum delay between 4 and 7 days
  - Number (%) of cycles delayed with a maximum delay on > 7 days

- Total number of isatuximab administration level
  - Total number of isatuximab administration (used for % calculation for this level)
    - Number (%) of isatuximab administration interrupted
    - Number (%) of isatuximab infusions interrupted more than once
  - Number of infusion interrupted at (with % calculated using the total number of infusions interrupted): 1st infusion, 2nd infusion, subsequent infusions.
    - Time from infusion start to first interruption in minutes (quantitative (descriptive statistics) and qualitative: <5, 5–10, 11-30, 31–40, 41 –50, 51 –60, 61–90, 91–120, >120), missing.
  - Number (%) of infusions not completed (patients who received less than 90% of the planned dose).

Duration of infusion is defined as the time from the start (date/time) of infusion to the end (date/time) of infusion. It will be summarized with descriptive statistics for first and subsequent infusions. A listing of dosing data will be provided and include the following variables, number of cycles started, cycle-day, start date, cycle delayed, actual dose in mg/kg, dose interruption, dose reduced and dose not complete.

2.4.4 Analyses of efficacy endpoints

All primary, secondary and exploratory analyses of efficacy endpoints will be performed using the all treated/safety population.

2.4.4.1 Analysis of primary efficacy endpoint

The primary analysis is based on the dose level determined as MTD combined in phase 1 and phase 2. ORR as assessed by IAC will be summarized. 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. A 95% two-sided confidence interval will be computed for ORR using Clopper-Pearson method.

2.4.4.2 Analyses of secondary efficacy endpoints

The following analyses will be performed.

- A 95% two-sided confidence interval will be computed for CBR using Clopper-Pearson method.
- OS and PFS will be analyzed by using the Kaplan-Meier method. The Kaplan-Meier estimates of the 25th, 50th and 75th percentiles and probability of surviving at every 4

months and the corresponding 95% confidence interval will also be computed. The Kaplan-Meier curves will be plotted.

- DOR and TTR will be summarized with descriptive statistics for patients who achieve a response ≥ PR.
- DFU will be summarized with descriptive statistics.
- Paraprotein, the change and the percent change from baseline will be summarized with descriptive statistics for each cycle. Best percent change in paraprotein will be displayed in a waterfall plot. In the waterfall plot, patients with BOR of ≥PR will have negative percentage change. The patients will be ordered from highest positive change to smallest negative change. Percent change >100% will be displayed as 100% increases.
- A swimmer plot of time on a treatment and a waterfall plot of best percent change in paraprotein will be provided. The patients will be ordered by BOR and duration of exposure. Patients with the best BOR and longest duration will be presented at the top of the plot.

A listing of best percent change in % plasma cell in bone marrow biopsy will be provided and will include the following variables: measurable paraprotein at baseline, best percent change in paraprotein, BOR, baseline plasma cells count and post baseline plasma cells count (only for CR confirmation) and best percent change in plasma cells count.

A listing of MRD negative patients will be provided (if any).

2.4.4.3 Multiplicity issues

Not applicable

2.4.4.4 Additional efficacy analysis(es)

Not applicable

2.4.5 Analyses of safety data

All safety analyses will be performed on the safety population as defined in Section 2.3.1, unless otherwise specified, the baseline value is defined as the last available value before the first isatuximab administration.

2.4.5.1 Analyses of adverse events

Generalities

The primary focus of adverse event reporting will be on treatment-emergent adverse events. Pre-treatment and post-treatment adverse events will be described separately.

If an adverse event date/time of onset (occurrence, worsening, or becoming serious) is incomplete, the adverse event will be classified as pre-treatment, treatment-emergent, or post-treatment, according to the cycle number or visit of onset. The algorithm for imputing date of onset will be conservative and will classify an AE as treatment emergent unless there is definitive information to determine it is pretreatment or post-treatment. Details on classification of adverse events with missing or partial onset dates are provided in Section 2.5.

The grade will be taken into account in the summary. For patients with multiple occurrences of the same event during the observation period, the maximum grade is used.

Sorting within tables ensures the same presentation for the set of all adverse events within the observation period (pre-treatment, treatment-emergent, and post-treatment). For that purpose, the table of all treatment-emergent adverse events presented by SOC and PT sorted by the internationally agreed SOC order and decreasing frequency of PTs within SOCs will define the presentation order for all other tables unless otherwise specified.

The following treatment-emergent adverse event summaries will be generated for the safety population.

Overview of TEAEs

An overview of TEAEs including the number (%) of patients with the following events will be provided:

- Treatment-emergent adverse event (TEAE)
- Grade 3-5 TEAE
- Drug-related TEAE
- Grade 3-5 drug-related TEAE
- Serious TEAE
- Drug-related serious TEAE
- TEAE leading to death
- TEAE leading to permanent treatment discontinuation
- AESI
- Grade 3-5 AESI
- Infusion associated reaction (excluding symptoms)
- Grade 3-5 infusion associated reaction (excluding symptoms)

Display of adverse events

- All TEAEs by PT presented by all grades and grade≥3.
- All TEAEs by primary SOC and PT presented by all grades and grade≥3. SOC will be sorted by internationally agreed order. PT will be sorted by decreasing order of frequency,

- All TEAEs by primary SOC, HLGT, HLT and PT, showing number (%) of patients with at least 1 treatment-emergent adverse event sorted by the SOC internationally agreed order. The other levels (HLGT, HLT and PT) will be presented in alphabetical order.
- All drug-related TEAEs by PT presented by all grades and grade≥3.
- All drug-related TEAEs by primary SOC and PT presented by all grades and grade≥3.

Deaths, serious adverse events, adverse events leading to withdrawal, and other significant adverse events

- Death: see Section 2.4.5.2.
- Serious adverse events
  - All serious TEAEs by PT presented by all grades and grade≥3.
  - All serious TEAEs by primary SOC and PT, showing the number (%) of patients with at least 1 treatment-emergent adverse event.
  - All drug-related serious TEAEs related to isatuximab, by primary SOC and PT, showing the number (%) of patients with at least 1 treatment-emergent adverse event.
  - Listing of serious AEs.
- TEAEs leading to treatment discontinuation
  - Summary of TEAEs leading to treatment discontinuation by SOC and PT. If the number of patients who discontinued treatment due to a TEAE is ≤ 5, no summary table will be provided. Instead, listing(s) will be provided.

Other significant adverse events, including IARs, respiratory TEAEs, hematological adverse events, TEAE leading to dose modification, other AESI, pre- and post-treatment AE).

- IAR-AESI (using the CMQ corresponding to the generic term of infusion related reaction reported by investigator as an AESI):
  - Analysis by patient: number of patients (used as denominator), worst grade by patient, number of episodes by patient (only 1 episode, ≥1 episode, ≥2 episodes, …. - an episode corresponds to a unique AE reference ID), first occurrence of IARs, patients with IAR at the first and/or subsequent isatuximab infusion, and number (%) of patients with at least 2 episodes of IARs at the same infusion.
  - Analysis by infusion: number of infusions (used as denominator), worst grade by infusion (a patient can have several IAR episodes at the same infusion).
  - Analysis by episode: number of episode (used as denominator), proportion of IARs occurring at each infusion, IAR duration, and day of onset.
- IAR-AESI including symptoms as reported by investigator
  - Summary of IAR-AESI by SOC and PT,
  - Listing of IAR-AESI
- Respiratory TEAEs:

- Lower respiratory TEAEs analyzed by IAR status (IAR or Non-IAR).
- Respiratory infection TEAEs analyzed by IAR status (IAR or Non-IAR).

In addition, late respiratory adverse events (i.e., occurring, worsening or becoming serious more than 30 days after last dose) will be analyzed as part of the post-treatment AEs analysis.

- Hematological abnormalities (including analysis of both AE and laboratory neutropenia):
  - Number (%) of patients with neutropenia (from laboratory abnormalities) neutropenic infections and febrile neutropenia (from AE CMQs) by grade.
- Summary of TEAEs leading to dose interruption of isatuximab, summary of TEAEs leading to dose reduction (if any), summary of TEAEs leading to dose delay.
- Pregnancy and overdose being part of the AESIs, will be listed if observed.

2.4.5.2 Deaths

Number (%) of patients who died by study period (on-treatment and post-treatment) and within 60 days from first dose of study treatment, and cause of death will be summarized. A listing of patients who died while participating in the study including cause of death, death date and days from first and last dose to death, preferred term, and causal relationship to isatuximab will be provided.

2.4.5.3 Analyses of laboratory variables

Each laboratory test result will be graded by NCI CTCAE (version 4.03), when applicable. Sponsor generic ranges are used for the grading of laboratory results, otherwise site ranges are used. For patients with multiple occurrences of the same laboratory variable during the on-treatment period, the maximum grade (worst) per patient will be used.

The number (%) of patients with abnormal laboratory tests at baseline and during the on-treatment period will be presented by all grades and each grade. At baseline, the last available value before or on the date of first study treatment administration (excluding repeated tests) will be used.

Shift tables showing the number of patients in each grade at baseline by worst grade during the on-treatment period will be provided for selected laboratory tests.

For creatinine clearance in mL per minute using MDRD formula (Revised equations for eGFR in Japanese), the number (%) of patients by category (<15, [15-30[, [30-60[, [60-90], >90) and by period (baseline and on-treatment) as well as a shift table will be provided.

2.4.5.4 Analyses of vital sign variables

The incidence of potentially clinically significant abnormalities (PCSAs) (Table 6) at any time during the on-treatment period will be summarized.

Table 6 - Potentially clinically significant abnormalities criteria for vital signs

Parameter	PCSA	Comments
HR	≤50 bpm and decrease from baseline ≥20 bpm ≥120 bpm and increase from baseline≥20 bpm	To be applied for all positions (including missing) except STANDING.
SBP	≤95 mmHg and decrease from baseline ≥20mmHg ≥160 mmHg and increase from baseline ≥20 mmHg	To be applied for all positions (including missing) except STANDING.
DBP	≤45 mmHg and decrease from baseline ≥10 mmHg ≥110 mmHg and increase from baseline ≥10 mmHg	To be applied for all positions (including missing) except STANDING.
Weight	≥5% increase from baseline ≥5% decrease from baseline	FDA Feb 2007.

Temperature and respiratory rate will be summarized at baseline and end of treatment.

A listing of vital signs will be provided.

2.4.5.5 Analyses of electrocardiogram variables

A listing of ECG results will be provided.

2.4.5.6 Analyses of other safety endpoints

ECOG PS and results of bone lesions and chest X-ray will be listed.

The number (%) of patients with TLS reported under the TLS standard MedDRA query (SMQ) (i.e., haemorrhagic tumor necrosis, TLS, tumor necrosis) will be provided. Among those patients, the number (%) of patients with laboratory and clinical parameters which could be indicative of TLS prior to first dose and during the on-treatment period will also be provided.

2.4.6 Analyses of pharmacokinetic

2.4.6.1 Pharmacokinetic variables

The population PK of isatuximab will be characterized in the population of patients using a nonlinear mixed effect modeling approach by MONOLIX software version 2016 R1 (or more recent version) (Lixoft). Both rich and sparse sampling PK data available from Phase 1, 2 and

possibly phase 3 studies will be used for the analysis. Additional details of the analysis plan (Population PK Analysis Plan) and the results will be provided in a separate document. The population estimates from this analysis will provide a prior distribution from which individual Bayesian estimates of the PK parameters and of individual exposure (C_{max}, C_{trough} and cumulated AUC) for each patient in this study will be derived.

Pharmacokinetic parameters of isatuximab (listed in Section 2.1.5) will be summarized by descriptive statistics (such as mean, geometric mean, median, standard deviation, standard error of mean, coefficient of variation, minimum, and maximum).

Predose dose concentration ($Ctrough_{obs}$) of isatuximab will be tabulated with standard descriptive statistics by visit (up to Cycle 10) and will be represented graphically as function of sampling time (day/cycle) over the study period to visualize the steady state achievement. A listing of $Ctrough_{obs}$ for individual patients will also be provided. $Ctrough_{obs}$ will be kept for the descriptive statistics if sampling occurs after 7 days ± 2 days from previous infusion for sampling done until Cycle 1 Day 22 and after 14 days ± 3 days from previous infusion for sampling done from Cycle 1 Day 22 up to Cycle 10.

Cycles in patients with dose delay and/or dose reduction, and samples with missing date and/or time and/or date and time of the previous dose, will be discarded from the analyses.

2.4.7 Immune response

Using the ADA evaluable population, the number (%) of patients will be provided for the following if at least one positive observed:

- Pre-existing ADA
- ADA negative at baseline
- On study ADA
  - Treatment-induced ADA
  - Persistent ADA
  - Transient ADA
  - Indeterminate ADA
  - Treatment boosted ADA
  - Last sample positive
- ADA prevalence
- ADA incidence

In addition, a data listing of each ADA sample result will be provided. The impact on PK, safety and efficacy endpoints may be further explored by graphical methods or descriptive, depending on the ADA prevalence.

2.4.8 Analyses of Biomarker variables

2.4.8.1 Receptor density

CD38 RD will be summarized with descriptive statistics for responders/non-responders. A responder is a patient with IAC assessment response ≥ PR. In addition, summary of BOR will be provided by CD38 RD level and a graph showing ORR/non-responder rate (in y-axis) by CD38 RD level (ranging from 0 to 500 000 by increment of 1000 in x-axis) will be provided.

2.4.8.2 Genetic variables

Summary of BOR will be provided for the following patients:

- FcGR3A types: F/F, F/V, V/V and missing.
- HLA and KIR genotypes including:
  - HLA-B BW4-80Ile+ and KIR3DL1+ vs HLA-B BW4-80Ile- or KIR3DL1-.
  - KIR3DS1- vs KIR3DS1+.

2.4.8.3 Other variables

Soluble CD38 will be summarized with descriptive statistics for responders/non-responders and listed.

In addition, graphs showing responder/non-responder rate by biomarker levels will be provided for the following parameters at baseline:

- Soluble CD38.
- Immune cell level (B-cell, T-cell and NK-cell subsets respectively in blood and bone marrow samples).

A listing of response data will be provided for patients with MRD.

2.4.9 Further therapy after discontinuation of investigational medicinal product administration during the study

Further therapy for MM will be listed and not summary table will be provided.

2.5 DATA HANDLING CONVENTIONS

2.5.1 General conventions

For the data censored at detection limits, its value will be substituted by DL/2.

2.5.2 Data handling conventions for secondary efficacy variables

Not applicable

2.5.3 Missing data

For categorical variables, patients with missing data are not included in calculations of percentages unless otherwise specified. When relevant, the number of patients with missing data is presented.

Handling of disease characteristics missing/partial dates

- If the day is missing, it will be estimated by 1.
- If the month is missing, it will be estimated by 1 (only for medical history variables).
- If the year is missing, no estimation will be performed.

Handling of medication missing/partial dates

No imputation of medication start/end dates or times will be performed. If a medication date or time is missing or partially missing and it cannot be determined whether it was taken prior or concomitantly, it will be considered a prior, concomitant, and post-treatment medication.

For post anticancer treatments, if the anticancer treatment start date is missing, it will be imputed as follows:

1. If the anticancer treatment start day is missing and the anticancer treatment start month and year are the same as the study treatment end month and year, the anticancer treatment start day will be set equal to the date of last study treatment administration + 1.
2. If the anticancer treatment start day is missing and the anticancer treatment start month is not missing and the anticancer treatment start year is after the study treatment end year, the anticancer treatment start day will be set to 01.
3. If the anticancer treatment start day is missing and the anticancer treatment start month is after the study treatment end month and the anticancer treatment start year is the same as treatment end year, the anticancer treatment start day will be set to 01.
4. If the anticancer treatment start day and month are missing and the anticancer treatment start year is the same as study treatment end year, the anticancer treatment start date will be set equal to the date of last study treatment administration + 1
5. If the anticancer treatment start day and month are missing and the anticancer treatment start year is after the study treatment end year, the anticancer treatment start day and month will each be set to 01
6. If the anticancer treatment start day is missing and anticancer treatment start month is before the study treatment end month and the anticancer treatment start year is the same as treatment end year, the anticancer treatment start day will be set to 01

7. If the anticancer treatment start day, start month and start year is missing, the anticancer treatment start date will be set equal to the treatment end date + 1.

Handling of adverse events with missing/partial dates

Missing or partial adverse event onset dates and times will be imputed so that if the partial adverse event onset date/time information or cycle/visit number does not indicate that the adverse event started prior to treatment or after the treatment-emergent adverse event period, the adverse event will be classified as treatment-emergent. No imputation of adverse event end dates/times will be performed. These data imputations are for categorization purpose only and will not be used in listings. No imputation is planned for date/time of adverse event resolution.

Handling of adverse events with missing grade

Missing grades, if any, will be included in the "all grades" category.

Handling of missing assessment of relationship of adverse events to investigational medicinal product

If the assessment of the relationship to isatuximab is missing, then the relationship to isatuximab has to be assumed and the adverse event considered as such in the frequency tables of possibly related adverse events, but no imputation should be done at the data level.

Handling of potentially clinically significant abnormalities

If a patient has a missing baseline he will be grouped in the category "normal/missing at baseline."

For PCSAs with 2 conditions, one based on a change from baseline value or a normal range and the other on a threshold value, with the first condition being missing, the PCSA will be based only on the second condition.

Measurements flagged as invalid by the laboratory will not be summarized or taken into account in the computation of PCSA values.

Missing or partial adverse event onset dates and times will be imputed so that if the partial adverse event onset date/time information or cycle/visit number does not indicate that the adverse event started prior to treatment or after the treatment-emergent adverse event period, the adverse event will be classified as treatment-emergent. No imputation of adverse event end dates/times will be performed. These data imputations are for categorization purpose only and will not be used in listings. No imputation is planned for date/time of adverse event resolution.

2.5.4 Windows for time points

An episode occurred during a cycle if the date of sampling is after the first date of the cycle, but prior or equal to the first day of the next cycle.

2.5.5 Unscheduled visits

Unscheduled visit measurements of laboratory data and vital signs will be used for only computation of worst values and/or grades.

2.5.6 Pooling of centers for statistical analyses

Data from all sites will be pooled together for analyses.

2.5.7 Statistical technical issues

Not applicable.

3 INTERIM ANALYSIS

Not applicable.

4 DATABASE LOCK

The database lock is planned to be twice in phase 2. The cut off for the first database lock is at approximately 4 months after last patient first dosed. The cut off for the second database lock is at approximately 12 months after last patient first dosed.

5 SOFTWARE DOCUMENTATION

All summaries and statistical analyses will be generated using SAS version 9.2 or higher.

6 REFERENCES

Not applicable.

7 LIST OF APPENDICES

Appendix A: Sponsor generic ranges

Appendix A Sponsor generic ranges

Table 7 - Hematological parameters

LBTESTCD	LBTEST	GENDER	LBSTRESU	LBGNNRLO
HGB	Hemoglobin	F	g/L	120
HGB	Hemoglobin	M	g/L	135
LYM	Lymphocytes		10^9/L	1
NEUT	Neutrophils		10^9/L	1,8
PLAT	Platelets		10^9/L	150
WBC	Leukocytes		10^9/L	4,5
EOS	Eosinophils		10^9/L	0
BASO	Basophils		10^9/L	0
MONO	Monocytes		10^9/L	0,18
HCT	Hematocrit	M	%	0,41
HCT	Hematocrit	F	%	0,36
RBC	Erythrocytes	F	10^12/L	4
RBC	Erythrocytes	M	10^12/L	4,5
INR			Ratio	0.8

Table 8 - Biochemistry parameters

LBTEST	LBSTRESU	LBGNNRLO - LBGNNRHI
Albumin	g/L	35 - 55
Blood Urea Nitrogen (BUN)	mmol/L	3.6 – 7.1
Coreccted calcium	mmol/L	2,2 - 2,6
Chloride	mmol/L	80 - 115
Glucose	mmol/L	3,9 - 7
Bicarbonate (HCO3)	mmol/L	22 – 29
Potassium	mmol/L	3,5 – 5
Magnesium	mmol/L	0,8 - 1,2
Sodium	mmol/L	136 – 145
Phosphate	mmol/L	1 - 1,4
Protein	g/L	55 – 80
Urea	mmol/L	3,6 - 7,1

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm)
[redacted]	Clinical Approval	[redacted]
[redacted]	Clinical Approval	[redacted]