NCT Number: NCT01084252

STATISTICAL ANALYSIS PLAN

A Phase 1/2 Dose Escalation Safety, Pharmacokinetic and Efficacy Study of Multiple Intravenous Administrations of a Humanized Monoclonal Antibody (SAR650984) Against CD38 In Patients with Selected CD38+ Hematological Malignancies

SAR650984-TED10893 (Phase 2 - Stage 2)

STATISTICIAN: [redacted]

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AE:	adverse event
AESI:	adverse event of special interest
ANC:	absolute neutrophil count
AT:	all treated
BOR:	best overall response
[redacted]	[redacted]
CBR:	clinical benefit rate
CL:	clearance
CMQ:	customized MedDRA queriies
CR:	complete response
CTCAE:	common terminology criteria for adverse events
DOR:	duration of response
ECOG:	eastern cooperative oncology group
eCRF:	electronic case report form
FCGR:	fc gamma receptor
FDR:	false discovery rate
FIH:	first in human
FISH:	fluorescence in situ hybridization
FLC:	free light chain
GVHD:	graft vs. host disease
HLA:	human leukocyte antigen
HLGT:	high-level group term
HLT:	high-level term
HRQL:	health related quality-of-life
IAC:	independent adjudication committee
IAR:	infusion associated reaction
IFN-γ:	interferon-gamma
IL:	interleukin
IMiD:	immunomodulatory drug
IVRS:	interactive voice response system
IWRS:	interactive web response system
KIR:	killer-cell immunoglobulin-like receptor
KPS:	karnofsky performance status
LLT:	lower level term
MDRD:	Modification of Diet in Renal Disease
MedDRA:	medical dictionary of regulatory activities
MR:	minimal response
NCI:	national cancer institue
NE:	not evaluable
ORR:	overall response rate
OS:	overall survival
PCSA:	potentially clinically significant abnormalities
PD:	progressive disease

PFS:	progression free survival
PI:	proteasome inhibitor
PK:	pharmacokinetic
PR:	partial response
PS:	performance status
PT:	preferred term
RRMM:	relapsed refractory multiple myeloma
SAP:	statistical analysis plan
SD:	standard deviation, stable disease
SI:	serum immunoglobulin
SOC:	system organ class
TLS:	tumor lysis syndrome
TNF-α:	tumor necrosis factor alpha
VGPR:	very good partial response

1 OVERVIEW AND INVESTIGATIONAL PLAN

TED10893 is the first in human (FIH) study of isatuximab (SAR650984) and was originally designed as a dose escalation study to evaluate the safety and pharmacokinetics (PK) of isatuximab. The protocol was subsequently amended to include a Phase 2 part for the treatment of patients with relapsed refractory multiple myeloma (RRMM) consisting in a dose/schedule finding portion (Stage 1) and in a Stage 2 expansion to further evaluate the activity and safety of isatuximab alone or in combination with dexamethasone at a dose and schedule selected in Stage 1. This statistical analysis plan (SAP) describes the statistical methods to be used for the analyses of data collected during the Phase 2 Stage 2 part of the study. This SAP should be read in conjunction with the amended study protocol (Version - 12, 12 July 2017) and electronic case report form (eCRF).

1.1 STUDY DESIGN AND RANDOMIZATION

The Phase 2 Stage 2 part of TED10893 will evaluate the activity and safety of isatuximab [redacted] with or without dexamethasone (denoted by ISAdex and ISA arms, respectively) in patients with multiple myeloma who had previously received an immunomodulatory drug (IMiD) and a proteasome inhibitor (PI) and have relapsed or relapsed/refractory disease. In the Phase 2 part, a cycle is 28 days. The dose and schedule were selected from the interim analysis of Stage 1a and b: 20 mg/kg every week for 4 infusions followed by 20 mg/kg every 2 weeks. This dose was determined based on response rate along with safety, PK/PD and overall efficacy from Phase 1 and Phase 2 Stage 1. For Patients in the ISAdex arm, dexamethasone will be administered at the dose of 40 mg/day (20 mg/day for ≥75 year old patients) on day 1, 8, 15, 22 of each cycle.

Patients will be randomly assigned to one of the 2 treatment arms in a 2:1 ratio (for ISA and ISAdex arms, respectively) using an Interactive Voice Response System/Interactive Web Response System (IVRS/IWRS). Enrollment will stop when the targeted number of patients is reached in both arms.

The data cutoff date for the protocol planned interim analysis of safety will be 15 Nov 2017. According to protocol, the data cutoff for the primary analysis of the overall response rate (ORR) will be 4 months after the last enrolled patient receives first study treatment. However, for operational reasons and to provide mature data on time-to-event endpoints, only 1 analysis using cutoff date 12 months after the date of the first dose of the last patient will be reported in the clinical study report.

1.2 OBJECTIVES

1.2.1 Primary objectives

The primary objective of the Phase 2 Stage 2 part of the study is to evaluate the activity of single-agent isatuximab (ISA arm) and in combination with dexamethasone (ISAdex arm), as assessed by the overall response rate (ORR) in patients with RRMM.

1.2.2 Secondary objectives

The secondary objectives of the Phase 2 Stage 2 part of the study were to evaluate:

- Safety.
- Efficacy as measured by:
    - Duration of response (DOR).
    - Clinical benefit rate (CBR).
    - Progression free survival (PFS).
    - Overall survival (OS).
    - Very good partial response (VGPR) or better rate
- Pharmacokinetic profile of isatuximab.
- Immunogenicity of isatuximab.

1.2.3 Exploratory objectives

- To assess minimal residual disease (MRD) in patients achieving a CR and correlate with clinical outcome.
- To investigate the relationship between tumor cell CD38 mRNA, multiple myeloma molecular subtype (as defined by marker expression, cytogenetics, and/or genomics) and parameters of clinical response.
- To investigate the relationship of soluble CD38 and parameters of PK and clinical response.
- To investigate the relationship between immune genetic determinants, immune phenotype, adaptive immune response and parameters of clinical response.

1.3 DETERMINATION OF SAMPLE SIZE

Isatuximab arm (ISA arm): 105 patients need to be randomized and treated in the ISA arm. Given an assumed true ORR of 28%, the null hypothesis ORR ≤15% will be rejected using an exact binominal test at a one-sided alpha of 0.025 with 90% power, if the observed ORR is greater than or equal to 22.9% (24 responders).

Isatuximab+dexamethasone arm (ISAdex arm): 55 patients need to be randomized and treated in the ISAdex arm. Given an assumed true ORR of 33%, the null hypothesis ORR ≤ 15% will be rejected using an exact binominal test at a one-sided alpha of 0.025 with 85% power, if the observed ORR is greater than or equal to 27.3% (15 responders).

The sample size calculation was performed using nQuery Advisor 7.0 software.

1.4 STUDY PLAN

Safety evaluations will be performed continuously throughout the study and will include the following:

- Adverse events (AEs) evaluation. Severity grade determined according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.
- Laboratory tests in blood and urine.
- Physical examinations and vital signs.
- ECOG performance status.
- Cytokines (tumor necrosis factor alpha [TNF-α], interleukin [IL]-1-β, IL-6, interferon-gamma [IFN-γ]), markers of complement (C3, C4, CH50), serum tryptase, markers of potential tumor lysis syndrome (TLS) (uric acid, lactate dehydrogenase [LDH], BUN/creatinine, potassium, sodium and calcium) (removed following Amendment Version - 12, 12 July 2017).
- Chest X-ray and ECG (baseline only).

Disease response evaluation will be performed at screening and Day 1 of every cycle, starting from Cycle 1 unless otherwise stated, and include:

- M-protein quantification (serum and/or 24-hour urine), serum free light chain levels.
- Serum β2-microglobulin (only at baseline).
- Corrected serum calcium.
- Bone marrow biopsy/aspiration to be performed to confirm a CR/sCR, at the end of treatment (EOT) visit and as clinically indicated.
- Radiologic imaging of plasmacytoma (every 12 weeks if present at baseline).
- Skeletal survey or low-dose whole-body CT scan (to be performed once a year and anytime during the study if clinically indicated).

The following additional evaluations will also be performed:

- Level of soluble CD38 (removed following Amendment Version - 12, 12 July 2017).
- Level of human anti-drug antibodies (ADA).
- Immune phenotyping and molecular analysis on blood and bone marrow.
- Adaptive immune response (including TCR repertoire).

- Optional pharmacogenetic sample.

Pharmacokinetic (PK) samples will be 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

No modifications to the statistical section of the protocol were made in this SAP.

1.6 STATISTICAL MODIFICATIONS MADE IN THE STATISTICAL ANALYSIS PLAN

SAP version number	Date approved	Rationale	Description of statistical changes
Amendment n°1		Safety analyses were added to better characterize the safety profile.	The following analyses have been added: - Neutropenic complications - Thrombocytopenia and haemorrhages - Hemolytic disorders - Autoimmune disorders - Second primary malignancies
		Additional endpoints were added to further characterize the efficacy of study treatments.	The following analyses have been added: - VGPR or better rate - Time to best response - Additional evidence of clinical benefit. - Duration of follow-up

SAP version number	Date approved	Rationale	Description of statistical changes
		Subgroup analyses were added to further evaluate the efficacy in specific subgroups.	The following subgroups have been added: - Age - Regulatory region - Race - MM type at diagnosis - At least four prior lines of therapy and refractory to at least two PIs and refractory to at least two IMIDs - At least three prior lines of therapy including at least one PI and at least one IMID.
		The following exploratory analyses were added to further evaluate difference between the 2 arms in efficacy	- Comparison of ORR according to IRC between the 2 arms using the Fisher test - Hazard ratio PFS from Cox proportional hazard model and comparison of PFS between the 2 arms using the logrank test
		The following analysis was added to further evaluate clinical benefit in term of further anti-cancer therapies	- Time to next treatment

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 on or before the date of first study treatment (isatuximab or dexamethasone) administration. For efficacy laboratory parameters (eg, serum and urine M-protein), unscheduled assessment performed on the date of first study treatment administration (Cycle 1 Day 1) will be considered as baseline value; for other laboratory tests, unscheduled assessment performed on the date of first study treatment administration will be considered as post baseline. For patients randomized and not treated, the baseline value is defined as the last available value obtained up to the date and time of randomization.

All baseline safety and efficacy parameters (apart from those listed below) will be 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 include gender (Male, Female), race (White, Black or African American, Asian, American Indian or Alaska Native, Not reported, Unknown), ethnicity (Hispanic or Latino, Not-Hispanic or Latino, Not reported, Unknown), age in years (quantitative and qualitative variable : <65, [65 - 75[and ≥75 years), geographical region (Eastern Europe, Western Europe, North America, Other countries, see definition in Appendix B), regulatory region (Western countries, Other countries, see definition in Appendix B), weight (kg) and Eastern Cooperative Oncology Group (ECOG) performance status (PS).

Medical or surgical history

Medical or surgical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) in effect at Sanofi at the time of database lock.

Disease characteristics at initial diagnosis

The following MM characteristics at initial diagnosis will be summarized: time from initial diagnosis to first study treatment administration in years (quantitatively and by category : <5 years and ≥5 years), International Staging System (ISS) stage, and subtype (as collected in the eCRF).

Disease characteristics at study entry

The following MM characteristics at study entry will be summarized: ISS stage (Table 1), measurable paraprotein at baseline (Table 2), % of plasma cells in bone marrow at baseline (quantitatively and by category: 0,]0 - 5%[, [5-20%[, [20-50%[, and ≥50%), patients with plasmacytomas (as per investigator and IAC), patients with bone lesions (as per investigator and IAC), β2-microglobulin level in mg/L (quantitatively and by category: <3.5 mg/L, [3.5-5.5 mg/L[and ≥5.5 mg/L), albumin in g/L (quantitatively and by category: <35 g/L and ≥35 g/L).

Table 1 - ISS staging definition

Stage	Definition
Stage I	β2-microglobulin <3.5 mg/L and albumin ≥ 35 g/L
Stage II	[β2-microglobulin <3.5 mg/L and albumin <35 g/L] or [β2-microglobulin 3.5 - <5.5 mg/L]
Stage III	β2-microglobulin ≥5.5 mg/L

ISS=International Staging System

Table 2 – Derivation of measurable paraprotein at study entry

Measurable paraprotein	Criteria
Serum M-Protein	Serum M-protein ≥ 1 g/dL (or 0.5 g/dL in case of IgA)
Urine M-Protein	Serum M-protein <1 g/dL (or <0.5 g/dL in case of IgA) and urine M-protein ≥200 mg/24hours
Kappa LC	Serum M-protein <1 g/dL (or <0.5 g/dL in case of IgA) and urine M-protein <200 mg/24 hours and kappa LC>lambda LC and kappa LC ≥ 10mg/dL and abnormal FLC ratio (<0.26 or >1.65)
Lambda LC	Serum M-protein <0.5 g/dL or missing and urine M-protein <200 mg/24 hours or missing and lambda LC>kappa LC and lambda LC ≥10 mg/dL and abnormal FLC ratio (<0.26 or >1.65)

Cytogenetic abnormalities (Molecular subtype)

Molecular subtypes will be determined on cytogenetic analysis from central or local (if central assessment is not available) fluorescence in situ hybridization (FISH) or karyotyping reports. A patient is considered as high risk if bearing del17p and/or t(4;14) and/or t(14;16) abnormalities. The cut-offs for positivity are as follows:

- t(4;14) single fusion >15%, Dual fusion >3%;

- t(14;16) single fusion >15%, dual fusion >3%;
- del17p13 >10%,
- ≥ 3 copies of 1q and at least one copy missing for 1p.

Prior anticancer therapies

- Prior anticancer treatments: Prior anticancer treatment will be collected by both line and regimen in the eCRF. The following variables will be derived: number of prior lines (quantitatively and by category: 1, 2, …7 and ≥ 8), number of prior regimen (quantitatively and by category: 1, 2, …7 and ≥ 8), main anticancer treatments (ie, alkylating agent, IMiD, PI agent, PI or IMiD agent, PI and IMiD agent, monoclonal antibodies, anthracyclines, vinca alkaloids, corticosteroids and histone deacetylase inhibitors), main anticancer treatments in last regimen before study entry, time from completion of last regimen of treatment to first study treatment administration (months), best response to last regimen, duration of last regimen of therapy.

  In addition, the refractory status to main anticancer treatment (as listed above) and refractory status of the last prior anticancer treatment received before enrolment 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: patients with transplant, type of transplant, number of transplant by patient, time from last transplant to first study treatment administration (months).
- Prior surgery: patients with any prior surgery related to cancer, type of surgery and time from last surgery to first study treatment administration (months).
- Prior radiotherapy: number (%) of patients with any prior radiotherapy related to cancer, intent, and time from last radiotherapy to first study treatment administration (months).

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

Vital signs

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

Renal status

Renal function, ie, glomerular filtration rate (GFR) in mL/min/1.73 m^2 (qualitative variable: [15-30[, [30-60[, [60-90], >90) will be calculated from serum creatinine concentration measured at baseline using Modification of Diet in Renal Disease (MDRD) formula, whenever race will be allowed to be collected.:

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

with serum creatinine in mg/dL and age in year.

2.1.2 Prior or concomitant medications (other than anticancer therapies)

All medications taken by the patient within 21 days prior to randomization into the study, at any time during the treatment period until end of treatment will be reported in the eCRF.

The following information will be collected in the medication eCRF page: drug/medication (brand or generic name), reason (eg, curative, prophylaxis), dose and unit, route, start date and end date (if applicable)/ongoing (otherwise).

All medications will be coded using the World Health Organization-drug Dictionary (WHO-DD) version in effect at Sanofi at the time of database lock.

- Prior medications are those the patient used prior (<) to first study treatment administration. Prior medications can be those discontinued before first administration or those ongoing during the treatment phase.
- Concomitant medications are any treatments received by the patient concomitantly to study treatment, 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. Any anti-cancer treatment administered after the date of the last study treatment administration will not be considered as a concomitant medication and will be regarded as further anti-myeloma therapy regardless of the date of initiation (see Section 2.4.10). The analysis of concomitant medications will include premedication (see below).
- Post-treatment medications (excluding post anticancer treatments) are those the patient took from 31 days after last study treatment administration up to the death or cut-off date.

Premedications

As defined in Section 8.2.1 of the amended study protocol (version 12, 12 July 2017), patients were to routinely receive premedications prior to isatuximab infusion to reduce the risk and severity of hypersensitivity reactions commonly associated with monoclonal antibodies. Premedications are defined in the protocol as non-investigational medicinal product(s). Premedications are reported on a specific eCRF page.

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

2.1.3 Efficacy endpoints

Response assessments will be performed on Day 1 of each cycle prior to study treatment administration and at the EOT visit using the updated International Myeloma Working Group (IMWG) response criteria (1) and include:

- M-protein quantification and qualification (immunofixation) (serum and 24-hr urine).
- Serum free light chain levels, free light chain ratio.
- Plasma cell count in Bone marrow biopsy/aspiration (if clinically indicated).
- Plasmacytoma assessment by PET-CT/MRI (if clinically indicated).
- Bone disease assessment: Skeletal survey or low-dose whole-body CT scan at baseline (within 21 days prior to randomization) then once a year and anytime during the study if clinically indicated.
- Corrected serum calcium.

In case of plasmacytoma at baseline, radiological evaluations will be performed at baseline and repeated every 12 weeks (± 1 week), and if clinically indicated. Will also be done in case of suspicion of progression or if clinically indicated in a patient with no previous positive image for extramedullary disease.

In case of bone lesions at baseline, bone lesion evaluations will be performed when clinically indicated or to assess progression. Bone marrow biopsy/aspiration will be performed to confirm a sCR, CR, at the EOT visit and as clinically indicated.

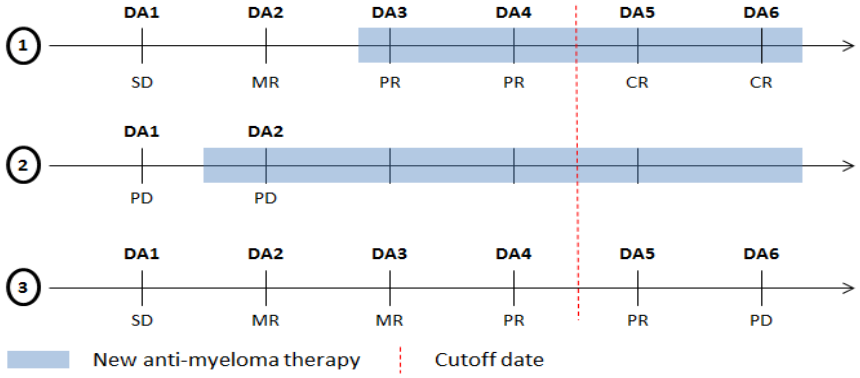
An independent adjudication committee (IAC), blinded to treatment arm, will independently assess clinical response using the IMWG response criteria.

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

2.1.3.1 Primary efficacy endpoint

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 disease progression confirmation, the cutoff date or following the start of further therapies for MM. The first disease assessment performed during further therapy will be used to confirm PD if performed within 3 months of last study treatment administration (see Figure 1). 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’.

Figure 1 – Determination of BOR when disease assessments are performed after new anti-myeloma therapies are started or performed after the cutoff date



DA= Disease assessment – PR=Partial response; PD= progressive disease.
① DA3 and subsequent are excluded from the BOR determination. BOR will be MR.
② DA2 will be used to confirm PD since PD was first documented at DA1 before initiation of a new anti-myeloma therapy. BOR will be PD.
③ DA5 and subsequent will be excluded from the analysis since performed after the cutoff date. BOR will be MR.

Subgroup analyses of BOR using IAC assessment will be performed for the variables listed in Table 3.

Table 3 – List of variables for subgroup analyses

Variable	Description
Age	<65 years vs [65-75] years vs ≥70 years
Number of previous lines of therapy	≤3 vs > 3
Gender	Male vs female
Race	Caucasian vs Non caucasian vs other
Region of the world (geographical)[a]	Western Europe vs North America vs Other countries
ECOG PS at baseline	0-1 vs 2
ISS staging at study entry	I-II vs III
High risk cytogenetic	Yes vs No
Baseline creatinine clearance (GRF)	<60 ml/min/1.73m^2 vs ≥60 ml/min/1.73m^2
Refractory to IMiD	Yes vs No
Refractory to PI	Yes vs No
Quadruple refractory (refractory to lenalidomide and bortezomid and pomalidomide and carfilzomib)	Yes vs No
At least four prior lines of therapy and refractory to at least two PIs and refractory to at least two IMIDs	Yes vs No
At least three prior lines of therapy including at least one PI and including at least one IMID	Yes

Subgroup analyses will be conducted when at least 10 patients will be included in a subgroup.

a If the number of patients in North America is too small, North America will be merged with Europe.

Table 4 – List of variables for exploratory subgroup analyses

Variable	Description
Region of the world (regulatory)	Western countries vs Other countries
Previous transplant	Yes vs No
MM type at diagnosis	IgG vs. non IgG
Measurable paraprotein at baseline	Serum M-Protein; Urine M-Protein, Light chain
Refractory to lenalidomide and bortezomib	Yes vs No
Refractory to IMiD and PI	Yes vs No
Refractory to pomalidomide and carfilzomib	Yes vs No

Subgroup analyses will be conducted when at least 10 patients will be included in a subgroup.

A sensitivity analysis of ORR will be performed using investigator's assessment of response. For this analysis, BOR will be the best sequential response as determined by the criteria defined in Table 5. Same as IAC BOR analysis, the investigator BOR will be derived using disease assessments performed from the start of treatment through the entire study excluding any assessments performed after disease progression (sequential response per Table 5), the cutoff date or following the start of further therapies for MM. In addition, the following rules will be applied:

- BOR will be NE for patients who received at most 2 isatuximab administrations with investigator assessment of response of SD or better at Cycle 1 or end of treatment.
- BOR will be PD for patients without response assessment who received 1 cycle of treatment and died due to PD or had symptomatic deterioration within 30 days of last study treatment administration.

Table 5 - Sequential response determination for investigator response assessment

Overall response at cycle n	Overall response at cycle n+1[a]	Sequential response
sCR	sCR	sCR
CR	sCR	CR
sCR	CR	CR
CR	CR	CR
sCR/CR	VGPR	VGPR[b]
sCR/CR	PR	PR
VGPR	sCR/CR/VGPR	VGPR[b]
VGPR	PR	PR
PR	sCR/CR/VGPR/CR/PR	PR
sCR/CR/VGPR/PR	NE/No further evaluation/SD/PD	MR[c]
MR	Any	MR
Any	MR	MR
NE/SD/PD	sCR/CR/VGPR/PR	MR[c]
NE/PD/SD	SD	SD
SD	No further evaluation/NE/PD	SD
NE	SD	SD
PD	No further evaluation/NE	unPD[e]
PD	PD	PD
NE	PD	unPD[e]
NE	No further evaluation	NE
No evaluation[d]		PD[d]

a Disease assessment are planned to be performed every cycle. Disease assessment performed after the start of new anticancer treatment will be excluded from the derivation of BOR.
b Sequence provided for programming purpose.
c Unconfirmed PR or CR will be considered MR.
d Only for analysis based on investigator assessment, BOR will be PD for patients without response assessment who received 1 cycle of treatment and died due to PD or had symptomatic deterioration within 30 days of last study treatment administration
e Unconfirmed PD, unless PD is based on radiological assessment that does not need confirmation.
BOR=best overall response; sCR=stringent complete response; CR=complete response; MR=minor response; NE=not evaluable; PD=progressive disease; PR=partial response; SD=stable disease; VGPR=very good partial response.

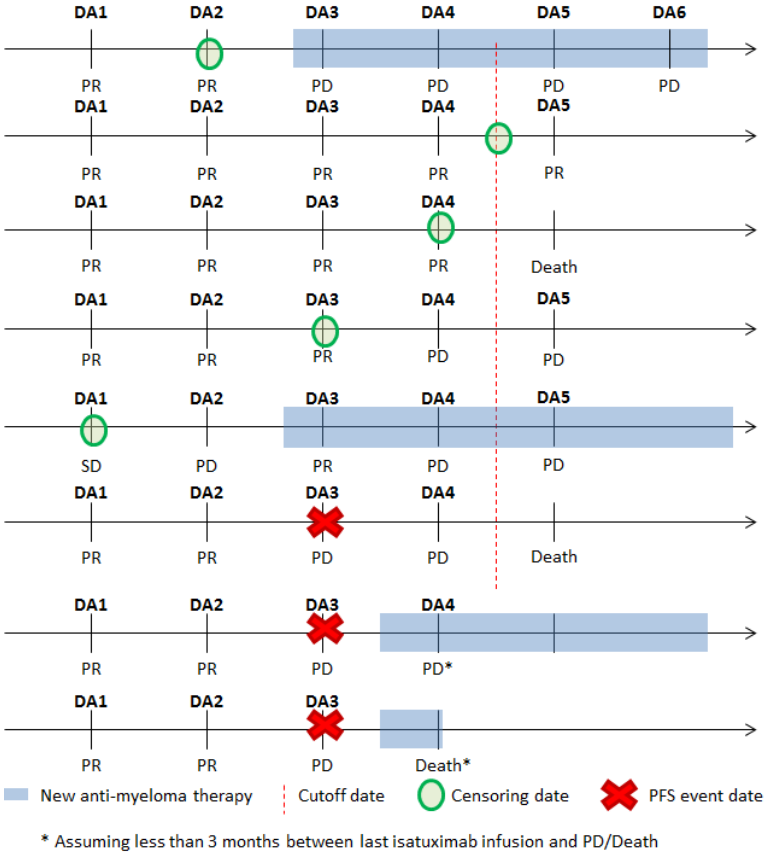
2.1.3.2 Secondary efficacy endpoints

Secondary efficacy endpoints (based on IAC) are defined below.

- Duration of Response (DOR): 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 confirmed PD or death (if reported before the analysis cutoff date or the date of initiation of a new anticancer treatment), whichever happens earlier. 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.

- 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.
- PFS (in months): defined as the time interval from the date of first study treatment administration to the date of the first IAC-confirmed disease progression or the date of death due to any cause before the analysis cut-off, whichever occurs first. For patients who did not experience IAC-confirmed disease progression or death before the analysis cut-off date 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 occurs first. As defined in Section 2.1.3.1, the first disease assessment performed during further therapy or death due to PD reported after further therapy will be used to confirm PD if performed within 3 months of last study treatment administration. Progression based on radiological assessment does not require confirmation. Date of PFS event/censoring relative to date of further anti-myeloma therapies and cutoff date are illustrated in Figure 2. In addition, patient without PFS event (death or disease progression) and without any valid post-baseline disease assessments will be censored at the day of first dose (Cycle 1 Day 1). Subgroup analysis for variables defined in Table 3 and Table 4 will be performed.
- OS (in months): defined as the time interval from the date of first study treatment 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.
- VGPR or better rate is defined as the proportion of patients achieving a VGPR or better rate as BOR.

Figure 2 - Date of PFS event/censoring relative to the date of further anti-myeloma therapies and the cutoff date based on IAC assessment



Sensitivity analyses of DOR, CBR and PFS will be performed using the investigator's assessment of response. For these analyses, the rules for the criteria of confirmation of PD will be the same as for IAC (see Section 2.1.3.1). The definitions are included below:

- Duration of response (DOR) per investigator assessment: DOR is defined as the time from the first response (sCR, CR, VGPR, PR) that is subsequently confirmed to the first sequential disease progression, clinical / symptomatic deterioration, or death (if reported before the analysis cutoff date or the date of initiation of a new anticancer treatment), whichever occurs first. 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 per investigator assessment.
- Progression free survival (PFS) (in months) per investigator assessment: PFS is defined as the time interval from the date of first study treatment administration to the date of first sequential assessment of PD confirmed, clinical symptomatic deterioration or the date of death due to any cause, whichever occurs first. For patients who did not experience disease progression or death before the analysis cut-off date 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. Date of PFS event/censoring relative to date of further anti-myeloma therapies and cutoff date are illustrated in Figure 3. In addition, patient without PFS event (death or disease progression) and without any valid post-baseline disease assessments will be censored at the day of first dose (Cycle 1 Day 1).

Other efficacy endpoints include:

- Best percent change in paraprotein: Best percent change in paraprotein will be calculated for the measurable paraprotein parameter defined at baseline (Section 2.1.1) excluding anytime point following the start of other anticancer therapy.
- Duration of follow-up (DFU) (in months): DFU is defined as the time interval from the date of randomization to the date of last contact with the patient. Patients who have died will be censored on their date of death. Median follow-up duration (months) will be estimated using the Kaplan-Meier method.
- Time to first response (TTR) (in months) is defined as the time from first dose to first response (PR or better) that is subsequently confirmed. In the absence of response patients will be censored at the earliest of the date of the last valid disease assessment before disease progression or death, the date of the last valid disease assessment before initiation of a further anti-myeloma treatment (if any) or the analysis cut-off date, whichever comes first.
- Time to best response (TTBR) is defined as the time from first dose to the date of first occurrence of IAC determined best overall response (PR or better) that is subsequently confirmed. In the absence of response, patients will be censored at the earliest of the date of the last valid disease assessment before disease progression or death, the date of the last valid disease assessment before initiation of a further anti-myeloma treatment (if any) or the analysis cut-off date, whichever occurs first.
- Additional evidence of clinical benefit : Renal response and renal function deterioration

Renal function impairment rate defined as patients with a GFR <60 mL/min/1.73m2 at baseline or during the treatment, the progression to severe or end stage renal impairment (<30) rate and the progression from moderate renal impairment ([30; 60[mL/min/1.73m2) to severe or end stage renal impairment will be described by treatment arm.

Renal response (MR/CR) rate among patients with GFR <50 mL/min/1.73m2 at baseline by treatment arm will also be described.

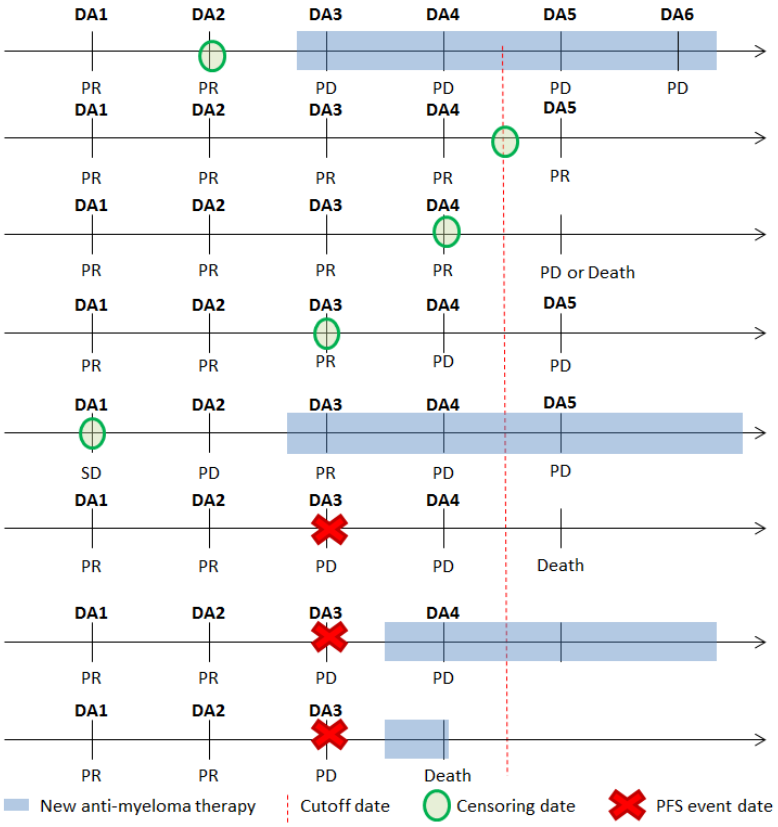
A renal response:

- **A complete renal response** is defined as an improvement in eGFR from <50 mL/min/1.73m2 at baseline to ≥ 60 mL/min/1.73m2 at least 1 assessment during the on-treatment period.
- **A partial response** is defined as an improvement in eGFR from <15 mL/min/1.73m2 at baseline to at least 1 assessment in the range [30 to 60[mL/min/1.73m2 during the on-treatment-period.
- **A minor response** is defined as an improvement in eGFR from <15 mL/min/1.73m2 at baseline to at least 1 assessment in the range [15 to 30[mL/min/1.73m2 during the

on-treatment-period or from [15 to 30[mL/min/1.73m2 at baseline to at least 1 assessment in the range [30 to 60[mL/min/1.73m2 during the on-treatment-period.

- **A durable renal response** is defined as a response that lasted ≥ 60 days.

Figure 3 - Date of PFS event/censoring relative to the date of further anti-myeloma therapies and the cutoff date using investigator's assessment



2.1.4 Safety endpoints

The safety analysis will be based on the reported AEs and other safety information, such as clinical laboratory data, vital signs, and ECG (Section 1.4).

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 patient gave informed consent and the start of study treatment administration.
- The **on-treatment period** is defined as the time from the first dose of study treatment up to 30 days after the last dose of study treatment.

- The **post-treatment period** is defined as the time starting the day after the end of the on-treatment period up to the end of the study (as defined in the protocol).

2.1.4.1 Adverse events variables

Adverse events occurring from signature of informed consent form up to at least 30 days after the last study treatment administration will be recorded in the eCRF. In addition, all study treatment related AEs and SAEs ongoing at time of study treatment discontinuation will be followed during the follow-up period until resolution or stabilization.

All AEs (including serious AEs [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 will be assessed according to NCI-CTCAE version 4.03.

The following AEs will be described:

- **Pre-treatment AEs**: defined as any AE reported during the pre-treatment period.
- **Treatment-emergent AEs (TEAEs):** defined as any AE that developed, worsened (according to the Investigator's opinion), or became serious during the on-treatment period.
- **Post-treatment AEs:** defined as any AE reported during the post-treatment period.

In addition, deaths (Section 2.1.4.2), serious adverse events, adverse events leading to withdrawal, and other significant adverse events will be analyzed. Other significant events will include:

Adverse events of special interest (AESIs):

- 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 typically occur within 24 hours from the start of each isatuximab infusion (See Section 6.5 of the TED10893 protocol for guidelines for IARs management). As described above, IARs are AESIs.

Two analyses of IARs will be performed. The first one will be based on the investigator's reporting of IARs (ie, 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.

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

Respiratory TEAEs

Analysis of respiratory TEAEs will focus particularly on the following groupings using customized MedDRA queries (CMQ):

- Lower respiratory events, selected using CMQ 'Lower respiratory events'.
- Respiratory infections, selected using infections, selected using CMQ 'Respiratory infections'.

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

Neutropenia and neutropenic complications

Neutropenia, febrile neutropenia and neutropenic infections will be analyzed using the following data source:

- Neutropenia based on laboratory results.
- Febrile neutropenia selected using CMQ 'Febrile neutropenia'
- Neutropenic infections: defined as NCI-CTCAE Grade≥2 infections from SOC 'Infections and Infestations' (selected using CMQ 'GLB_SOC infections and infestation') concomitant with NCI-CTCAE Grade 3-4 neutropenia from laboratory results. Infection and Grade 3-4 neutropenia will be considered as concomitant if one of the following condition is met:
    - neutrophils count value measured the day of the start of the AE infection,
    - the last neutrophils count value measured before the start date of the AE infection is within 7 days before the start of the AE infection,
    - the first neutrophils count value measured after the start date of the AE infection is within 2 days after the start of the AE infection.

Thrombocytopenia and hemorrhages

- Thrombocytopenia will be analyzed based on laboratory results
- Hemorrhages will be selected using the TEAEs from the CMQ 'Haemorrhage terms (excl laboratory terms)'.
- Moreover, severe thrombocytopenia (ie, Grade 4) with concomitant hemorrhage will be displayed if relevant. The first hemorrhages event occurring within 8 days after any occurrence of the thrombocytopenia (Lab) will be used for this analysis.

Hemolytic disorders

Hemolytic disorders will be selected using the TEAEs from the CMQ 'Haemolytic disorders Broad'.

Hemolytic disorders that occurred within 8 days after the blood cell transfusion (red blood cells or platelets) will be displayed.

Autoimmune disorders

Autoimmune disorders will be selected using the TEAE from the CMQ 'GLB_HLGT Autoimmune disorders'.

Second primary malignancies

Second primary malignancies will be selected using CMQ 'Second primary malignancies' and will be sub-categorized as 'haematological', 'non-hematological skin tumors', 'non-hematological non-skin tumors' and 'other tumors'.

2.1.4.2 Deaths

The deaths observation periods 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.
- Death within 60 days from first dose of study treatment.

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 these international units will be used in all listings and tables.

Blood samples for clinical laboratories parameters 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), partial thromboplastin time
  - **White blood cells:** white blood cell count, neutrophils, lymphocytes, monocytes, basophils, eosinophils
  - **Blood type:** Indirect Coombs Test, Indirect Antiglobulin Test (Only listing will be provided)

- **Clinical chemistry**
  - **Metabolism:** glucose, total protein, albumin,
  - **Electrolytes**: sodium, potassium, chloride, calcium, phosphorus, bicarbonate/carbon dioxide, magnesium,
  - **Renal function**: creatinine, creatinine clearance, blood urea nitrogen, uric acid,
  - **Liver parameters**: alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, lactate dehydrogenase, bilirubin (total and direct).
- **Urinalysis**
  - **Urinalysis - qualitative analyses**: blood, protein, glucose, ketones, bilirubin , leucocyte, nitrates,
  - **Urinalysis - quantitative analyses**: pH.

The baseline value of a laboratory parameter is defined as the last available value from the local laboratory assessment on or before the date first study treatment (isatuximab or dexamethasone) administration. In addition, unscheduled assessment performed on the date of first study treatment administration will be considered as post baseline. Note that since Phase 2 Stage 2 was initiated with both central and local laboratory assessment, and a change was made in amendment 12 to only collect local laboratory assessment. Therefore in the primary analysis of laboratory parameters during the on-treatment period, only local results will be used. In the sensitivity analysis of laboratory parameters during the on-treatment period, both local and central results will be used. Technical formulas are described in Section 2.5.1.

2.1.4.4 Vital signs variables

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

2.1.4.5 Electrocardiogram variables

Twelve-lead ECG will be performed at screening and as clinically indicated.

2.1.4.6 Other safety endpoints

Other safety endpoints include:

- Chest X-ray at baseline and as clinically indicated.
- Tumor lysis syndrome (TLS) as reported in the eCRF AE forms.

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) for linear non-specific elimination pathway
- Accumulation ratios (AUCss/AUC1W). AUCss is AUC at steady state.

2.1.6 Immunogenicity

Human ADA to isatuximab will be 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 the first isatuximab administration until the end of the study (Note that ADA was collected until Cycle 10 following Amendment Version 12, 12 July 2017).

Patients with at least one evaluable ADA result during the ADA pre-treatment period will be considered as evaluable at baseline. 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 on-study 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).
- **Indeterminate ADA** is defined by:
  - Treatment-induced ADA detected only the last sampling time point with all prior samples being negative, OR,
  - The last two samples are 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 ADA on-study observation period.
- **ADA incidence** is defined as the number of ADA positive patients among evaluable patients divided by the number of patients in the ADA evaluable population.
- **ADA prevalence** is defined as the sum of the number of patients with preexisting ADA among evaluable patients and the number of patients with treatment induced ADAs, divided by the number of patients in the ADA evaluable population.

2.1.7 Biomarker endpoints

2.1.7.1 Immune Genetic Determinants

Germline genetic data of Fc gamma receptor (FCGR), human leukocyte antigen (HLA) and killer-cell immunoglobulin-like receptor (KIR) genes will be analyzed on blood samples collected on Day 1 of Cycle 1:

- FCGR polymorphisms (FCGR2A and FCGR3A): For each gene, the results will be of the form AA, Aa or aa with A and a-alleles, the major and minor allele, respectively.
- HLA genotypes: HLA-A, HLA-B and HLA-C have been typed for each gene. The results will be epitope genotypes (Table 6) and allele genotypes.

Table 6 - Epitopes of HLA Class I recognized by KIR

		Amino-acid at position[a]					
HLA class I	Epitope	77	80	81	82	83	
HLA-B	Bw6	Ser	Asn	Leu	Arg	Gly	
	Bw4	Asn	Thr	Ala	Leu	Arg	
	Bw4	Asn	Ile	Ala	Leu	Arg	
	Bw4	Asp	Thr	Leu	Leu	Arg	
	Bw4	Ser	Thr	Leu	Leu	Arg	
	Bw4	Ser	Thr	Ala	Leu	Arg	
HLA class I	Epitope	77	80	81	82	83	Associated allotypes
HLA-A	Aw4	Asn	Ile	Ala	Leu	Arg	A*23; A*24
	Aw4	Ser	Ile	Ala	Leu	Arg	A*32
	A3	Key residues not yet published					A*03
	A11	Key residues not yet published					A*11
HLA class I	Epitope	77	80				
HLA-C	C1	Ser	Asn				
	C2	Asn	Lys				

a Numbering from the first codon of the mature protein

- KIR genotypes: The presence or absence of 16 KIR genes will be screened. A KIR gene will be defined as present if at least one assay gives positive results; otherwise it will be defined as negative.

2.1.7.2 Immune phenotyping

Immune phenotyping in bone marrow (baseline) and/or peripheral blood (D1 of Cycle 1, D1 of Cycle 3 and EOT) will be assessed. The immune cell populations including B-cell, T-cell and NK-cell subsets will be determined by multiparametric flow cytometry based on the expression of different cell surface markers.

2.1.7.3 CD38 mRNA

Not applicable.

2.1.7.4 Soluble CD38

Soluble CD38 will be assessed at baseline, C3D1 and EOT.

2.1.8 Health related quality-of-life (HRQL) endpoints

Not applicable following Protocol Amendment 12.

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 study treatment will be collected on a specific eCRF page. The following information will be collected: drug/medication (brand or generic name), start date and end date (if available)/ongoing (otherwise).

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

Time to Next Treatment

TNT is defined as the time from the date of first study treatment administration to the start of further anti-myeloma treatment. Patients who do not receive any further anti-myeloma treatment before the cut-off date will be censored at the date of their last FU visit or the cut-off date, whichever comes first. Patients with no FU visit will be censored at their last study treatment administration or the cut-off date whichever comes first.

2.2 DISPOSITION OF PATIENTS

Patients in each of the following categories will be provided in a summary table:

- Number of screened patients (those who signed the screening informed consent form)
  - Number of screened patients not randomized.
- Number of randomized patients
  - Number and percentage of randomized but not treated patients.
  - Number and percentage of randomized and treated patients.

Percentages will be calculated using the number of randomized patients. In addition, a listing of screened failed patients and reason for screening failure (when available) will be provided.

The number and percentage of patients in analysis populations (defined in Section 2.3) will be provided in a summary table.

The number and percentage of patients in each of the following categories will be provided using the AT/safety population:

- Patients in each country and center.

- Patients off treatment and reasons for treatment discontinuation.
- For ISAdex arm only: Patients premature discontinuation of treatment.
- Patients on treatment at time of the analysis.
- Status at last study contact.

Listing of the reasons for treatment discontinuation and patients still on treatment at time of the analysis will be provided.

A summary of the key dates of the study including the following will be presented:

- Date of first consent signed (using all screened patients).
- Date of last consent signed (using all screened patients).
- Date of first randomization.
- Date of last randomization.
- Date of first patient first dose.
- Date of last patient first dose.
- Last cycle day 1 date.
- Date of last visit completed.

Major deviations potentially impacting efficacy/safety analyses include:

Protocol deviations at inclusion:

- No known diagnosis of MM.
- No evidence of measurable disease ie, none of the following:
    - Serum M-protein <1.0 g/dL (or <0.5 g/dL for IgA).
    - Urine M-protein <200 mg/24 hours.
    - Serum immunoglobulin (SI) free light chain (FLC) <10mg/dL or 0.26 ≤ SI serum kappa lambda FLC ratio ≤ 1.65.
- No prior treatment with IMiD and/or PI (for ≥2 cycles of ≥2 months of treatment).
- Did not receive at least three prior lines of therapy for MM and is not double refractory to IMiD and PI.
- Did not achieve an MR or better to at least one prior line of therapy.
- Did not have evidence of disease progression on or after the most recent prior regimen
- Informed consent not signed.
- Age <18 years.
- Prior autologous stem cell transplant within 12 weeks of the first dose of study treatment.

- Prior allogenic transplant within 1 year with evidence of active graft vs. host disease (GVHD).
- Patients with a ECOG performance status score >2.
- Total bilirubin ≥2.5 x ULN.
- AST or ALT ≥5 x ULN.
- Calculated or measured creatinine clearance <15 mL/minute/1.73 m^2
- Absolute neutrophil count (ANC) ≤900/mm3.
- Hemoglobin ≤7.5 g/dL.
- Platelet count ≤40 000/mm3.

Protocol deviations during treatment:

- Treatment different from randomization.
- No premedication given for prevention of IAR during any infusion of Cycle 1.
- No pregnancy test and age <55, or pregnancy test is positive.
- Received other anti-MM therapy during treatment.

All major deviations will be summarized showing the number and percentage of patients with major deviations. Major protocol deviations will also be listed. A separate table on the eligibility deviations with number of violators per criterion by order of frequency will be provided.

2.2.1 Randomization and drug dispensing irregularities

All randomization and drug-dispensing irregularities will be documented in the clinical study report. If the number of irregularities is large enough to make a tabular summary useful, the irregularities will be categorized and summarized among randomized patients (number and percentages). Nonrandomized and treated patients in Stage 2 (if any) will be described separately.

Randomization and drug-dispensing irregularities to be prospectively identified include but are not limited to:

- Study treatment administration without IVRS/IWRS transaction.
- Randomization by error.
- Patient randomized twice.
- Treatment from the wrong arm is given.
- For ISAdex arm only: initial dexamethasone dose not dispensed per age class (should be 20 mg for age ≥75; 40 mg otherwise).

2.3 ANALYSIS POPULATIONS

2.3.1 Randomized population

The randomized population includes all patients from Stage 2 who gave their informed consent and were assigned a randomization number by the IVRS/IWRS.

2.3.2 All treated (AT)/safety population

The AT/safety population will include all randomized patients who gave their informed consent and who have received at least 1 dose (even incomplete) of isatuximab; patients who received dexamethasone in addition to isatuximab (excluding when given as part of premedication) will be included in the ISAdex arm. Non-randomized but treated patients will not be part of the safety population; however, their safety data will be presented separately.

This population is the primary population for the analyses of efficacy and safety parameters. All analyses using this population will be based on the actual treatment given at Cycle 1 - Day 1 (ISA or ISAdex).

2.3.3 Pharmacokinetic population

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

2.3.4 ADA evaluable population

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

2.3.5 Biomarker population

There will be no population flag for biomarker. Biomarker endpoints will be analyzed using patients from the all treated population who have one assessment on the biomarker of interest.

2.4 STATISTICAL METHODS

In the summary tables, treatment groups will be presented as follows:

- ISA
- ISAdex
- All

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

Important data listings will be provided, such as, patient disposition, AEs leading to discontinuation, SAEs, deaths, and specific TEAEs. Listings will be sorted by treatment arm and patient number. Repeated values of these key variables will be blanked out in the listings.

2.4.1 Demographics and baseline characteristics

Parameters described in Section 2.1.1 will be summarized using descriptive statistics on the all treated population. Analyses for the randomized population will be included in the appendices if the size of the randomized population is different (>10%) from the size of the randomized population for any treatment group.

Past medical or surgical history will be summarized by primary SOC and PT (both sorted by alphabetical order). Past medial history occurring in ≥10% of patients will also be summarized by PT sorted by decreasing frequency.

MM disease characteristics at diagnosis and at study entry, molecular subtype, and prior anticancer therapies will be described for the AT/safety population.

2.4.2 Prior or concomitant medications (other than anticancer therapies)

The prior and concomitant medications will be presented for the AT/safety population.

Medications will be summarized by treatment group and overall according to the WHO-DD dictionary, considering the first digit of the anatomic category (ATC) class (anatomic 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 (anatomic or therapeutic) linked to the medication. Therefore, patients may be counted several times for the same medication.

The table for prior medications will be sorted by decreasing frequency of ATC followed by all other therapeutic classes based on the overall incidence across treatment groups. In case of equal frequency regarding ATCs, alphabetical order will be used.

The tables for concomitant and post treatment medications will be sorted by decreasing frequency of ATC followed by all other therapeutic classes based on the incidence in the all column. In case of equal frequency regarding ATCs (anatomic or therapeutic categories), alphabetical order will be used.

Premedications

Number (%) of patients with premedications including diphenhydramine, methylprednisolone, ranitidine, and paracetamol as defined in Section 2.1.2 will be provided. Number of infusions with

premedications and number of infusions without IR premedications may be summarized when applicable.

2.4.3 Extent of investigational medicinal product exposure and compliance

The extent of study treatment exposure will be assessed and summarized by treatment group within the AT/safety population.

2.4.3.1 Overall exposure

The dose information will be assessed by the following variables:

- Number of cycles started, defined by maximum of isatuximab/dexamethasone cycles started.
- Duration of overall exposure (or time on-treatment) (in weeks) is defined as (last day of last cycle – first day of first cycle)/7. The first day of first cycle is defined by the earliest of isatuximab and dexamethasone administration date. The last day of last cycle is defined by the last date among the following:
    - date of last dose of isatuximab + 7 days if last cycle is QW cycle, or date of last dose of isatuximab + 14 days if last cycle is Q2W cycle.
    - date of last dexamethasone + 7 days for ISAdex arm.

Total number of cycles started, number of cycles started by patients as a quantitative variable and by category (ie, number (%) of patients receiving at least 1 cycle, at least 2 cycles etc), duration of overall exposure will be summarized by descriptive statistics.

Cycle delay 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.

Cycle delayed will be analyzed at the patient and cycle levels, as follows (the number of patients who received ≥2 cycles will be used for % calculation):

- Number of patients who could have a cycle delayed (patients who received ≥2 cycles, used for % calculation in this section)

    Number (%) of patients with a least 1 cycle delayed

    - Number (%) of patients with a cycle delayed between 4 and 7 days (using maximum delay).
    - Number (%) of patients with a cycle delayed >7 days (using maximum delay).
- Number of cycles that could be delayed (cycle ≥2, used for % calculation in this section)

    Number (%) of cycles delayed

    - Number (%) of cycles delayed between 4 and 7 days.
    - Number (%) of cycles delayed >7 days.

2.4.3.2 Isatuximab exposure

The dose information will be assessed by the following:

- Total number of cycles started
- Number of cycles started by patient
- 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 (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 each time point divided by the actual body weight as measured at each time point (cycle and day)
- Cumulative dose (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 by the duration of isatuximab exposure (in weeks)
- Relative dose intensity (RDI) in %: $100 \times \frac{\text{ADI (mg/kg/week)}}{\text{Planned Dose Intensity (mg/kg/week)}}$

    Planned dose intensities in mg/kg/week corresponds to the planned dose (20 mg/kg) multiplied by the theoretical total number of doses during the started cycles (count 2 for Q2W cycles, 4 for QW cycles), and divided by the theoretical cycle duration expressed in weeks (ie, 4 weeks per cycle started).

The total number of cycles started, number of cycles started by patients as a quantitative variable and by category (ie, number [%] of patients receiving at least 1 cycle, at least 2 cycles, etc), duration of isatuximab exposure, cumulative dose, ADI and RDI will be summarized by descriptive statistics.

The following variables will be derived to describe dose delays/modifications:

- Dose delay (within a cycle): A dose is deemed as delayed if the actual start date of the infusion – theoretical start date of an infusion is >1 day for weekly administration, is >2 days for Q2W administration. Dose delay does not apply to the first infusion of each cycle.
- 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). Analysis of dose interruption will be performed using the dose interruption section of the drug administration page in the eCRF.
- Dose omission: a dose is considered omitted if the dose is not administered for the scheduled visit and there are positive dose(s) afterwards.

- 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 7, 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 7 – Isatuximab dose reduction criteria

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

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

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

- Patient level
    - Number (%) of patients with at least 1 dose delayed (using number of patients with ≥2 infusions as denominator for % calculation).

    For the following variables, number of patients treated will be used for % calculation:

    - Number (%) of patients with at least one dose omission.
    - Number (%) of patients with at least one dose reduction.
    - Number (%) of patients with a least 1 infusion interrupted.
    - Number (%) of patients with at least 2 infusions interrupted.
- Infusion level
    - Total number of isatuximab infusions (used for % calculation for this section).
    - Number (%) of isatuximab infusions :
        - Total interrupted.
            - Re-started
            - Not re-started
    - 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 and qualitative: 5-10, 11-30, 31–40, 41 –50, 51 –60, 61–90, 91–120, >120).
    - 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 for first and subsequent infusions.

2.4.3.3 Dexamethasone exposure (ISAdex arm only)

The dose information will be assessed by the following:

- Total number of cycles started
- Number of cycles started by patient
- Duration of dexamethasone exposure (or time on-treatment) (in weeks) is defined as [date of last dose of dexamethasone + 7 days – date of first dose of dexamethasone]/7.
- Actual dose (mg): for a given cycle and day of administration, the actual dose in mg corresponds to the actual dose in mg administered at each time point. Note that the planned dose is 40 mg for patients <75 years old, and 20 mg for patients ≥75 years old.
- Cumulative dose (mg): the cumulative dose is the sum of all actual doses of dexamethasone, expressed in mg, given from first to last administration
- Actual dose intensity (ADI) in mg/week: defined as the cumulative dose (in mg) divided by the duration of dexamethasone exposure (in weeks)
- Relative dose intensity (RDI) in %: $100 \times \frac{\text{ADI (mg/week)}}{\text{Planned Dose Intensity (mg/week)}}$
- Planned dose intensities in mg/week correspond to the planned dose (mg) at Cycle 1-Day 1 (taking into account patient's age), regardless of dose changes.

The total number of cycles started, number of cycles started by patients as a quantitative variable and by category (ie, number [%] of patients receiving at least 1 cycle, at least 2 cycles, etc), duration of dexamethasone exposure, cumulative dose, ADI and RDI will be summarized by descriptive statistics.

The following variables will be derived to describe dose delays/modifications:

- Dose delay (within a cycle): A dose is deemed as delayed if the actual start date of the dose – theoretical start date of a dose is >1 day for weekly administration. Dose delay does not apply to the first dose of each cycle.
- Dose omission: a dose is considered omitted if the dose is not administered for the scheduled visit and there are positive dose(s) afterwards.
- Dose reduction: The first administration will not be counted as a dose reduction. For the second and subsequent dexamethasone administrations, dose reduction will be determined using the dose level intervals provided in Table 7, 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 8 – Dexamethasone dose reduction criteria

Actual dose level	Dose level interval if starting dose is 40mg[1]	Dose level interval if starting dose is 20mg[2]
Dose level 1 (low dose)	>0 mg and ≤8 mg	>0 mg and ≤4 mg
Dose level 2 (16mg[1]/8mg[2])	>8 mg and ≤20 mg	>4 mg and ≤ 10 mg
Dose level 3 (24mg[1]/12mg[2])	>20 mg and ≤32 mg	>10 mg and ≤16 mg
Dose level 4 (40mg[1]/20mg[2]):	>32 mg	>16 mg

[1] in patients <75 y.o

[2] in patients ≥75 y.o

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

- Patient level
  - Number (%) of patients with at least 1 dose delayed (using number of patients with ≥2 dose as denominator for % calculation).

  For the following variables, number of patients treated will be used for % calculation:
  - Number (%) of patients with at least one dose omission.
  - Number (%) of patients with at least one dose reduction.

2.4.4 Analyses of efficacy endpoints

All primary, secondary and exploratory analyses will be performed using the AT/safety population.

The following hypothesis will be tested:

- ISA arm: the null hypothesis ORR ≤15% will be tested using an exact binomial test at a one-sided alpha of 0.025. If there are 105 patients, then the null hypothesis will be rejected when the observed ORR is greater than or equal to 22.9% (24 responders).
- ISAdex arm: the null hypothesis ORR ≤ 15% will be tested using an exact binominal test at a one-sided alpha of 0.025. If there are 55 patients, then the null hypothesis will be rejected when the observed ORR is greater than or equal to 27.3% (15 responders).

2.4.4.1 Analysis of primary efficacy endpoint(s)

ORR, including BOR, CBR and at least VGPR rate as assessed by IAC will be summarized with descriptive statistics. A 95% two-sided confidence interval will be computed for ORR, CBR and VGPR or better rate using Clopper-Pearson method. The same analysis will be performed using investigator assessments of response. In addition, for exploratory purpose, ORR and VGPR or better rate according to IAC assessment between the 2 arms will be compared using the Fisher exact test.

ORR as assessed by IAC will also be summarized descriptively for subgroups variable defined in Table 3.

The relationship between Responder/Non responder (binary variable, BOR of PR or better) and parameters defined in Table 3 and 4 will be analyzed by fitting a logistic regression model. Model development will involve univariate analyses for each parameter and Responder/Non responderendpoint. Considering the most significant parameters of the univariate analyses, multivariate analyses with stepwise inclusion and deletion of covariates will be performed. The significance level for variable entry or removal at each step will be less than 0.15 for entry and 0.10 for removal.

2.4.4.2 Analyses of secondary efficacy endpoints

The following analyses will be performed using both IAC and investigator assessments of response.

- CBR: see above.
- DOR: Kaplan-Meier estimates of the 25th, 50th and 75th percentiles including the 95% confidence interval as well as Kaplan-Meier curves will be provided for DOR for patients who achieve a response ≥ PR.
- PFS:

  PFS will be analyzed using the Kaplan-Meier method by treatment group:

  - Kaplan-Meier estimates of the 25th, 50th and 75th percentiles and their associated 95% confidence interval will be provided. The 95% confidence intervals will be constructed using a log-log transformation of the survival function and the methods of Brookmeyer and Crowley.
  - Number of patients at risk as well as the probabilities of surviving without disease progression at least 2, 4, 6, 8, 10, 12, 14 and 16 months with 95% CIs will be estimated for each treatment group using the Kaplan-Meier method.
  - The Kaplan-Meier curves will be plotted. These plots will include the number of patients at risk at key time points by treatment group.
  - The log rank test from the comparison of PFS between the 2 arms will be provided for exploratory purpose.

  In addition, the hazard ratio (HR) and its 95% confidence interval (CI) will be estimated using the Cox proportional hazards model. Underlying assumptions of the Cox Proportional hazards model will be assessed by graphical methods (ie, log-log graphical methods).

A multivariate Cox proportional hazards model will be used to identify prognostic factors among the demographic and baseline characteristics factors described in the table above using a stepwise selection procedure with a 15% significance level for removing effects. For significant prognostic factors identified in the multivariate model, the balance between treatment groups will be assessed. If major confounding is identified through screening for treatment group imbalances in a prognostic factor at baseline, the treatment effect for PFS will be re-estimated after adjusting for the prognostic factors in the multivariate Cox proportional hazards model. Differences between the adjusted and unadjusted models will be discussed in the clinical study report.

- For patients with events, the type of event (confirmed disease progression or death) will be summarized by treatment group using counts and percentages. The type of disease progression will also be presented (progression diagnosed on M-protein or radiological progression).
- For patients who died without evidence of disease progression, the time from the last disease assessment to the death will be summarized by treatment group using number, mean, standard deviation, median and range.
- The number (%) of censored patients, the reason and timing of their censoring (ie, censored at randomization, censored at the last valid disease assessment before the initiation of further anti-myeloma treatment, censored at last valid disease assessment before the cut-off date, censored at the cut-off date), and the time from the last disease assessment to the cut-off date will be summarized by treatment group. For each censoring reason, when applicable, distinction will be made between cases where no event was observed and cases where an event was observed after the censoring.
- Follow-up duration (months) will be defined as the time interval from the date of randomization to the date of last contact with the patient. Patients who have died will be censored on their date of death. Median follow-up duration (months) will be estimated using the Kaplan-Meier method.
- VGPR or better rate: same as CBR

OS will be analyzed using the same method as PFS.

DFU and TTR will be analyzed using Kaplan-Meier methods and summarized with descriptive statistics (among responders only for TTR).

A listing of response (as assessed by IAC) data will be provided for the all treated population and for patients who are ADA positive (Section 2.1.4.4), and will include the following variables: high risk status, number of prior lines of anti-myeloma treatment, selected prior treatments given (alkylating agent, bortezomib, carfilzomib, lenalidomide, pomalidomide, thalidomide), duration of exposure (weeks), reason for treatment discontinuation, measurable paraprotein at baseline, best percent change in paraprotein, best overall response, date of first response ≥PR, date of first disease progression/last disease assessment, indication of progressive disease, time to first response, time to best response and DOR.

A listing of best percent change in % plasma cell in bone marrow biopsy will be provide and will include the following variables: measurable paraprotein at baseline, best percent change in paraprotein, BOR, baseline plasma cells count, post baseline plasma cells count and best percent change in plasma cells count.

A swimmer plot of time on a treatment (ie, duration of exposure) will be provided. Best percent change in paraprotein will be displayed in a waterfall plot. In the waterfall plot, patients will be ordered from highest positive change to smallest negative change. Patients with BOR ≥PR will have a negative percentage change. Patients with a >100% increase in paraprotein will be shown as 100% increase.

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

Additional evidence of clinical benefit : Renal response and renal function deterioration

Number and percentage of patients in each renal response and renal function deterioration will be provided by treatment arm.

2.4.4.3 Multiplicity issues

Not applicable.

2.4.5 Analyses of safety data

The analysis of safety data will be presented by treatment group and overall (see Section 2.4).

All safety analyses will be performed on the AT/safety population as defined in Section 2.3.1. Unless otherwise specified, the baseline value is defined as the last available value before or on the date of first isatuximab/dexamethasone administration. In addition, unscheduled assessment performed on the date of first study treatment administration will be considered as post baseline.

2.4.5.1 Analyses of adverse events

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

If an AE date of onset (occurrence, worsening, or becoming serious) is incomplete, an imputation algorithm will be used to classify the AE as pretreatment, treatment-emergent, or post-treatment. 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 2.5.3.

For patients with multiple occurrences of the same AE within the observation period (pre-treatment, treatment emergent and post-treatment), the maximum severity grade will be used.

Overview of TEAEs

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

- TEAE.
- TEAE of Grade ≥3.
- Drug-related TEAE (related to either isatuximab or dexamethasone).
- Drug-related TEAE of Grade ≥3.
- Serious TEAE.
- Serious drug-related TEAE.

- TEAE with a fatal outcome.
- TEAE leading to definitive study drug discontinuation, ie, discontinuation of isatuximab in ISA arm, and discontinuation of isatuximab and dexamethasone in ISAdex arm.
- TEAE leading to premature dexamethasone discontinuation, ie, discontinuation of dexamethasone before isatuximab, only applicable to ISAdex arm.
- TEAE leading to premature isatuximab discontinuation, ie, discontinuation of isatuximab before dexamethasone, only applicable to ISAdex arm.
- AESI.
- AESI of Grade ≥3.
- IAR (excluding symptoms).
- IAR of Grade ≥3 (excluding symptoms).

Analysis of adverse events

Analysis of adverse events will be performed according to following:

- TEAEs (regardless relationship to study treatment),
- Drug related TEAEs,
- Deaths, serious adverse events, adverse events leading to withdrawal, and other significant adverse events as defined below.

Additional analyses will include:

- IAR-AESI (using the CMQ corresponding to the generic term of infusion related reaction reported by investigator as an AESI):
    - Analysis by patient: worst grade, 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 (first and subsequent isatuximab infusion), patients with IAR at the first and subsequent isatuximab infusion and number (%) of patients with at least two episodes of IARs at the same infusion.
    - Analysis by infusion: worst grade by infusion (a patient can have several IAR episodes at the same infusion).
    - Analysis by episode: proportion of IARs occurring at each infusion (infusion 1, 2, 3, 4, 5 and >5), IAR duration and day of onset.
- Summary (as described in Table 9) and listing of IAR-AESI including symptoms as reported by investigator.
- IAR-AE (ie, TEAE occurring within 24 hours of each isatuximab administration) (see Table 9).

- Respiratory TEAEs:
    - Lower respiratory TEAEs analyzed by IAR status (IAR or Non-IAR). They may also be analyzed with regards to medical history data (eg, chronic obstructive pulmonary disease, cough, dyspnea) and smoking history.
    - Respiratory infection TEAEs analyzed by IAR status (IAR or Non-IAR). They may also be analyzed with regards to medical history and smoking history.

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

- Thrombocytopenia and hemorrhages

The number (%) of patients will be provided for:

- On-treatment thrombocytopenia (Lab) identified through grading of laboratory data per the NCI-CTCAE 4.03, by grade
- Hemorrhages as defined in Section 2.1.4.1 by grade
- Hemorrhages following Grades 4 thrombocytopenia (Lab). The first hemorrhages event occurring within 8 days after any occurrence of the thrombocytopenia (Lab) will be used for this analysis.

- Hemolytic disorders

  Hemolytic disorders that occurred within 8 days after the blood cell transfusion will be analyzed using selection defined in Section 2.1.4.1 and will be presented by PT. A listing of patients with hemolytic disorders will be provided. This listing will include the PT, study day of diagnosis (from first dose of study treatment), interval to onset from the last study treatment before the diagnosis (last drug administered), duration of AE, the cycle of occurrence, severity, seriousness, outcome, action taken on study treatment, study day of the blood transfusion, and results and sampling date of indirect anti-globulin test.

- Autoimmune disorders

  A listing of patients with autoimmune disorders (selected using definition in Section 2.1.4.1) will be provided. This listing will include the PT, study day of diagnosis (from first dose of study treatment), interval to onset from the last study treatment before the diagnosis (last drug administered in a combination treatment), duration of AE, the cycle of occurrence, severity, seriousness, action taken on study treatment, and outcome.

- Neutropenia and neutropenic complications

  Neutropenia (from laboratory abnormalities) will be displayed along with febrile neutropenia and neutropenic infections (see Section 2.1.4.1).

  Duration of Grade 3/4 neutropenia episode, cumulative duration of Grade 4 neutropenia by patient and time to first Grade 3/4 neutropenia will be analyzed using laboratory data.

The start date of a Grade 4 laboratory neutropenia episode is defined as the date of first Grade 3/4 assessment for that episode. The end date of a Grade 4 neutropenia episode is defined as the first date of neutropenia assessment afterwards of Grade 0/1/2 for that episode assuming there will be at least 3 days between the first Grade ≤2 neutropenia and the next Grade≥3 assessment (if any).

If the start date of a new episode is within 3 days of the previous episode, then the two episodes will be considered as one episode. The worst grade of an episode is the worst grade of all assessments included in that episode

Duration of a Grade 3/4 neutropenia episode (in days) is defined as end date of an episode – start date of an episode +1. If a patient does not have an end date before the cutoff date in an episode then the duration of the episode will be censored at the last neutrophil assessment of Grade 3/4 or the cutoff date, whichever comes first.

Time to first Grade 3/4 neutropenia (in days) is defined as: date of the first on-treatment Grade 3/4 neutropenia assessment – date of first treatment +1. If a patient does not have Grade 3/4 neutropenia, time to first Grade 3/4 neutropenia will be censored at the last assessment of neutropenia of Grade 0/1/2 or the cutoff date, whichever comes first. If a patient does not have any on-treatment assessment of neutropenia, then the patient will be censored at Day 1.

- Second primary malignancies

  A listing of patients who reported second primary malignancies during the study will be provided (as per the CMQ) and by categories ('haematological', 'non-hematological skin tumors', 'non-hematological non-skin tumors' and 'other tumors'). This listing will include diagnosis, study day of diagnosis (from first dose), number of days from last study treatment to diagnosis, prior exposure to anti-myeloma treatments, and whether or not patient received subsequent anti-cancer treatment.

- Analysis of all treatment-emergent adverse event(s) leading to definitive treatment discontinuation. Analysis of all treatment-emergent adverse event(s) leading to premature dexamethasone discontinuation. Analysis of all treatment-emergent adverse event(s) leading to premature isatuximab discontinuation.
  - 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.
- Summary of TEAEs leading to dose interruption of isatuximab, summary of TEAEs leading to dose reduction includes reduction of isatuximab or dexamethasone (ISAdex arm), summary of TEAEs leading to dose delay includes delay of isatuximab or dexamethasone (ISAdex arm).
- Pregnancy and overdose being part of AESI, will be listed besides IARs) will be listed.
- Deaths: see Section 2.4.5.2.

The description of the main summary tables that will be provided for the analysis of TEAEs, drug-related TEAEs, serious TEAEs, drug-related serious TEAEs, IAR-AESI, IAR-AE, as well as TEAEs leading to dose discontinuation or modification is given in Table 9.

Sorting within tables will ensure the same presentation for the set of all AEs within the observation period (pre-treatment, treatment-emergent, and post-treatment). For that purpose, the table of all TEAEs 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. Sorting will be based on the incidence of AEs in the AT/safety population (ie, all patients).

Table 9 – Description of summary tables to be provided for the analysis of TEAEs

MedDRA coding variables	Sorting (all patients column)	Layout	Events
PT	• PT: Decreasing order of frequency	**Treatment groups and All patients:** n (%) of patients with any event and n (%) of patients with event of Grade ≥3	• TEAEs occurring in ≥5% of the patients (all patients) • Drug-related TEAEs occurring in ≥5% of the patients (all patients) • Serious TEAEs in ≥5%[a] of the patients (all patients)
SOC, HLGT, HLT, and PT	• Primary SOC: internationally agreed order • HLGT, HLT, PT: alphabetical order	**Treatment groups and All patients:** n (%) of patients with any event and n (%) of patients with event of Grade ≥3	• All TEAEs • Drug-related TEAEs • Serious TEAEs • Drug-related serious TEAEs • Lower Respiratory TEAEs by IAR status and medical history • Respiratory infection TEAEs by medical history
SOC and PT	• Primary SOC: internationally agreed order • PT: decreasing order of frequency defined be the all TEAEs table (see previous page)	**Treatment groups and All patients:** n (%) of patients with any event and n (%) of patients with event of Grade ≥3	• All TEAEs • TEAEs occurring in ≥5% of the patients (all patients) • Drug-related TEAEs • Drug related TEAEs occurring in ≥5% of the patients (all patients) • Serious TEAEs • Serious TEAEs in ≥5%[a] of the patients (all patients) • Drug related serious TEAEs • TEAEs leading to definitive treatment discontinuation • TEAEs leading to premature dexamethasone discontinuation • TEAEs leading to premature isatuximab discontinuation • TEAEs leading to dose interruption • TEAEs leading to dose delay • TEAEs leading to dose reduction
SOC and PT	• Primary SOC: internationally agreed order • PT: decreasing order of frequency (all patients)	**Treatment groups and All patients:** n (%) of patients with any event and n (%) of patients with event of Grade ≥3	• IAR-AESI • IAR-AE • Pre-treatment and post-treatment AEs

a The threshold presented is 5%, however, other threshold(s) could be used if deemed clinically relevant.

MedDRA coding variables	Sorting (all patients column)	Layout	Events

AE=adverse event; AESI=adverse event of special interest; HLGT=high-level group term; HLT=high-level term; IAR=infusion associated reaction; MedDRA=Medical Dictionary for Regulatory Activities; n (%)=number and percentage of patients; PT=preferred term; SOC=system organ class; TEAE=treatment-emergent adverse event.

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 (PD, AE with subdivision of drug-related AE and non-drug related AE, other) will be summarized. A listing of patients who died while participating in the study including cause of death, death date, days from first and last dose to death, preferred term, and causal relationship to isatuximab/dexamethasone (when applicable) will be provided.

The following summaries of deaths will be generated:

- Summary of AEs leading to death, by Primary SOC and PT
  - In context of disease progression (death within 30 days from last study treatment administration and the cause of death is disease progression),
  - In context other than disease progression (death within 30 days from last study treatment administration and for whom cause of death is not disease progression or the death occurred more than 30 days from last study treatment administration and the cause of death is adverse event).

2.4.5.3 Analyses of laboratory variables

Each laboratory test result will be graded by CTCAE criteria (version 4.03), when applicable. For hematological parameters and for some biochemistry parameters, Sanofi sponsor generic normal ranges will be used for the grading of laboratory abnormalities (see list of parameters in Appendix A, Table 11 and Table 12). For other biochemistry parameters (eg, for hepatic parameters), grading will be derived using the local laboratory normal ranges.

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. For patients with multiple occurrences of the same laboratory variable during the on-treatment period, the maximum grade (worst) per patient will be used. At baseline, the last available value before or on the date of first study treatment administration will be used (excluding repeated tests).

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 test.

For renal function using MDRD formula, the number (%) of patients by category ([15-30[, [30-60[, [60-90], >90 mL/min/1.73m^2) and by period (baseline and on-treatment) as well as a shift table will be provided.

For urate, Chloride and BUN, potentially clinically significant abnormalities (PCSA) values defined as abnormal values considered medically important by the Sponsor according to predefined criteria/thresholds based on literature review (Table 10) will be derived. 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. The incidence of PCSA any time during the on-treatment period will be summarized by treatment group and overall, irrespective of the baseline level.

Table 10 - Potentially clinically significant abnormalities criteria for laboratory tests

Parameter	PCSA	Comments
Clinical Chemistry		
eGFR (mL/min/1.73m2) (Estimate of GFR based on an MDRD equation)	≥15 - <30 (severe decrease in GFR) ≥30 - <60 (moderate decrease in GFR) ≥60 - <90 (mild decrease in GFR) ≥ 90 (normal GFR)	Use is optional. FDA draft Guidance 2010 Pharmacokinetics in patients with impaired renal function-study design, data analysis, and impact on dosing and labeling
Uric Acid		Harrison- Principles of internal Medicine 17th Ed., 2008.
Hyperuricemia	>408 µmol/L	
Hypouricemia	<120 µmol/L	
Blood Urea Nitrogen	≥17 mmol/L	
Chloride	<80 mmol/L >115 mmol/L	

Listings of patients with laboratory abnormalities of Grade 3 and Grade 4 during the on-treatment period will be provided. The baseline value will be included in the listing.

2.4.5.4 Analyses of vital sign variables

The incidence of PCSA (Table 11) any time during the on-treatment period will be summarized by treatment group irrespective of the baseline level and/or according to the following baseline status categories:

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

Table 11 - 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, by treatment group and all.

A listing of patients with at least one PCSA will be provided.

2.4.5.5 Analyses of electrocardiogram variables

The number (%) of patients with normal/abnormal ECG result at baseline will be summarized by treatment group and all. A listing of ECG results will be provided.

2.4.5.6 Analyses of other safety endpoints

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

A listing of patients with TLS reported in eCRF AE forms (using a SMQ: Tumor lysis syndrome) during the study will be provided. The clinical chemistry parameters regarding hyperkalemia, hyperphosphatemia, hypocalcemia, and hyperuricemia will be listed to corroborate any report of TLS identified with the above SMQ.

A listing of chest x-ray results will be provided.

2.4.6 Analyses of pharmacokinetic and pharmacodynamic variables

2.4.6.1 PK variables

Isatuximab plasma concentrations after single and repeated dose administrations will be analyzed using a nonlinear mixed-effects modelling approach using MONOLIX software version 2016 R1 (or more recent version) (Lixoft). Individual estimates of PK parameters will be obtained using parameter estimates from the basic population model developed in TED10893 Phase 1 and Phase2 stage 1 (POH0458 study) as priors (Empirical Bayes estimates) and individual concentrations. Exposure parameters (C_{max}, C_{trough} and cumulated AUC) will be derived using the individual parameters.

Pharmacokinetic parameters of isatuximab (listed in Section 2.1.5) will be summarized by descriptive statistics (such as the number of observations available, arithmetic and geometric mean, median, standard deviation (SD), coefficient of variation (CV), minimum, and maximum) under the responsibility of Pharmacokinetic, Dynamic and Metabolism, Translational Medicine and Early Development Sanofi. Steady state (based on C_{trough}) will be assessed as well as the extent of the accumulation.

Summary (number of patients, mean and CV%) of $Ctrough_{obs}$ of isatuximab by visit will be provided. A listing of $Ctrough_{obs}$ for individual patient will also be provided. $Ctrough_{obs}$ will be kept for the descriptive statistics if sampling occurs within 7 days ± 1 day after the previous start of infusion for sampling done during Cycle 1 and within 14 days ± 3 days after the previous start of infusion for sampling done for subsequent cycle 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 removed from the analyses.

2.4.7 Immune response

Using the ADA evaluable population, the number (%) of patients will be provided for the following:

- Preexisting 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 descriptively, depending on the ADA prevalence.

2.4.8 Analyses of Biomarker variables

2.4.8.1 Genetic variables

Summary of BOR will be provided for the following patients:

- High risk cytogenetic markers (del17p and/or t(4;14) and/or t(14;16))
- Chromosomal abnormalities(gain(1q) and del(1p32)).
- FcGR3A types: F/F, F/V, V/V and missing.
- FCGR2A genotypes
- HLA and KIR genotypes including:
    - HLA-B BW4-80Ile+ and KIR3DL1+ vs HLA-B BW4-80Ile- or KIR3DL1-.
    - KIR3DS1- vs KIR3DS1+.

2.4.8.2 Other variables

Descriptive statistics of soluble CD38 for the all treated population as well as for responders/non-responders will be calculated. In addition, graphs showing responder/non-responder rate by soluble CD38 levels will be provided.

Graphs showing ORR/non-responder rate by biomarker levels will be provided for the following parameters at baseline for soluble CD38

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

- Immune cell level (B-cell, T-cell and NK-cell subsets respectively in blood and bone marrow samples) will be described
- Measurable paraprotein will be described as define below:

Table 12 - Derivation of measurable paraprotein type at baseline

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

2.4.8.2.1 Descriptive analysis

Each biomarker will be summarized with descriptive statistics by treatment group and overall.

2.4.8.2.2 Univariate analysis

When applicable, each biomarker will be tested for a potential prognostic/predictive effect for ORR.

A logistic regression will be conducted separately for each genetic biomarker with a treatment effect, a biomarker effect and a biomarker×treatment interaction. Since the number of patients in each treatment group is small, only the main effect of the biomarkers may be investigated ignoring the interaction with treatment.

In this analysis, some dose/schedules may be pooled together or removed from the model.

For biomarkers coded as genotype (0, 1, 2), different coding may be investigated: additive, dominant or recessive.

Distribution of p-values will be presented and Benjamini-Hochberg multiple correction procedure will be used to control the false discovery rate (FDR).

Additional analyses using PFS instead of ORR might also be performed.

2.4.8.2.3 Multivariate analysis

If some biomarkers are determined to be potentially prognostic/predictive in the previous step, multivariate analysis combining several biomarkers will be considered (eg, logistic regression, SVM, Random Forest). A proper cross-validation scheme including the univariate selection step, will be put in place to estimate the generalization error of the model.

Sensitivity, specificity and accuracy will be calculated to assess the predictive properties of the multivariate biomarker.

2.4.9 Analyses of quality of life variables

No analysis is planned for quality of life variables.

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

Further therapies will be descriptively summarized by treatment group and overall.

Time to next treatment

TNT will be analyzed using Kaplan-Meier methods.

2.5 DATA HANDLING CONVENTIONS

2.5.1 General conventions

Not applicable. General conventions are provided in the relevant sections.

2.5.2 Data handling conventions for secondary efficacy variables

Not applicable.

2.5.3 Missing data

The analyses and summaries of continuous and categorical variables will be based on observed data only. Percentages will be calculated using as the denominator the number of patients with a non-missing observation in the considered population. When relevant, the number of patients with missing data will be presented.

When incomplete or missing dates were found in the eCRF, attempts were made to retrieve the complete date, especially for dates within the month prior to first dose. However, if some dates remain incomplete, the following rules will be applied:

Handling of disease characteristics missing/partial dates

- If the day is missing, it will be imputed to be 1.
- If the month is missing, it will be imputed to be 1 (only for medical history variables).
- If the year is missing, no imputation 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 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 or partial date of onset

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

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 study treatment is missing, then the relationship to isatuximab/dexamethasone has to be assumed and the AE considered as such in the frequency tables of possibly related AEs, but no imputation will be done at the data level.

Handling of death with missing or partial date of death

The imputation for missing or partial death date will proceed as follows:

1. If the death day is missing and the death month and year are the same as the last month and year the patient was last known to be alive, the death day will be set equal to the last day the patient was known to be alive + 1.
2. If the death day is missing and the death month is after the month the patient was last known to be alive and the death year is the same as the year the patient was last known to be alive, the death day will be set to 01.
3. If the death day and month are missing and the death year is the same as the year the patient was last known to be alive, the death date will be set equal to the date the patient was last known to be alive + 1.
4. If the death day and month are missing and the death year is after the year the patient was last known to be alive, the death day and month will both be set to 01.

If the date the patient was last known to be alive is partial or missing, no imputation for missing or partial death date will be performed. The last date the patient was known to be alive is the last of: date of last dose, date of last visit performed (when the patient is known to be alive according to subject vital status), date of last laboratory assessment, date of last vital signs.

Handling of parameters expressed as inequality or approximation

For some parameters (such as laboratory parameters), if the value is expressed as an inequality or an approximation, the numeric portion of the entry may be used in calculations.

2.5.4 Windows for time points

Laboratory data

A protocol planned laboratory test is considered to have occurred during a cycle if the date of sampling is after (>) the first day of the cycle, but prior to or equal (≤) to the first day of the next cycle. For unscheduled tests, a test is considered to have occurred during a cycle if the date of sampling is equal to or after (≥) the first day of the cycle, but prior (<) to the first day of the next cycle.

Sponsor specified reference ranges will be used to calculate laboratory toxicities (see Section 2.4.5.3).

2.5.5 Unscheduled visits

Unscheduled visit measurements of laboratory data, vital signs and ECG will be used for computation of baseline and 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

An interim analysis of the safety data from Phase 2 Stage 2 may be performed if the enrollment is not completed by December 2017. No formal statistical hypothesis will be tested in this analysis.

A cutoff date will be defined for this analysis, and all patients treated before the cutoff date - 28 days will be included in the analysis. The analyses will include the following parameters/analyses (defined in Section 2): demographics and baseline characteristics, prior or concomitant medication, safety endpoints (AE, deaths, laboratory variables, vital signs, ECG, and other safety endpoint), PK variables, immunogenicity.

4 DATABASE LOCK

The database will be locked when clinical review of the database has been completed and all critical queries have been resolved.

5 SOFTWARE DOCUMENTATION

All summaries and statistical analyses, except for biomarker analysis, will be generated using SAS® version 9.2 or higher. Biomarker analyses will be performed using R software version 3.3.2 (2016-10-31).

6 REFERENCES

1. Palumbo A1, Rajkumar SV, San Miguel JF, Larocca A, Niesvizky R, Morgan G, et al. International Myeloma Working Group consensus statement for the management, treatment, and supportive care of patients with myeloma not eligible for standard autologous stem-cell transplantation. J. Clin Oncol. 2014 Feb 20;32(6):587-600.

2. Kratz A, Ferraro M, Sluss P, Lewandrowski K. Laboratory reference values.

7 LIST OF APPENDICES

Appendix A: Generic ranges for hematological and biochemistry

Table 13 – Generic ranges for hematological parameters

Test	Gender	Unit	Lower limit of normal
Hemoglobin	F	g/L	120
Hemoglobin	M	g/L	135
Lymphocytes		109/L	1
Neutrophils		109/L	1.8
Platelets		109/L	150
Leukocytes		109/L	4.5
Eosinophils		109/L	0
Basophils		109/L	0
Monocytes		109/L	0.18
Hematocrit	M	%	0.41
Hematocrit	F	%	0.36
Erythrocytes	F	1012/L	4
Erythrocytes	M	1012/L	4.5
INR		ratio	0.8

Based on Kratz et al. (2)

The current list of generic ranges for biochemistry parameters (for adults) is provided in the table below:

Table 14 – Generic ranges for biochemistry parameters

Test	Unit	Lower – Upper limit of normal
Albumin	g/L	35 - 55
Blood Urea Nitrogen (BUN)	mmol/L	3.6 – 7.1
Calcium	mmol/L	2.2 - 2.6
Corrected calcium	mmol/L	2.2 – 2.6
Glucose	mmol/L	3.9 - 7
Bicarbonate (HCO3)	mmol/L	22 - 29
Carbon dioxide	mmol/L	21 - 30
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

Appendix B: Definition of regions

1) Geographical regions

Western Europe	North America	Other countries
Belgium	United States	Ukraine
Finland	Mexico	Turkey
Greece		Russian Federation
Italy		Argentina
Spain		Brazil
United Kingdom		Chile
		Israel
		Peru

2) Regulatory regions

Western countries	Other countries
Belgium	Ukraine
Finland	Mexico
Greece	Turkey
Italy	Russian Federation
Spain	Argentina
United Kingdom	Brazil
United States	Chile
	Israel
	Peru