NCT01084252

AMENDED CLINICAL TRIAL PROTOCOL 14

COMPOUND: SAR650984 (isatuximab)

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

STUDY NUMBER: SAR650984-TED10893

VERSION DATE/STATUS: 22-Jul-2020/Approved

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PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY

Amended Clinical Trial Protocol 14	Version number: 1 (electronic 18.0)	Date: 22-Jul-2020
Amended Clinical Trial Protocol 13	Version number: 1 (electronic 17.0)	Date: 11-Jun-2019
Amended Clinical Trial Protocol 12	Version number: 1 (electronic 16.0)	Date: 12-Jul-2017
Protocol Amendment 12	Version number: 1 (electronic 1.0)	Date: 12-Jul-2017
Amended Clinical Trial Protocol 11	Version number: 1 (electronic 12.0)	Date: 22-Apr-2016
Protocol Amendment 11	Version number: 1 (electronic 1.0)	Date: 22-Apr-2016
Amended Clinical Trial Protocol 10	Version number: 1 (electronic 12.0)	Date: 22-Aug-2014
Protocol Amendment 10	Version number: 1 (electronic 2.0)	Date: 22-Aug-2014
Amended Clinical Trial Protocol 9	Version number: 1 (electronic 11.0)	Date: 08-Apr-2014
Protocol Amendment 9	Version number: 1 (electronic 1.0)	Date: 08-Apr-2014
Amended Clinical Trial Protocol 8	Version number: 1 (electronic 8.0)	Date: 19-Mar-2014
Protocol Amendment 8	Version number: 1 (electronic 2.0)	Date: 19-Mar-2014
Amended Clinical Trial Protocol 7	Version number: 1 (electronic 6.0)	Date: 13-Aug-2013
Protocol Amendment 7	Version number: 1 (electronic 1.0)	Date: 13-Aug-2013
Amended Clinical Trial Protocol 6	Version number: 1 (electronic 5.0)	Date: 05-Apr-2013
Protocol Amendment 6	Version number: 1 (electronic 1.0)	Date: 05-Apr-2013
Amended Clinical Trial Protocol 5	Version number: 1 (electronic 3.0)	Date: 10-Sep-2012
Protocol Amendment 5	Version number: 1 (electronic 2.0)	Date: 10-Sep-2012
Amended Clinical Trial Protocol 4	Version number: 1 (electronic 1.0)	Date: 05-Jan-2011
Protocol Amendment 4	Version number: 1 (electronic 1.0)	Date: 05-Jan-2011
Amended Clinical Trial Protocol 3	Version number: 1 (electronic 1.0)	Date: 11-Oct-2010
Protocol Amendment 3	Version number: 1 (electronic 1.0)	Date: 11-Oct-2010
Amended Clinical Trial protocol 2	Version number: 1 (electronic 3.0)	Date: 07-Apr-2010
Protocol Amendment 2	Version number: 1 (electronic 1.0)	Date: 07-Apr-2010
Amended Clinical Trial Protocol 1	Version number: 1 (electronic 2.0)	Date: 16-Dec-2009
Protocol Amendment 1	Version number: 1 (electronic 2.0)	Date: 16-Dec-2009
Clinical Trial Protocol	Version number: 1 (electronic 2.0)	Date: 27-Oct-2009

Amended protocol 14 (22 July 2020)

This amended protocol (amendment 14) is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

OVERALL RATIONALE FOR THE AMENDMENT

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

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
1.13 Study flowchart for Phase 2, Stage 1a; 1.14 Study flowchart for Phase 2, Stage 1b; 1.15 Study flowchart for Phase 2, Stage 2; 6.8 Guidance in case of hepatitis B reactivation occurring under study treatment	Additional hepatitis viral serology if HBV status unknown before treatment start, to be repeated if clinically indicated.	A risk of hepatitis reactivation has been identified.
6.8 Guidance in case of hepatitis B reactivation occurring under study treatment	Description of study treatment discontinuation and restart procedure in case of viral reactivation.	A risk of hepatitis reactivation has been identified.
6.8 Guidance in case of hepatitis B reactivation occurring under study treatment; 12.3 Data collection after final analysis cutoff date	Description of monitoring of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) in case of viral reactivation.	A risk of hepatitis reactivation has been identified.
8.1.6.3 Administration	Oral dexamethasone may be provided to the participant via a Sponsor-approved courier company.	Treatment supply option for patients who are unable to come to study site because of a regional or national emergency declared by a governmental agency.
10.5.2 Serious adverse events	Hospitalization and examination reports for serious adverse events (SAEs) will not be systematically requested.	Only necessary copies of medical records are to be shared with the Sponsor.
12.3 Data collection after final analysis cutoff date	Patients will be followed for a minimum of 30 days following the last use of study drug.	Consistency: anti-drug antibodies (ADA) are not tested anymore so a 30-day follow-up is sufficient.
All document	Minor editorial and format changes.	Accuracy

NAMES AND ADDRESSES OF

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

CLINICAL TRIAL SUMMARY

COMPOUND: SAR650984	**STUDY No: TED10893**
TITLE:	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
STUDY OBJECTIVES:	***Primary*** ***Phase 1*** To determine the maximum tolerated dose (MTD)/maximum administered dose (MAD) of SAR650984 according to the investigational product (IP) related dose limiting toxicities (DLTs) observed in patients with selected CD38+ hematological malignancies. ***Phase 2*** In Stage 1: To evaluate the activity of single-agent SAR650984 at different doses/schedules and to select dose and regimen to further evaluate the overall response rate (ORR) of SAR650984 as a single agent or in combination with dexamethasone, in patients with relapsed or relapsed/refractory multiple myeloma in Stage 2. In Stage 2: To evaluate the activity in terms of overall response rate (ORR) of SAR650984 at the selected dose/schedule from Stage 1, as single agent (ISA arm) and in combination with dexamethasone (ISAdex arm) in patients with relapsed or relapsed/refractory multiple myeloma. ***Secondary*** ***Phase 1*** • To characterize the global safety profile including cumulative toxicities. • To evaluate the pharmacokinetic (PK) profile of SAR650984 in the proposed dosing schedule(s). • To assess the pharmacodynamics, immune response, and preliminary disease response. ***Phase 2 Stage 1*** **To evaluate the followings objectives for SAR650984 as single agent:** • Safety • Efficacy as measured by: - Duration of response (DOR) - Clinical benefit rate (CBR) - Progression free survival (PFS) - Overall survival (OS) ***Phase 2 Stage 2*** **To evaluate the following objectives in each arm (ISA and ISAdex):** • Safety • Efficacy as measured by - Duration of response (DOR) - Clinical benefit rate (CBR) - Progression free survival (PFS) - Overall survival (OS)

STUDY OBJECTIVES (cont'd)	***Exploratory*** ***Phase 2*** • To assess minimal residual disease (MRD) in patients achieving a complete response (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 (Stage 1 only) • To investigate the relationship between immune genetic determinants, immune phenotype, adaptive immune response and parameters of clinical response
STUDY DESIGN:	This is an open-label, international multi-center study conducted in 2 parts (Phase 1 and Phase 2). **Phase 1 Part** The Phase 1 part is a dose escalation study of SAR650984 administered as single agent as an intravenous (IV) infusion every week or every 2 weeks to adult patients with selected $CD38^+$ hematological malignancies. The administration of the IP will start at 0.0001 mg/kg (representing 10% of theoretical CD38 receptor occupancy (RO) on normal B and T cells). Two dose escalation schemes will be used based upon toxicities observed during the first two cycles of treatment (28 days). In this first in man (FIM) study, potential DLTs are defined as any Grade 3 or higher non-hematological toxicity (excluding allergic reaction/hypersensitivity), Grade 4 neutropenia and/or Grade 4 thrombocytopenia lasting longer than 5 days, attributed to SAR650984 and as defined by the NCI-CTCAE v.4 (Section 9.1.2). In the Phase 1 part, a cycle is 14 days. ***Accelerated dose escalation scheme*** One evaluable patient per dose level (DL) unless Grade 4 neutropenia and/or Grade 4 thrombocytopenia lasting longer than 5 days, or Grade 1 or higher IP related non-hematological toxicity including fever, but excluding nausea, vomiting, diarrhea, fatigue, asthenia, anorexia, alkaline phosphatase elevation and local (injection site) reaction. Log dose escalation will be used between DLs until 0.1 mg/kg (representing the dose with minimal antitumor activity in an animal model) unless MAD reached. Cohort 1: 0.0001 mg/kg Cohort 2: 0.001 mg/kg Cohort 3: 0.01 mg/kg Cohort 4: 0.03 mg/kg Cohort 5: 0.1 mg/kg • Patient(s) will receive two administrations (cycles) of SAR650984 (at 2 week intervals) followed by a 2-week post-second dose administration observation period. The data obtained from this 4-week period will be used for acute safety monitoring and to make decisions regarding cohort expansion and/or dose escalation for the next cohort. PK and CD38 RO data will be collected and may also be used for dose escalation decisions. • After completing two cycles, patients may continue to receive additional administrations of SAR650984 (at the same DL) every 2 weeks upon Investigator's decision. If this dosing regimen is considered safe, the patient can continue treatment until unacceptable toxicity, disease progression, death, withdrawal of consent, Investigator's decision and/or availability of study drug. Additional PK, safety and disease response will be assessed.

	• In the event of a Grade 1 or higher treatment-emergent, IP related non-hematological toxicity including fever, the cohort will be expanded to 3 patients and a semi-log escalation will be used between DLs for all future doses. All successive cohorts will then include 3 patients per DL. In addition, in the event of a Grade 2 or higher treatment-emergent nausea, vomiting, diarrhea, fatigue, asthenia, anorexia, alkaline phosphatase elevation or local (injection site) reaction, the cohort will be expanded to 3 patients with a switch to semi-log dose escalation. All successive cohorts will also include 3 patients. In the event that a potential DLT is reported during the accelerated dose escalation scheme, up to 6 patients will be assessed at this DL. If <2 out of 6 patients experienced an IP related DLT at this DL, the dose escalation will proceed with 3 patients per DL. • If ≥2 out of 6 patients experience an IP related DLT, the MAD is reached and dose escalation will be stopped. ***Basic dose escalation scheme*** Successive patient cohorts will include at least 3 evaluable patients if no potential DLT is reported, or up to 6 evaluable patients if a potential DLT is experienced by 1 of the first 3 patients, semi-log dose escalation will be used between DLs. In each cohort, at least 7 days must pass after dosing the first patient before dosing the second patient. Cohort 6: 0.3 mg/kg every 2 weeks Cohort 7: 1 mg/kg every 2 weeks Cohort 8: 3 mg/kg every 2 weeks Cohort 9: 5mg/kg every 2 weeks Cohort 10: 10 mg/kg every 2 weeks Cohort 11: 10 mg/kg every week Cohort 12: 20 mg/kg every 2 weeks Cohort 13: 20 mg/kg every week • Patients in Cohorts 6-10 and 12 will initially receive two administrations of SAR650984 (at 2 week interval) followed by a 2-week post-second dose administration observation period. Patients in Cohort 11 and 13 will initially receive four administrations of SAR650984 (at a 1 week interval) followed by a 1-week post-fourth dose administration observation period. The data obtained from this 4-week period will be used for acute safety monitoring. PK and CD38 RO data will be collected and may be used to make the dose escalation decision to the next cohort. • After completing two cycles, patient(s) may continue to receive additional administrations of SAR650984 (at the same DL and schedule). If this dosing regimen is considered safe patients can continue treatment until unacceptable toxicity, disease progression, death, withdrawal of consent, Investigator's decision and/or availability of study drug. Additional PK, safety and disease response will be assessed. A Study Committee will be set up, including at least the Principal Investigator(s) and Clinical Study Director from sanofi-aventis. When needed, ad hoc members will be added. Upon completion of enrollment in each cohort, the Study Committee will review collected data and will make the decision to continue the enrollment in subsequent DL cohort. Additional (optional) cohort(s) beyond Cohort 13 may be evaluated (such as 15 mg/kg every week, evaluation of a loading dose followed by a weekly or every 2-week schedule, or evaluation of intermediate doses such as 7.5 mg/kg every week or 15 mg/kg every 2 weeks), however, the decision to proceed to these optional cohort(s) will be discussed with the Study Committee and based on the totality of safety and PK data.

	Dose escalation will stop when the MAD is reached with MAD defined as the dose at which ≥33% of evaluable patients have experienced an IP related DLT following the first administration of IP and occurring during the first two cycles (28 days) from a cohort of 3 to 6 patients. The MTD will then be defined as the highest DL at which no more than 1 patient of a maximum of 6 patients experienced an IP related DLT. Usually, the MTD is one DL below the MAD. The RP2D is defined as the dose selected for the expansion cohorts and for further evaluation in the Phase 2 part of the study. The Study Committee will review the overall safety and PK data observed up to and including Cohort 12 and will decide the dose and schedule for the RP2D. Once the MTD or RP2D dose and schedule is defined based on Cohorts 1-12, a cohort expansion is planned in standard risk MM patients. An additional (optional) expansion cohort may also be considered for high risk MM patients. The decision to proceed to these 2 expansion cohorts will be based on the overall safety and PK observed during dose escalation. Patients will be enrolled to the 2 expansion cohorts (up to 18 patients per expansion) for a maximum total enrollment of 36 patients treated at the MTD or RP2D dose to further evaluate the safety, PK and possible disease response. Patients enrolled in the expansion cohorts will follow the every 2 week schedule detailed in Section 1.5 (PK/PD Flowchart) and Section 1.12 (Study Flowchart) corresponding to Cohort 12 visit schedules. Patients enrolled in Cohort 13 will follow the every week schedule detailed in Section 1.6 (PK/PD Flowchart) and Section 1.11 (Study Flowchart) corresponding to Cohort 11 visit schedules. **Phase 2 Part** The Phase 2 Stage 1 part is to commence after the Phase 1 standard risk cohort has completed enrollment and will further evaluate the activity and safety of SAR650984 as a single agent, in patients with multiple myeloma who have previously received an immunomodulatory imide 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 Phase 2 study will be conducted in 3 stages; Stage 1a dose finding to evaluate 3 dose levels, Stage 1b dose finding to evaluate 1 dose level and Stage 2 expansion to evaluate the dose and schedule selected Stage 1: • Stage 1a will determine the dose and schedule of single agent SAR650984 by evaluating the activity and safety of SAR650984 at 3 dose levels: - Arm 1: 3 mg/kg (Q2W) every 2 weeks (Day 1 and 15 of each 28-day cycle) - Arm 2: 10 mg/kg Q2W (Day 1 and 15 of each 28-day cycle) - Arm 3: 10 mg/kg Q2W for 2 cycles (Day 1 and 15 of each 28-day cycle), then 10 mg/kg Q4W (every 4 weeks (Day 1 of each 28-day cycle)) • Patients in Stage 1a will be randomly assigned to one of 3 treatment arms (Arm 1, 2 or 3), in a 1:1:1 ratio using an Interactive Voice Response System/Interactive Web Response System (IVRS/IWRS). Randomization will be stratified according to the patients prior multiple myeloma therapy; Stratum 1: prior treatment with pomalidomide and/or carfilzomib, Stratum 2: no prior treatment with pomalidomide and/or carfilzomib. • Stage 1b will commence after Cohort 13 has completed the DLT-observation period and enrollment in Stage 1a is completed, whichever is last. The following dose/schedule will be evaluated if fewer than 1/3 or 2/6 patients experiences a DLT in Cohort 13: - Arm 4[1]: 20 mg/kg (QW) every week for 1 cycle (Day 1, 8, 15 and 22 of Cycle 1) then 20 mg/kg Q2W (Day 1 and 15 of each 28-day cycle)

[1] The planned dose for arm 4 is 20 mg/kg, however during the Phase 1, if 20 mg/kg QW is the MAD then a lower dose (such as 15 mg/kg QW) would be evaluated in this arm.

	The Phase 2 Stage 2 will further evaluate the activity and safety of SAR650984 with or without dexamethasone at the dose and schedule selected based on response rate along with safety, PK, PD and overall efficacy from Phase 1 and the interim analysis of Stage 1a and 1b (see Section 13.5): 20 mg/kg every week for 4 infusions followed by 20 mg/kg every 2 weeks. For patients in the ISAdex arm, dexamethasone will be administered at the dose of 40 mg/day (20 mg/day for ≥75 y.o patients) on Days 1, 8, 15, 22 of each cycle. In Stage 2, patients will be randomly assigned to one of the 2 treatment arms in a 2:1 ratio using an IVRS/IWRS. Enrollment will stop when the targeted number of patients is reached in both arms. In Phase 2, the primary efficacy endpoint is overall response rate defined as the proportion of patients with stringent complete response (sCR), (CR), very good partial response (VGPR) and partial response (PR) using the International Myeloma Working Group (IMWG) Uniform Response Criteria (1) in Stage 1 and the IMWG Response Criteria updated in 2014 (2): in Stage 2.
Main selection criteria:	***Phase 1 Inclusion criteria*** I 01. **A. For dose escalation Cohorts 1 to 10 and the Cohort 10 expansion:** Patients with confirmed selected CD38+ hematological malignancies (as outlined below) who have progressed on or after standard therapy or for whom there is no effective standard therapy (refractory/relapsed patients) 1. B-cell Non-Hodgkins Lymphoma (NHL) patients having at least 1 measurable lesion 2. Multiple Myeloma (MM) patients with measurable M-protein (serum and/or 24-hr urine, or serum free light chains) 3. Acute Myeloid Leukemia (AML) patients, all types except M3 based on FAB classification 4. Acute Lymphoblastic Leukemia (B-cell ALL) patient 5. Chronic Lymphocytic Leukemia (CLL) patients **B. For dose escalation Cohorts 11, 12 and 13 (and additional optional cohorts):** Patients must have relapsed/refractory MM with measurable M-protein (serum M-protein of >0.5 g/dL and/or urine M-protein of >200 mg (24-hr urine)), or elevated serum free light chains (FLC >10 mg/dL with abnormal FLC ratio) who have progressed on or after standard therapy that includes an IMiD and a proteasome inhibitor. **For the standard risk expansion cohort:** Patients with relapsed/refractory MM with measurable M-protein (serum M-protein of >0.5 g/dL and/or urine M-protein of >200 mg [24-hr urine]), or elevated serum free light chains (FLC >10 mg/dL with abnormal FLC ratio) who meet the following criteria: • have progressed on or after at least 2 prior lines of standard therapy that includes an IMiD and a proteasome inhibitor **For the high risk expansion cohort:** Patients with relapsed/refractory MM with measurable M-protein (serum M-protein of >0.5 g/dL and/or urine M-protein of >200 mg [24-hr urine]), or elevated serum free light chains (FLC >10 mg/dL with abnormal FLC ratio) who have progressed on or after standard therapy that includes an IMiD and a proteasome inhibitor and who meet one of the following criteria: • have relapsed within 6 months of autologous transplantation • have 17p deletion, t (4, 14), t (14, 16), t (14, 20) or >3 copies of 1q21 • have a high-risk gene expression profiling (GEP) signature (if available) I 02. Signed written informed consent

	Phase 1 Exclusion criteria
	E 01. No previous treatment with any anti-CD38 agent is allowed
	E 02. Patient less than 18 years old
	E 03. Karnofsky performance status <60
	E 04. Poor bone marrow reserve as defined by absolute neutrophils count <1.0 x 10^9/L or hemoglobin <9.0 g/dL or platelets <50 x 10^9/L
	E 05. Poor organ function as defined by one of the following: • Liver function tests – AST, ALT, alkaline phosphatase, bilirubin >2.5 x upper limit of normal [ULN] if no liver metastasis; >5 x ULN if liver metastases – >5 x ULN alkaline phosphatase if bone involvement • Serum creatinine >2 x ULN (>3 x ULN for multiple myeloma)
	E 06. Received any investigational drug within 30 days or 5 half-lives of the investigational drug, whichever is longer
	E 07. Prior anticancer therapy (chemotherapy, targeted agents, radiotherapy, immunotherapy) within 21 days except for alkylating agents (eg, melphalan) where 28 days will be required. Hydroxyurea may be used up to 24 hours prior to the first IP administration and leukophoresis may be used up to 1 week prior to the first drug infusion
	E 08. Known intolerance to infused protein products, sucrose, histidine, polysorbate 80 or known hypersensitivity to any of the components of study therapy that is not amenable to pre-medication with steroids and H2 blockers
	E 09. Allogeneic bone marrow transplant or an allogeneic peripheral blood stem cell transplant within 1 year prior to study entry or evidence of active graft versus host disease (GVHD) requiring >10 mg prednisone. Patients having undergone autologous stem cell transplantation(s) may be included in the study. For AML patients, prior allogeneic stem cell transplantation or donor lymphocytes infusion within 3 months preceding the first dose of SAR650984
	E 10. Any serious active disease (including clinically significant infection that is chronic, recurrent, or active) or co-morbid condition, which, in the opinion of the Investigator, could interfere with the safety, the compliance with the study or with the interpretation of the results
	E 11. Any other severe underlying medical conditions including presence of laboratory abnormalities, which could impair the ability to participate in the study or the interpretation of its results
	E 12. Concomitant or prior malignancy (other than the one under study) except adequately treated basal cell or squamous cell carcinoma of the skin, carcinoma in situ of the cervix, or other cancer for which the subject has been disease-free for ≥5 years
	E 13. Concurrent treatment with other anti-cancer therapy not specified in the protocol
	E 14. Central nervous system (CNS) metastatic disease
	E 15. Pregnant or breast-feeding women
	E 16. Female patients of childbearing potential and male subjects with female partners of childbearing potential who are not willing to avoid pregnancy by using an adequate method of contraception (2-barrier method or 1 barrier method with a spermicide or intrauterine device for 2 weeks prior to screening, during and 5 months after the last does of trial medication). Adequate methods of contraception are provided as examples. Other acceptable and effective methods of birth control are also permitted (eg, abstinence).

	E 17. Known HIV seropositivity, AIDS, hepatitis C or active hepatitis B infection E 18. Autoimmune disease (eg, inflammatory bowel disease such as Crohn's disease, systemic lupus or multiple sclerosis) E 19. Unresolved specific toxicities (excluding alopecia) related to any prior anti-cancer therapy to Grade ≤1 according to the NCI CTC AE v.4.03 E 20. Any of the following within 6 months prior to enrollment: myocardial infarction, severe/unstable angina, or coronary/peripheral artery bypass graft surgery, clinically symptomatic and uncontrolled cardiovascular disease, or clinically significant cardiac arrhythmias (Grade 3-4) E 21. Mental condition rendering the patient unable to understand the nature, scope and possible consequences of the study. Patient unlikely to comply with protocol eg, uncooperative attitude, inability to return for follow up visits, and unlikelihood of completing the study ***Phase 2 Stage 1 and Stage 2 Inclusion criteria*** I 01. Patients must have a known diagnosis of multiple myeloma with evidence of measurable disease, as defined below: - Serum M-protein ≥1 g/dL (≥0.5 g/dL in case of IgA disease in Stage 2), or urine M-protein ≥200 mg/24 hrs. OR - in the absence of measurable m-protein, serum immunoglobulin free light chain ≥10 mg/dL, and abnormal serum immunoglobulin kappa lambda free light chain ratio (<0.26 or >1.65). I 02. Patients must have received prior treatment with an IMiD (for ≥2 cycles or ≥2 months of treatment) and a proteasome inhibitor (PI) (for ≥2 cycles or ≥2 months of treatment). I 03. Patients must have received at least three prior lines of therapy (as defined in Appendix C) for multiple myeloma. Induction therapy and stem cell transplant (± maintenance) will be considered as one line OR Patients whose disease is double refractory to an IMiD and a PI. For patients who have received more than one type of IMiD and PI, their disease must be refractory to the most recent one. Refractory disease is defined as a disease that is progressive while being on treatment, or progressive within 60 days of the last administration of these therapies or never reached at least a minimal response (MR) with those drugs. I 04. Patients must have achieved an MR or better to at least one prior line of therapy. I 05. Patients must have received an alkylating agent (for ≥2 cycles or ≥2 months of treatment) either alone or in combination with other MM treatments (history of stem cell transplant is acceptable). Treatment with high dose melphalan for stem cell transplantation meets this requirement. I 06. Patients must have evidence of disease progression on or after the most recent prior regimen based on IMWG criteria (2) and Appendix E (Phase 2 Stage 2). I 07. Signed written informed consent and be willing and able to complete all study-related procedures, including completion of patient-reported endpoints.

	Phase 2 Stage 1 and Stage 2 Exclusion criteria E 01. Patients less than 18 years old E 02. Patients with multiple myeloma IgM subtype E 03. Previous treatment with any anti-CD38 therapy E 04. Patients with concurrent plasma cell leukemia E 05. Patients with known or suspected amyloidosis E 06. Patients treated with approved or investigative anticancer therapeutic agents (excluding dexamethasone in Phase 2 Stage 2 part), within 3 weeks or within five drug half-lives ($t_{1/2}$) prior to first dose, whichever time is greater E 07. Patients treated with systemic radiation therapy within 4 weeks prior to first dose or localized radiation therapy within 1 week prior to first dose E 08. Patients who have had major surgery within 3 weeks prior to first dose E 09. Prior autologous stem cell transplant within 12 weeks of the first dose of study treatment and/ or prior allogeneic transplant within 1 year or has evidence of active graft versus host disease (GVHD) requiring >10 mg prednisone daily E 10. Patients with a life expectancy of less than three months E 11. In Stage 1 part, patient with Karnofsky performance status <60 In Stage 2 part patient with Eastern Cooperative Oncology Group (ECOG) Performance status >2 E 12. Patients with laboratory values of: a) Total bilirubin ≥2.0 x ULN b) AST or ALT ≥3.0 x ULN c) In Phase 2 Stage 1: Calculated or measured creatinine clearance (CrCL) <30 mL/minute(min) (using Cockcroft and Gault formula [(140 - age) x mass (kg) / (72 x creatinine mg/dL)], multiply result by 0.85 if female. In Phase 2 Stage 2: Serum creatinine >2 x ULN and/or estimated glomerular filtration rate (eGFR) according the Modification of diet in Renal Disease (MDRD) equation <15 mL/min/1.73 m^2 (see formula in Appendix B), and/or on renal dialysis. d) Absolute neutrophil count ≤1000/mm^3 (use of colony-stimulating factors (CSFs) to achieve these counts is allowed) e) Hemoglobin <8.0 g/dL (patients may receive red blood cell transfusion or receive supportive care such as erythropoietin and darbepoetin in accordance with institutional guidelines) f) Platelet count ≤50 000/mm^3 (patients should be platelet transfusion independent for 2 weeks prior to screening lab values) E 13. No resolution of all specific toxicities (excluding alopecia) related to any prior anti-cancer therapy to Grade ≤1 according to the NCI CTC AE v.4.03 E 14. Patients with concurrent POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes) E 15. Patients with congestive heart failure (New York Heart Association class III to IV), symptomatic ischemia, conduction abnormalities uncontrolled by conventional intervention, or myocardial infarction in the 6 months prior to first dose E 16. Patients with active infection requiring systemic antibiotics, antivirals or antifungals within 2 weeks prior to first dose (except when used for chronic prophylaxis)

	E 17. Known intolerance to infused protein products, sucrose, histidine, polysorbate 80 or known hypersensitivity to any of the components of study therapy that is not amenable to pre-medication with steroids and H2 blockers E 18. Patients with known HIV E 19. Patients with active hepatitis B, or C infection E 20. Patients diagnosed or treated for a malignancy within the past 3 years except: a) adequately treated basal cell or squamous cell skin cancer, or b) carcinoma in situ of the cervix, or c) prostate cancer with < Gleason Grade 6 and stable PSA E 21. Patients with myelodysplastic syndrome (MDS) E 22. Patients with significant neuropathy (Grade 2 with pain or ≥ Grade 3) within 2 weeks prior to first dose E 23. Any clinically significant medical or psychiatric disease or condition that, in the Investigator's opinion, may interfere with protocol adherence, the ability to complete patient-reported measures or the ability to give informed consent E 24. Female patients of childbearing potential and male patients with female partners of childbearing potential who are not willing to avoid pregnancy by using an adequate method of contraception (2-barrier method or 1 barrier method with a spermicide or intrauterine device for 2 weeks prior to screening, during and 5 months after the last dose of trial medication) and/or who are unwilling or unable to be tested for pregnancy monthly for 5 months after the last administration of SAR650984. Adequate methods of contraception are provided as examples. Other acceptable and effective methods of birth control are also permitted (eg, abstinence). E 25. Female patients who are pregnant or breast feeding E 26. For Phase 2 Stage 2: the patient is the Investigator or an Sub-Investigator, research assistant, pharmacist, study coordinator, other staff or relative thereof directly involved in the conduct of the protocol.
Total expected number of patients:	Phase 1: Approximately 85 patients Phase 2: Stage 1 approximately 96 patients (24 patients per arm) Stage 2 approximately 160 patients
Expected number of sites:	Phase 1: Approximately 12 sites Phase 2: Approximately 80 sites
INVESTIGATIONAL PRODUCT(S): ***Formulation(s):***	**SAR650984 Phase 1 and Phase 2 Stage 1**
	The C1P1F1 drug product is presented as a concentrate for solution for infusion in vials containing 5 mg/mL (100 mg/20 mL) SAR650984 in 10 mM histidine, 10 % (w/v) sucrose, 0.005 % (w/v) polysorbate 80, pH 6.5 buffer. For administration to patients, the appropriate volume of SAR650984 will be diluted in an infusion bag of 0.9% sodium chloride solution. The final infusion volume corresponding to the dose of SAR650984 will be administered for period of time that will depend on dose administered and will be based on protein amount given per hour. After the study cut-off in Phase 2 Stage 1 and the start of Phase 2 Stage 2, patients in Phase 2 Stage 1 receiving C1P1F1 may be switch to C1P2F2.

	SAR650984 Phase 2 Stage 2 The C1P2F2 drug product concentrated solution for infusion in vials containing 20 mg/mL (500 mg/25 mL) SAR650984 in 20 mM histidine, 10%(w/v) sucrose, 0.02% (w/v) polysorbate 80, pH 6.0 buffer. For administration to patients, the appropriate volume of SAR650984 will be diluted in an infusion bag of 0.9% sodium chloride solution. The final infusion volume corresponding to the dose of SAR650984 will be administered for period of time that will depend on dose administered and will be based on protein amount given per hour.
	For **dexamethasone** please refer to Summary of Product Characteristics (SmPC) and United States product insert (USPI) of this compound
Route(s) of administration:	SAR650984 C1P1F1 will be administered by IV infusion. SAR650984 C1P2F2 will be administered by IV infusion. The appropriate volume of SAR650984 will be diluted in an infusion bag of 0.9% sodium chloride solution. **Dexamethasone (ISAdex arm),** initially given at 40 mg/day (20 mg/day in patient ≥75 year-old) IV or by mouth (PO). During Phase 1, the initial rate of infusion per dose will be as follows: ***In the Phase 1 accelerated dose cohorts:*** 0.0001 mg/kg ---------- 0.042 mg/hr for a total of 3 mL 0.001 mg/kg ---------- 0.42 mg/hr for a total of 3 mL 0.01 mg/kg ---------- 1.4 mg/hr 0.03 mg/kg ---------- 4.2 mg/hr 0.1 mg/kg ---------- 7 mg/hr ***In the Phase 1 basic dose cohorts:*** 0.3 mg/kg ---------- 10.5 mg/hr 1 mg/kg ---------- 17.5 mg/hr 3 mg/kg ---------- 52.5 mg/hr 5 mg/kg ---------- 87.5 mg/hr 10 mg/kg ---------- ----------175 mg/hr 20 mg/kg ---------- ----------250 mg/hr ***In the Phase 2*** During Phase 2, the initial rate of infusion will be 175 mg/hr.
***Dose regimen/duration*:**	**During Phase 1,** SAR650984 will be administered once every two weeks (Q2W) in the Accelerated dose escalation scheme and weekly or Q2W in the Basic dose escalation scheme. In each cohort, at least 7 days must pass after dosing the first patient before dosing the second patient. Subsequent cycles may be administered at the same dose and schedule until unacceptable toxicity, disease progression, death, withdrawal of consent, Investigator's decision and/or availability of study drug. **During Phase 2, Stage 1,** SAR650984 will be administered as follows: • Arm 1: 3 mg/kg on Day 1 and 15 of each 28-day cycle • Arm 2: 10 mg/kg on Day 1 and 15 of each 28-day cycle • Arm 3: 10 mg/kg on Day 1 and 15 of Cycle 1 and 2, then 10 mg/kg on Day 1 of each 28-day cycle • Arm 4: 20 mg/kg on Day 1, 8, 15 and 22 of Cycle 1, then 20 mg/kg on Day 1 and 15 of each 28-day cycle **During Phase 2 Stage 2,** in ISA and ISAdex arms, SAR650984 will be administered at the dose of 20 mg/kg on Day 1, 8,15 and 22 (QW) of Cycle 1 followed by 20 mg/kg on Day 1 and 15 (Q2W) of subsequent cycles (Day 1 of Cycle n correspond to Day 29 of Cycle n-1).

	In ISAdex arm, dexamethasone will be administered IV or PO on Day 1, 8, 15 and 22 of each cycle, at the following dose: • Patients of <75 year-old: 40 mg/day or in patients of ≥75 year-old: 20 mg/day. On the days of SAR650984 infusion, the administration of dexamethasone will be used as part of premedication and should follow the premedication rules. Dexamethasone is both part of the back bone treatment regimen and isatuximab premedication (Section 8.2)
PRIMARY ENDPOINT(S) AND MAIN **SECONDARY ENDPOINT(S):**	**Phase 1 primary endpoint** The safety of SAR650984 will be evaluated using the following assessments • Incidence of DLT observed during the first two cycles (4 weeks); • Allergic reactions/hypersensitivity and cytokine release syndrome/acute infusion reactions; • All reported adverse events; • Changes from baseline laboratory findings, baseline vital signs, neurological exams, and safety related parameters will be evaluated for clinical significance; • Clinically important electrocardiogram (ECG) findings since the first administration of SAR650984 including QTc interval. For the purposes of dose escalation and determination of the MTD/RP2D dose, only DLTs that occur during the first 28 days (Cycle 1 and Cycle 2) of treatment will be considered for decisions regarding dose escalation. DLTs are defined as any Grade 3 or higher non-hematological toxicity (with the exception of allergic reaction/hypersensitivity), Grade 4 neutropenia and/or Grade 4 thrombocytopenia lasting longer than 5 days, attributed to SAR650984 and as defined by the NCI-CTCAE v.4.03. Any other toxicity that the Investigator and the sponsor deem to be dose limiting, regardless of the grade, may also be considered as DLT. Before escalating SAR650984 dose to the next DL, the safety data and especially the reported potential DLTs will be reviewed to determine their relationship to the IP. Dose escalation or dose decrease decisions will be based on the assessment of IP related DLTs by the Safety Committee. Dose escalation will be stopped if ≥33% (≥2 in up to 6 patients) of patients experienced an IP related DLT observed during the first two cycles (4 weeks). In case of available usable prophylactic and/or curative treatment for a dose limiting non-hematologic adverse event (eg, diarrhea, hypersensitivity, nausea-vomiting, hyperglycemia), this treatment may be evaluated in an additional cohort of up to 6 patients treated at the same DL. Further dose escalation could be allowed if <33% of patients in this additional cohort experience DLT when receiving the prophylactic/corrective therapy. These prophylactic/corrective therapies will be systematically implemented in further DLs. In addition, in the expansion cohort at MTD, cumulative toxicities will be analyzed, in order to confirm the feasibility of the MTD selected in the dose escalation step. Although the dose escalation process is guided by the safety evaluation during two cycles of treatment, cumulative toxicities observed in subsequent administrations should also be considered for the dose escalation and the dose selection decisions (ie, smaller increases in dose, expansion of a given DL, intermediate DL), upon agreement by the Study Committee.

	Phase 1 secondary endpoints 1. Pharmacokinetic assessments: • Concentration observed at the end of an intravenous (IV) infusion (Ceoi) • Maximum observed concentration (C_{max}); • Time to reach C_{max} (t_{max}) • Concentrations just before drug infusion (C_{trough}) • AUC over the dosing interval (AUC1 week or AUC2 week) 2. Pharmacodynamic assessment: • Serum/plasma markers will include: - Hs-CRP. - Tumor necrosis factor alpha (TNF-α). - IL-6. - IL-1-β. - IFN-λ. - CD38 receptor density and occupancy. Please refer to Section 1.4 to Section 1.9 (study flowchart tables for more information regarding measurement and time points) 3. Immune response: • Antibodies to SAR650984 will be assessed (Section 9.4). 4. Clinical assessment will include: • Disease response according to standard criteria for hematologic malignancies and staging (at baseline). • Karnofsky performance status evaluation. • Results of additional procedures performed as part of standard of care to assess the current disease status may also be collected.
	Phase 2 Primary endpoint ORR is defined as the proportion of patients with stringent complete response (sCR), (CR), (VGPR), and partial response (PR) based on responses as assessed by the Independent Adjudication Committee (IAC) using the International Myeloma Working Group (IMWG) Uniform Response Criteria (1) in Stage 1 and the IMWG Response Criteria updated in 2014 (2) in Stage 2. Response evaluation will include: • M-protein quantification (serum and 24-hr urine). • Serum free light chain levels. • Bone marrow biopsy/aspiration. • PET-CT and/or CT/MRI scan of plasmacytoma. • Bone skeletal survey and/or low dose whole body CT scan. • Corrected serum calcium. **Phase 2 secondary endpoints** 1. Safety profile of SAR650984 in terms of treatment-emergent adverse events/serious adverse events (TEAE/SAE) and changes in laboratory parameters, vital signs, ECGs and assessment of physical examination. 2. Secondary efficacy endpoints: • Duration of Response (DOR): defined as the time from the date of the first IAC determined response to the date of subsequent IAC determined PD or death, whichever happens earlier. DOR will not be calculated for patients that do not achieve a response.

	• CBR: defined as the proportion of patients with sCR, CR, VGPR, PR or MR according to IMWG criteria, as determined by the IAC. • PFS: defined as the time interval from the date of first study treatment administration to the date of the first IAC-assessed disease progression or the date of death due to any cause, whichever comes first. • OS: defined as the time interval from the date of first study treatment administration to death from any cause. 3. HRQOL and disease-related symptoms will be assessed through the EORTC QLQ-C30 and MY20 questionnaires; generic health status will be assessed through the EQ-5D. These will be captured electronically throughout the study (Stage 1 only). 4. Pharmacokinetic parameters evaluated: • The PK profile of isatuximab will be assessed using population PK approach. This analysis will involve an estimation of inter-patient PK variability and the population PK parameters estimates. Empirical Bayesian estimation of individual parameters and of individual exposure (Ctrough and AUC) will also be performed. 5. Antibodies to SAR650984 (ADA, Anti-Drug Antibodies) will be assessed throughout the study. 6. CD38 receptor density from baseline bone marrow aspirates will be correlated with parameters of clinical response, including ORR, CBR, DOR, PFS and/or OS (Stage 1 only). 7. CD38 receptor occupancy from bone marrow aspirates will be correlated with PK and clinical response parameters (Stage 1 only).
	Phase 2 exploratory endpoints 1. MRD by sequencing and/or flow cytometry will be assessed in patients achieving a CR and correlated with clinical outcome. 2. Bone marrow and/or blood samples will be analyzed for genomic profiling and multiple myeloma molecular subtype (using cytogenetics and gene sequencing) and bone marrow for the levels of CD38 mRNA. These markers will be correlated with clinical response. 3. Blood samples will be analyzed for immune genetic determinants (such as FcGR polymorphisms, HLA and KIR genotypes, etc) and correlated with clinical response. 4. Correlation of immune phenotype (such as B-cell, T-cell, and NK-cell subsets) in bone marrow and peripheral blood with parameters of clinical response. 5. Blood samples will be analyzed to investigate the relationship between soluble CD38 and parameters of PK and clinical response. (Stage 1 only). 6. Blood samples will be analyzed for changes in the diversity of the adaptive immune response, including TCR repertoire, humoral and cellular immune responses to myeloma-related tumor antigens and correlated with clinical response. (Stage 2 only). 7. Additional molecular analysis, not specified in the protocol but related to the drug action and/or effect of SAR650984, may be conducted on remaining samples pending evolving literature.
EVALUATION CRITERIA:	Safety will be evaluated from physical examination, laboratory tests, and reports of adverse events, according to the NCI-CTCAE v. 4.03 grading scale. In the Phase 1 part, safety review will be conducted by the Study Committee. This review must take place prior to enrollment of patients in subsequent cohort.

	For Phase 1: Response information, ie, category of disease response such as CR (complete response or complete remission), PR (partial response), SD (stable disease) or PD (progressive disease) will be obtained and evaluated based on standard criteria for underlining disease. • Lymphomas: NCI-sponsored international Working Group (3) • Leukemias : NCI-sponsored International Working Group for CLL (4) and AML (5) • Multiple Myeloma: International Group of multiple myeloma and bone marrow transplant experts (6) **For Phase 2:** Stage 1 IMWG Uniform Response Criteria (1) Stage 2 updated IMWG Uniform Response Criteria (2)
ASSESSMENT SCHEDULE:	***Safety evaluation*** Safety evaluation will be performed continuously throughout the Phase 1 and Phase 2 parts, please refer to the Study Flowcharts for the assessment timings of the following: • PSA and pituitary hormones levels (GH, FSH/LH, ACTH, TSH) (Phase 1 only) • Cytokines (TNF-α, IL-1-β, IL-6, IFN-γ), markers of complement (C3, C4, CH50), serum tryptase (Phase 1 and Phase 2 Stage 1 only) • Pulmonary function tests (Phase 1 only) • ECG and Holter (Phase 1 only) monitoring • Chest x-ray ***PK evaluation*** During the Phase 1 and Phase 2 parts, PK samples will be collected per PK Study Flowcharts. ***Disease response evaluation*** The disease assessment in Phase 1 and Phase 2 will be performed according to the Study Flowcharts. • Multiple Myeloma (Phase 1 and Phase 2): - Bone marrow biopsy/aspiration. - Radiologic imaging of plasmocytoma. - Bone skeletal survey. - M-protein quantification (serum and/or 24-hr urine), serum free light chain levels. - Serum β2-microglobulin. • B-cell NHL (Phase 1 only): - Bone marrow biopsy/aspiration (leukemia) as clinically indicated. - Lymph node biopsy as clinically indicated. - Radiologic tumor assessment (by X-ray, computed tomography [CT] scan, PET scan, or magnetic resonance imaging [MRI]; ultrasound is not sufficient) (lymphoma). • B-cell ALL (Phase 1 only): - Bone marrow biopsy/aspiration. - Blood count with differential including blast count.

	• AML (Phase 1 only): - Bone marrow biopsy/aspiration. - Blood count with differential including blast count. • CLL (Phase 1 only): - Clinical examination. - Bone marrow biopsy/aspiration. - Lymph node biopsy as clinically indicated. - Blood count with differentials. - Serum β2-microglobulin. ***Other evaluations*** During the Phase 1 and Phase 2 parts, the following evaluations will be performed according to the Study Flowcharts • Receptor density (RD) on bone marrow samples (Phase 1 and Phase 2 Stage 1 only). • Receptor occupancy (RO) on bone marrow samples (Phase 1 and Phase 2 Stage 1 only). • Level of soluble CD38 (Phase 2 Stage 1 only). • Level of human anti-drug antibodies (ADA). • Immune phenotyping and molecular analysis on blood and bone marrow samples (Phase 2).
STATISTICAL CONSIDERATIONS:	***Determination* of the sample size**
	Phase 1 The Phase 1 part of this study aims to establish the MTD/RP2D of SAR650984 according to DLTs observed. The number of DLs examined and the emerging SAR650984 related toxicities will determine the sample size. It is anticipated that up to approximately 85 patients will be required to establish the selected dose of SAR650984. In Cohort 11, 12 and 13, approximately 6-12 patients may be enrolled in order to determine the RP2D dose. In addition, up to 18 patients in the standard risk and up to 18 patients in the (optional) high risk expansion cohorts will be enrolled and treated at the MTD. **Phase 2** <u>Stage 1:</u> Although Stage 1b has been added in protocol amendment 10 and will start after enrollment in Stage 1a is completed (ie, patients will not be randomized between the 4 doses/schedules tested), sample size for Stage 1 will be calculated considering Stage 1a and 1b as a whole with 4 arms. Stage 1 of the Phase 2 study is based on a selection design (7) Such a design is used to maximize the probability of selecting the best of the four SAR650984 doses tested during Stage 1 using ORR as endpoint. No statistically significant difference between the four treatment arms is required to select a recommended Stage 2 dose. A total of 96 patients (24 patients by arm) will provide at least 80% probability to select the better SAR650984 dose assuming an ORR of 10% in the 3 mg/kg arm and assuming the difference in ORR between the best dose and 3 mg/kg arm is at least 15%.

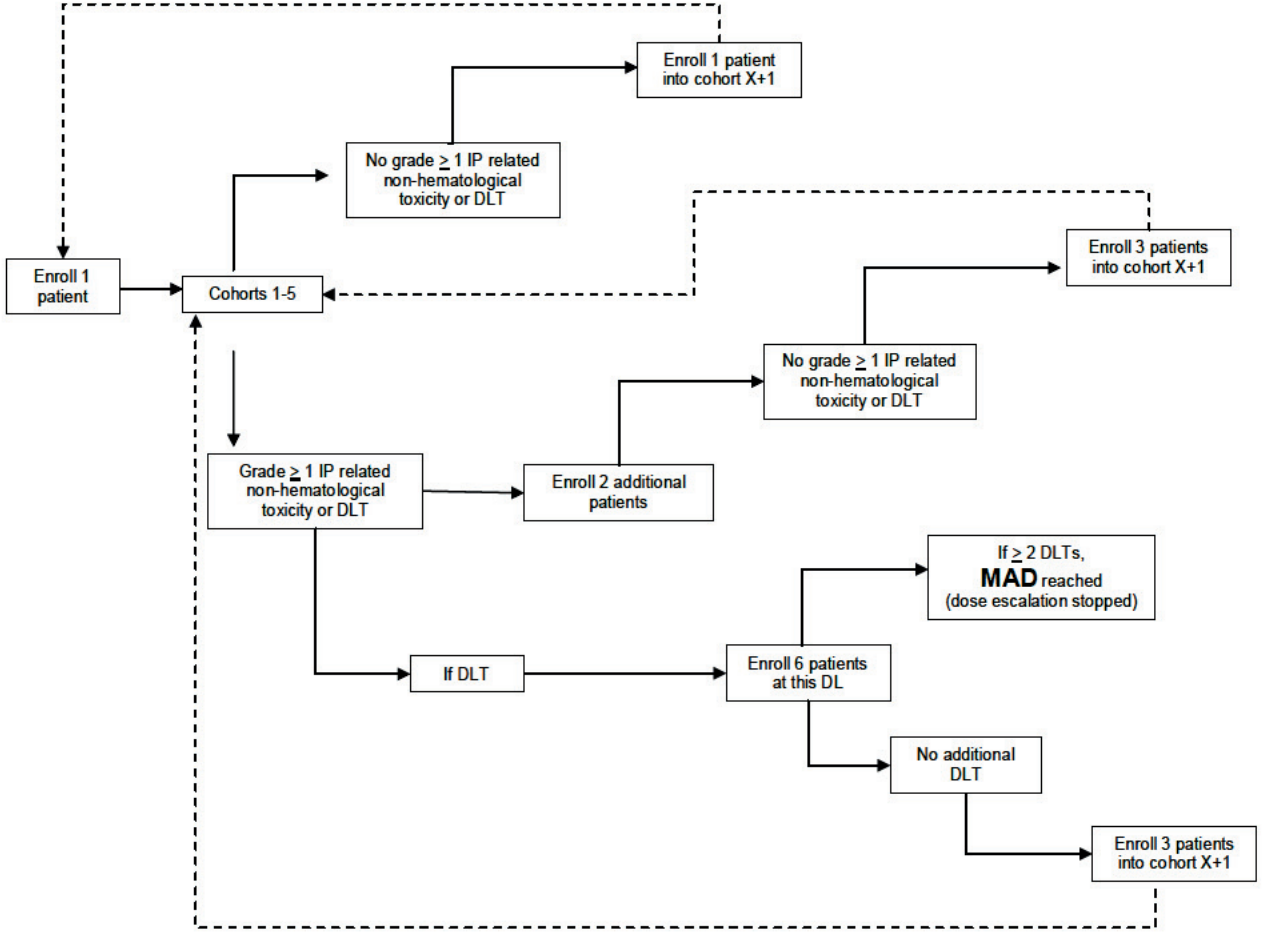
	Phase 2 Stage 2: ISA arm: 105 patients will be randomized in the SAR650984 arm. Given an assumed true ORR of 28%, the null hypothesis ORR ≤15% will be rejected using an exact binomial test at a one-sided alpha of 0.025 with 90% power, if the observed ORR is greater than or equal to 22.9% (ie, 24 responders). ISAdex arm: 55 patients will be randomized in the SAR650984+dexamethasone 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 at least 85% power, if the observed ORR is greater than or equal to 27.3% (15 responders). ***Main analysis populations*** For both Phase 1 and Phase 2 parts of the study, the all treated/safety population will include all patients who have given their informed consent and who have received at least one dose (even incomplete) of SAR650984. This population is the primary population for the analyses of efficacy and safety parameters. All analyses using this population will be based on the treatment actually received. For Phase 2 Stage 2, patients who received dexamethasone in addition to isatuximab (excluding when given as part of premedication) will be included in the ISAdex arm. In the Phase 1 part, the DLT evaluable population is the subset of patients from the all treated population with a DLT assessment at the end of Cycle 2. ***General statistical approach*** Data from Phase 1 and each stage of the Phase 2 will be analyzed and reported separately. In particular data from Stage 1a and Stage 1b will be presented in the same set of tables. Summary tables will be presented by dose levels/arm (when appropriate) and overall, unless otherwise noted. Phase 1 Dose escalation step. IP related DLTs will be assessed and analyzed on all treated patients. The type, frequency, seriousness and relatedness of IP emergent adverse events (TEAEs) will be summarized and listed according to MedDRA (Medical Dictionary for Regulatory Affairs). Laboratory abnormalities will be summarized according to the NCI-CTCAE v. 4.03. Pharmacokinetics parameters will be summarized with descriptive statistics (mean, geometric mean, median, standard deviation, standard error of the mean, coefficient of variation, minimum and maximum). Immune response, pharmacodynamics marker results will be descriptively summarized and tabulated. ORR and duration of response will be listed along with relevant patient/disease characteristics. In addition, ORR and duration of response will be summarized with descriptive statistics and 95% confidence interval (for ORR only) for patients with MM. Phase 1 Expansion cohort Similar analyses as described above will be performed. Phase 2 *Analysis of primary efficacy endpoint*: ORR will be summarized with descriptive statistics. A 95% two-sided confidence interval will be computed using Clopper-Pearson method. For Stage 2, the null hypothesis that the true response rate (ORR) is <15% will be tested in each arm using a one-sided exact binomial test with a significance level of 0.025.

	Analysis of secondary efficacy endpoints: DOR, PFS and OS will be analyzed using Kaplan-Meier methods. *Analysis of PRO endpoints*: Changes from baseline in HRQOL, disease-related symptoms, and health status will be descriptively summarized, along with an evaluation of PRO responses in relation to clinical responders. *Analysis of safety endpoints*: Number (%) of patients experiencing treatment-emergent adverse events (TEAEs) by primary system organ class and preferred term will be summarized by CTCAE grade (all grades and Grade ≥3) for the safety population. Same table will be prepared for drug-related TEAEs, TEAEs leading to treatment discontinuation, serious TEAEs and TEAEs with fatal outcome. For patients with multiple occurrences of the same AE within the on-treatment period, the worst grade will be used. Hematology and biochemistry results will be graded according to the CTCAE version 4.03, when applicable. Number (%) of patients with laboratory abnormalities (ie, all grades and Grade ≥3) using the worst grade during the on-treatment period will be provided for the safety population. **Interim Analysis** Interim analysis may be performed for Phase 2 Stage 2 if enrollment is not completed in December 2017.
DURATION OF STUDY PERIOD	
Per patient	For the Phase 1 part, study duration for an individual patient will include a screening period for inclusion of up to 2 weeks, up to 4 weeks of SAR650984 administration unless discontinued earlier due to safety or disease progression, followed by a minimum of 30 days following the last use of study drug or more than 30 days in case of unresolved toxicity, or up to initiation of another anticancer treatment. Patients with SD, or objective response (CR, PR) and no DLT at the end of 4 weeks of SAR650984 dosing may be considered for continue treatment as long as clinical benefit is possible, or until PD or for other reasons for discontinuation (see Section 11.2). During the follow-up period IP-related adverse events and all serious adverse events (regardless of relationship to study treatment) ongoing at the time of study treatment discontinuation will be followed until resolution or stabilization. For the Phase 2 part, study duration for an individual patient will include a screening period for inclusion of up to 3 weeks prior to the first administration of IP, then a treatment and a follow-up period. Following the screening period, eligible subjects will receive SAR650984 according to their assigned schedule. Treatment will continue until disease progression, unacceptable adverse reaction or other reason for discontinuation (see Section 11.2). Patients with documented disease progression at the end of treatment visit will receive follow-up visits at 30, 60 and 90 days after the last dose (in Phase 2 Stage 1 part) and at 60 days after the last dose of study treatment, in Phase 2 Stage 2 part, and the further follow up according to following rules. Patients discontinuing SAR650984 +/- dexamethasone for reason other than disease progression at the end of study treatment visit and have not started treatment with another anti-cancer therapy will be followed-up for efficacy and safety every 4 weeks until disease progression, death, cutoff date whichever comes first. Then, after documentation of disease progression, patients will be followed every 3 months until death or cutoff date whichever comes first. Patients discontinuing study treatment due to disease progression at the end of treatment visit will be followed every 3 months until death or cutoff date whichever comes first. However, female patients of childbearing potential will have the serum pregnancy test every month for 5 months after the last administration of SAR650984.

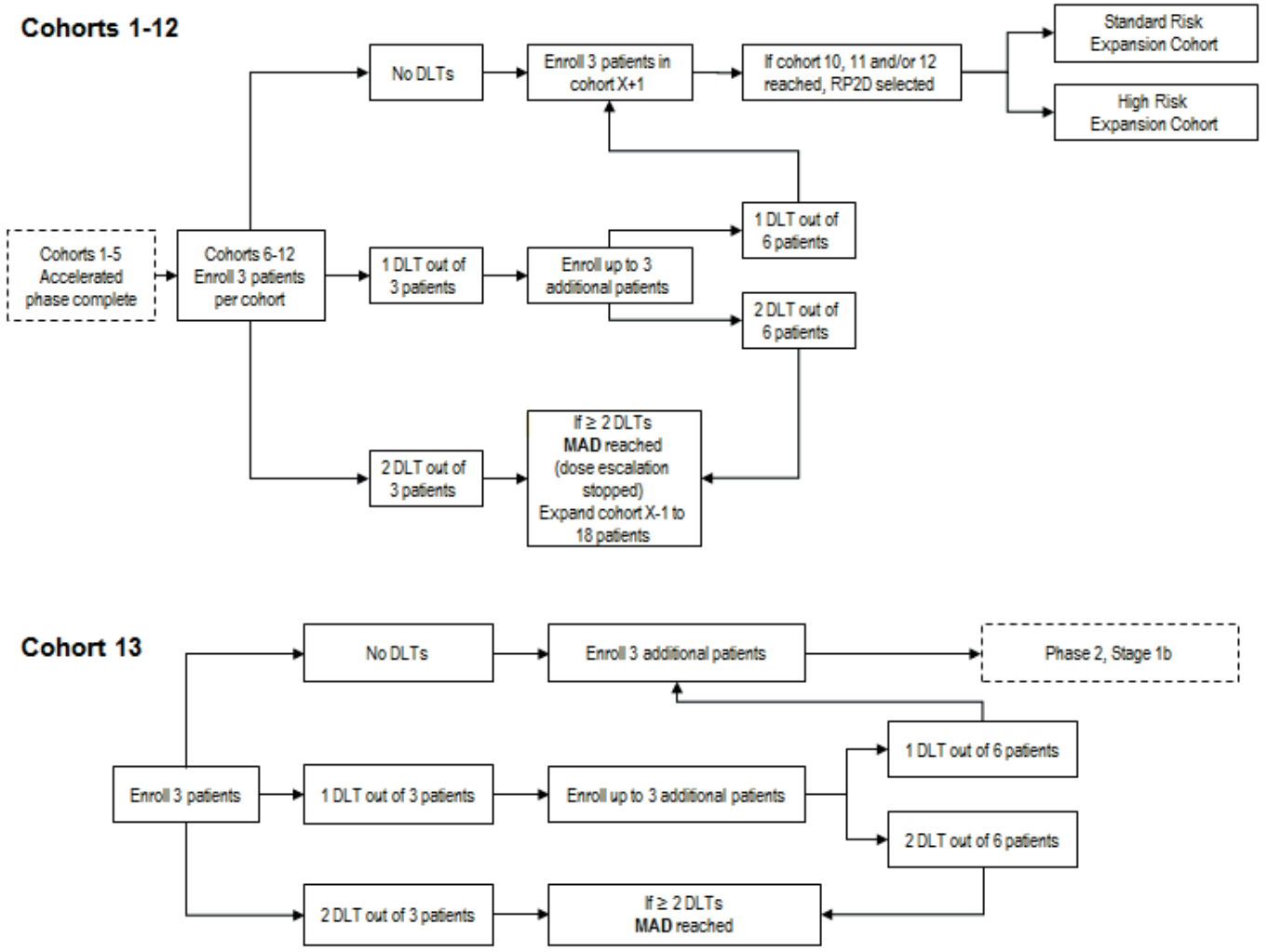
	During the follow-up period study treatment -related adverse events and all serious adverse events (regardless of relationship to study treatment) ongoing at the time of study treatment discontinuation will be followed until resolution or stabilization.
Per study	The Phase 1 study final analysis cutoff date will be 4 months after the date of the first dose of the last patient on the Phase 1 study. For the Phase 2 Stage 1 part, the cutoff date for the primary analysis of ORR and for the secondary analysis will be 12 months after the date of the first dose of the last patient. For the Phase 2 Stage 2 part, the cutoff date for the primary analysis of ORR will be 4 months after the date of the first dose of the last patient. Final analysis cutoff date for the updated analysis of ORR and final analysis of secondary endpoints will be 12 months after the date of the first dose of the last patient. Patients still on treatment at time of the final analysis cutoff dates who still continue benefiting from treatment with SAR650984 will have the option to continue treatment under this protocol until disease progression, unacceptable AEs, patient wish, or any other reason. For cycles completed after the cut-off date, all new related AEs (serious or not), all ongoing SAE (related or not) and all ongoing related non serious AEs, and reason of end of treatment will continued to be collected. Additionally, study treatment administration will be collected. No PK or ADA samples will be collected post data cut-off. If last ADA before cut-off date is positive, one additional sampling time for ADA evaluation should be collected 3 months later. No further ADA will be sampled, even if this 3-month sample is positive.

1 FLOWCHARTS

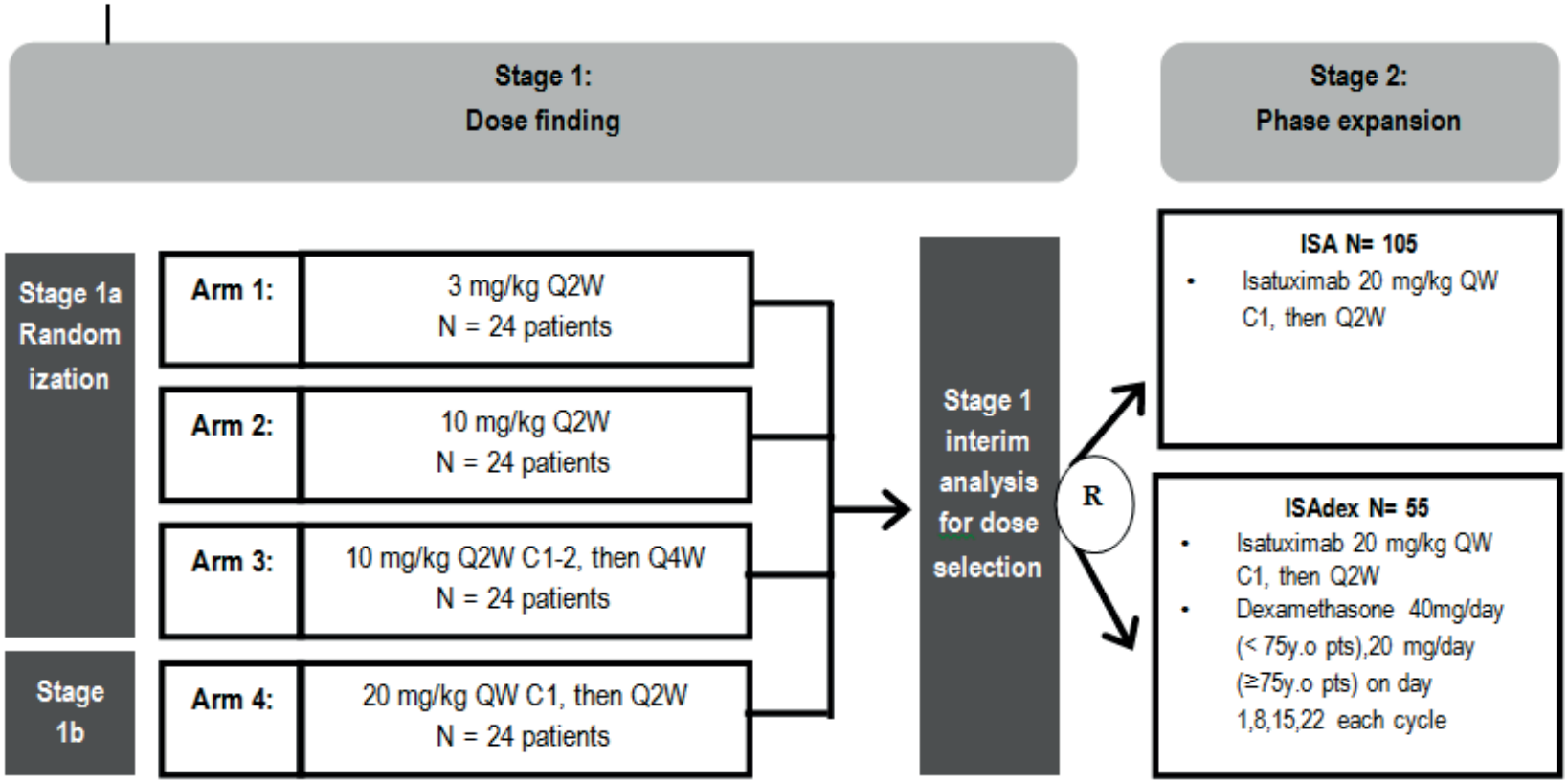
1.1 DIAGRAM 1: PHASE 1 ACCELERATED DOSE ESCALATION PHASE - METHODOLOGY



1.2 DIAGRAM 2: PHASE 1 BASIC DOSE ESCALATION PHASE - METHODOLOGY



1.3 DIAGRAM 3: PHASE 2 STUDY DESIGN



1.4 PHARMACOKINETICS/PHARMACODYNAMICS FLOWCHART PHASE 1 ACCELERATED PHASE

Day	Cycle 1								Cycle 2									Subsequent Cycles	EOT	Follow-up
	D1					D2	D3	D8	D1					D2	D3	D8	D14	D1	30 days after last IP administration	60 days after last IP administration
Time (decimal hours)[1]	0 start infusion	0.25	(0.5) EOI	EOI +3h	EOI +7h	24h	48h	168h	0 start infusion	0.25	(0.5) EOI	EOI +3h	EOI +7h	24h	48h	168h	312h	(0.5) EOI		
Indicative clock time	8 am	8:15 am	8:30 am	11:30 am	3:30 pm	8 am	8 am	8 am	8:00 am	8:15 am	8:30 am	11:30 am	3:30 pm	8 am	8 am	8 am	8 am	8:30 am	8 am	8 am
IP administration SAR650984	X---	---	---X						X---	---	---X							---X		
PK/PD Samples																				
PK	P00[2]	P01	P02#[3]	P03	P04	P05	P06	P07	P00*[2]	P01	P02#[3]	P03	P04	P05	P06	P07	P08	P00#[3]	PF0	PF1
RO in blood (ALL, AML, CLL only)	B00*[2]		B01#[3]			B02	B03		B00*[2]		B01#[3]			B02	B03		B04			
RO in bone marrow (MM only)	Y00*[2]																Y00			
ADA	P00*[2]						P01		P00*[2]								P01	P00#[3]	PF0	PF1

RO = CD38 receptor density and occupancy, ADA = Anti-Drug Antibody, P = Plasma, B = Blood, Y = Marrow.

1. (°) brackets pending actual infusion duration
2. *= Sample collected just before IP administration
3. # = Sample collected just before end of infusion (EOI).

1.5 PHARMACOKINETICS/PHARMACODYNAMICS FLOWCHART PHASE 1 BASIC PHASE (SAR650984 ADMINISTRATION EVERY 2 WEEKS - COHORTS 6-10)

Day	Cycle 1								Cycle 2			Subsequent cycles	EOT	Follow-up
	D1					D2	D3	D8	D1		D14	D1	30 days after last IP administration	60 days after last IP administration
Time (decimal hours)o	0 start infusion	(0.25) mid infusion	(0.5) EOI	EOI +3h	EOI +7h	24h	48h	168h	0 start infusion	(0.5) EOI	312h	(0.5) EOI		
Indicative clock time	8 am	8:15 am	8:30 am	11:30 am	3:30 pm	8 am	8 am	8 am	8 am	8:30 am	8 am	8:30 am	8 am	8 am
IP administration SAR650984	X---	---	---X						X---	---X		---X		
PK/PD Samples														
PK	P00*[1]	P01$[2]	P02#[3]	P03	P04	P05	P06	P07	P00*		P01	P00#[3]	PF0	PF1[4]
RO in blood (ALL, AML, CLL only)	B00*[1]		B01#[3]			B02	B03			B00#[3]	B01	B00#[3]		
RO in bone marrow (MM only)	Y00*[1]										Y00		YF0	
ADA	P00*[1]						P01			P00#[3]	P01	P00#[3]	PF0	PF1[4]

RO = CD38 receptor density and occupancy, ADA = Anti-Drug Antibody, P = Plasma, B = Blood, Y = Bone Marrow.

1. * = Sample collected just before IP administration
2. $ = Sample collected when half the IP volume is administered
3. # = Sample collected just before actual end of infusion (EOI)
4. At 60 days, if patient is positive for ADA or the sample is inconclusive, additional ADA and PK samples are required every 30 days (±5 days) until sample is interpretable or negative.

1.6 PHARMACOKINETICS/PHARMACODYNAMICS FLOWCHART PHASE 1 BASIC PHASE (SAR650984 ADMINISTRATION EVERY WEEK - FROM COHORT 11)

Day	Cycle 1								Cycle 2			Cycle 3								Subsequent cycles		EOT	Follow-up
	D1				D2	D3	D4	D8	D1	D8	D14	D1				D2	D3	D4	D8	D1	D8	30 days after last IP admin	60 days after last IP admin
Time (decimal hours)[o]	**0 start infusion**	mid infusion (0.25)	EOI (0.5)	EOI +4h	24h	48h	72h	**0 start infusion**	**0 start infusion**	**0 start infusion**	168h	**0 start infusion**	mid infusion (0.25)	EOI (0.5)	EOI +4h	24h	48h	72h	**0 start infusion**	**0 start infusion**	**0 start infusion**		
Indicative clock time	8 am	8:15 am	8:30 am	12:30 pm	8 am	8 am	8 am	8 am	8 am	8 am	8 am	8 am	8.15 am	8:30 am	12:30 pm	8 am	8 am	8 am	8 am	8 am	8 am	8 am	8 am
IP admin SAR650984	X---	----	---X					X---	X---	X---		X---	----	---X					X---	X---	X---		
PK/PD Samples																							
PK	P00[1]	P01[2]	P02[3]	P03	P04	P05	P06	P07[1]	P00[1]	P01[1]		P00[1]		P01[3]	P02	P03	P04	P05	P06[1]	P00[1]	P01[1, 5]	PF0	PF1[5]
RO in bone marrow	Y00[1]										Y00[4]											YF0	
ADA	P00[1]					P01		P02[1]		P00[1]									P00[1]		P00[1, 4]	PF0	PF1[5]

RO = CD38 receptor density and occupancy, ADA = Anti-Drug Antibody, P = Plasma, Y = Bone Marrow.

1. Sample collected just before IP administration
2. Sample collected when half the IP volume is administered
3. Sample collected just before actual end of infusion (EOI)
4. To be collected within 24h before IP administration
5. If patient modifies to an every 2 week schedule (see Section 6.4), the D8 PK and ADA should be collected on D1 just before IP administration
6. At 60 days, if patient is positive for ADA or the sample is inconclusive, additional ADA and PK samples are required every 30 days (±5 days) until sample is interpretable or negative.

1.7 PHARMACOKINETICS/PHARMACODYNAMICS FLOWCHART PHASE 1 BASIC PHASE (SAR650984 ADMINISTRATION EVERY 2 WEEKS - FROM COHORT 12)

Day	Cycle 1								Cycle 2		Subsequent cycles	EOT	Follow-up
	D1				D2	D3	D4	D8	D1	D14	D1	30 days after last IP administration	60 days after last IP administration
Time (decimal hours)[o]	**0 start infusion**	**mid infusion (0.25)**	EOI (0.5)	EOI +4h	24h	48h	72h	168h	**0 start infusion**	312h	**0 start infusion**		
Indicative clock time	8 am	8:15 am	8:30 am	12:30 pm	8 am	8 am	8 am	8 am	8 am	8 am	8 am	8 am	8 am
IP administration SAR650984	X---	----	---X						X---		X---		
PK/PD Samples													
PK	P00[1]	P01[2]	P02[3]	P03	P04	P05	P06	P07	P00[1]		P00[1]	PF0	PF1[5]
RO in bone marrow	Y00[1]									Y00[4]		YF0	
ADA	P00[1]					P01			P00[1]		P00[1]	PF0	PF1[5]

RO = CD38 receptor density and occupancy, ADA = Anti-Drug Antibody, P = Plasma, Y = Bone Marrow.

1. Sample collected just before IP administration
2. Sample collected when half the IP volume is administered
3. Sample collected just before actual end of infusion (EOI)
4. To be collected within 24h before IP administration
5. At 60 days, if patient is positive for ADA or the sample is inconclusive, additional ADA and PK samples are required every 30 days (±5 days) until sample is interpretable or negative.

1.8 PHARMACOKINETICS/PHARMACODYNAMICS FLOWCHART PHASE 2

Day	Cycle 1[1]							Cycles 2-3		Cycle 4				Subsequent cycles		EOT	Follow-up
	D1			D8	D15		D22	D1	D15	D1			D15	D1	D15	30 days after last IP admin	60 days after last IP admin
Time (decimal hours)	0 start infusion[3]	EOI[4]	EOI +1h[5]	0 start infusion[3]	0 start infusion[3]	EOI[4]	0 start infusion[3]	0 start infusion[3]	0 start infusion[3]	0 start infusion[3]	EOI[4]	EOI +1h[5]	0 start infusion[3]	0 start infusion[3]	0 start infusion[3]		
Indicative clock time	8 am	12 pm	1 pm	8 am	8 am	12 pm	8 am	8 am	8 am	8 am	12 pm	1 pm	8 am	8 am	8 am	8 am	8 am
PK Samples:[2]																	
Patients on schedule: 3 mg/kg Q2W or 10 mg/kg Q2W	P00	P01	P02		P00	P01[7]		P00	P00	P00			P00	P00	P00	PF0	PF1[10]
Patients on schedule: 10 mg/kg Q2W for C1-2, then 10 mg/kg Q4W	P00	P01	P02		P00	P01[7]		P00	P00[8]	P00	P01[9]	P02[9]		P00		PF0	PF1[10]
Patients on schedule: 20 mg/kg QW C1, then Q2W	P00	P01	P02	P00	P00	P01[7]	P00	P00	P00	P00	P01[9]	P02[9]	P00	P00[12]	P00	PF0[13]	PF1[10] *(Stage 1 only)*
PD samples:[2]																	
CD38 RO in bone marrow[11] (Stage 1 patients only)	Y00[6]							Y00 C2 only								YF0	
CD38 RD in bone marrow (Phase 2 Stage 1 patients only)	Y00[6]																
ADA (Anti-Drug Antibody)	P00				P00			P00		P00				P00[12]		PF0[13]	PF1[10] *(Stage 1 only)*
Cytokines	P00																

EOI = End of Infusion; P = Plasma; Y = Bone Marrow.

1. A cycle is 28 days.
2. Refer to lab manual for sample collection and shipping information.
3. Sample collected just before IP administration (within 24 hours prior).
4. Sample collected just before actual EOI (within -5 minutes).
5. Sampling to be adapted to actual EOI (within ±5 minutes).

6. Sample can be collected during the screening period.
7. If the PK sample at EOI is not collected on D15 of Cycle 1, this can be collected after the next IP administration.
8. Sample to be collected on D15 of Cycle 2 and 3 even though no SAR650984 is administered on D15 of Cycle 3.
9. If the PK sample at EOI is not collected on D1 of Cycle 4, this can be collected after the next IP administration.
10. At 60 days, if patient is positive for ADA or the sample is inconclusive, additional ADA sample are required every 30 days (±5 days) until sample is interpretable or negative. This will only be for Phase 2 Stage 1.
11. Only for Stage 1 patients enrolled at selected sites.
12. PK and ADA samples for patients in Phase 2 Stage 2 will be collected up to Cycle 10, inclusive. If ADA is positive at Cycle 10, one additional ADA sample will be collected 3 months later. For patients treated with less than 10 cycles at the cut-off or early discontinuation, both PK and ADA samples collection will be stopped from the cut-off or discontinuation date, If the ADA is positive, one additional ADA sample will be collected 3 months later.
13. PK and ADA sample only if the patient does not complete 10 cycles of treatment. If ADA is postive, one additional ADA sample should be collected 3 months later.

1.9 STUDY FLOWCHART FOR PHASE 1 ACCELERATED DOSE ESCALATION PHASE

Evaluation[1]	Screening/Baseline	Treatment Cycle 1					Treatment Cycle 2					Subsequent cycles[22]		End of treatment (EOT)[23]	Follow-up period[24]
	D-15 to D1	D1[2]	D2	D3	D8	D14	D1[2] (D15)	D2	D3	D8	D14	D1[2] (D15)	D2	30 days (+/-5 days) after last IP administration	>30 Days
Informed Consent/Inclusion/Exclusion Criteria	X														
Demography/Medical/Surgical and Disease History[3]	X														
Physical Examination[4]	X	X			X	X	X			X	X	X		X	
Weight/Height (height at baseline only)	X	X				X	X				X	X		X	
Vital Signs[5]	X	X	X		X	X	X	X		X	X	X	X	X	
Chest X-ray, Spirometry, Diffusion Capacity[6]		X					X					X		X	
Performance Status (Karnofsky)	X	X			X	X	X			X	X	X		X	
CD38 Expression[7]	X														
Serumβ2-microglobulin (CLL, MM only)	X					X					X	X (end of even-numbered cycles)		X	
Immunoglobulins: IgG, IgA, IgM (MM only)	X					X					X	X (end of even-numbered cycles)		X	
Disease Assessment[8] † (baseline within 28 days)	X†										X	X (end of even-numbered cycles)		X	
Pregnancy Test[9] ‡ (baseline within 7 days)	X‡	X					X				X	X		X	
Blood Chemistry[10]	X	X[11]	X[12]		X	X	X[11]	X[12]		X	X	X		X	
Hematology[13]	X	X			X	X	X			X	X	X		X	

Evaluation[1]	Screening/Baseline	Treatment Cycle 1					Treatment Cycle 2					Subsequent cycles[22]		End of treatment (EOT)[23]	Follow-up period[24]
	D-15 to D1	D1[2]	D2	D3	D8	D14	D1[2] (D15)	D2	D3	D8	D14	D1[2] (D15)	D2	30 days (+/-5 days) after last IP administration	>30 Days
PSA, Pituitary Hormones (GH, FSH/LH, ACTH, TSH)		X					X				X	X		X	
Coagulation (PT/INR, PTT)	X	X			X	X	X			X	X	X		X	
Urinalysis[14]	X	X			X	X	X			X	X	X		X	
hs-CRP[15]		X	X				X	X				X	X		
12-Lead ECG[16]		X			X		X			X	X	X		X	
Holter Monitoring[17]		X	X				X	X							
SAR650984 Administration[18]		X					X					X			
Central Labs:															
Cytokines (TNF-α, IL-1-β, IL-6, IFN-γ)[19]		X	X				X	X				X	X		
RO in blood (ALL, AML, CLL only) (Accelerated)[20]		X	X	X			X	X	X		X				
RO in bone marrow (MM only) (Accelerated)[20, 26]		X[25]									X				
PK (Accelerated)[21]		X	X	X	X		X	X	X	X	X	X		X	X (60 days (+/-5 days) after last IP administration)
ADA[21]		X		X			X				X	X		X	X (60 days (+/-5 days) after last IP administration)
AE/SAE Assessment	Continuously throughout the study period														X (related AE)
Prior/Concomitant Medication	Continuously throughout the study period														X (related AE)

1. **Evaluation:** Assessments should be performed prior to IP administration unless otherwise indicated. Results should be reviewed by the Investigator prior to the administration of the next dose. A Cycle is 14 days.
2. **D1:** Day 1 of Cycle 1 refers to the day the patient receives the first IP administration. Day 1 of each subsequent cycle corresponds to Day 15 (+/-1 day) of the previous cycle. Before Cycle 1, blood chemistry, hematology, coagulation, and urinalysis assessments are not required if acceptable screening assessment is performed within 1 day prior to first IP administration; before subsequent cycles, assessments not required if acceptable assessment is performed on D14 of previous cycle.
3. **Demography:** Includes age, gender and race. **Medical/Surgical History:** Includes relevant history of previous/associated pathologies, other than the tumor. **Disease History:** Includes date of initial diagnosis, stage and extent of the disease, previous anti-tumor therapy (type and response to), disease status at inclusion (primary refractory, refractory to last therapy, or recurrent). In addition, results of additional procedures (such as karyotype, FISH, etc) performed as part of standard of care to assess the current disease status may also be collected.
4. **Physical Examination:** Consists of examination of major body systems, including neurological, digestive exam, extramedullary myeloma localizations, respiratory, hepatomegaly, splenomegaly, lymphadenopathy. Only clinically relevant findings will be reported in the CRF as AEs.
5. **Vital Signs:** Blood pressure, heart rate, temperature, and respiration rate required at screening, Day 1 (just before starting infusion, end of infusion, and 1, 2, 4, 6, and 24 hours post-infusion) in each cycle, Day 8 and Day 14 (Cycles 1 and 2), and as clinically indicated. The final measurements will be performed at the EOT visit.
6. **Chest X-ray, Spirometry, Diffusion Capacity**: To be done within one week prior to IP administration in each cycle. The final measurements will be performed at the EOT visit.
7. **CD38 Expression:** Archival samples may be used. If no archival sample, will be assessed at screening by flow cytometry and/or immunohistochemistry using malignant cells from peripheral blood, bone marrow and/or lymph node tissue depending on the disease type. When feasible, bone marrow and tissue samples will be obtained by Fine Needle Aspiration (FNA).
8. **Disease Assessment:** To be done at screening up to 28 days prior to first IP administration. Response is assessed on the basis of clinical, laboratory, radiologic, and pathologic (ie, bone marrow) findings at the end of Cycle 2 to determine if patient is eligible to continue treatment. Patients continuing after Cycle 2 should be evaluated for disease status at least every 4 weeks (even-numbered cycles), whenever disease progression is suspected (eg, symptomatic deterioration), to confirm a partial or complete response (4-6 weeks after initial documentation of response), and at the EOT visit.)
   - MM: Bone marrow biopsy/aspiration, radiologic imaging of plasmocytoma as clinically indicated, bone skeletal survey as clinically indicated, M-protein quantification (serum and/or 24-hr urine), serum free light chain levels, or urinary light chain levels as clinically indicated
   - B-cell NHL: Bone marrow biopsy/aspiration as clinically indicated, lymph node biopsy as clinically indicated, radiologic tumor assessment (by X-ray, computed tomography [CT] scan, PET scan or magnetic resonance imaging [MRI]; ultrasound is not sufficient)
   - B-cell ALL: Bone marrow biopsy/aspiration, Blood count with differential including blast count
   - AML: Bone marrow biopsy/aspiration, Blood count with differential including blast count
   - CLL: Clinical examination, bone marrow biopsy/aspiration, lymph node biopsy as clinically indicated, Blood count with differential
9. Pregnancy Tests: Women of child bearing potential must have a negative serum pregnancy test result within 7 days prior to first IP administration and at the EOT visit; negative urine pregnancy test required prior to each subsequent IP administration.
10. Blood Chemistry:
    - Liver function tests: SGOT (AST), SGPT (ALT), bilirubin (total and direct), alkaline phosphatase, lactate dehydrogenase (LDH)
    - Renal function: sodium, potassium, chloride, bicarbonate/carbon dioxide, calcium, magnesium, phosphate, uric acid, blood urea nitrogen (BUN), serum creatinine and estimated creatinine clearance (Cockcroft-Gault Formula).
    - Other: glucose, albumin, total protein, peptide C
    - Erythrocyte sedimentation rate (ESR)
11. Samples to be drawn immediately before the start of infusion, at the end of infusion, and 6 hours after the end of infusion.
12. Sample to be drawn 24 hours after the end of infusion on D1.
13. Hematology: Hemoglobin, hematocrit, RBC, WBC with differential, MCV, platelet counts, blast counts (AML/B-cell ALL). If grade 4 neutropenia, assess ANC every 2-3 days until ANC $\geq 0.5 \times 10^9$/L and at least weekly thereafter until ANC $\geq 1.0 \times 10^9$/L.
14. Urinalysis: blood, protein, glucose, pH, ketones, bilirubin, leucocytes, nitrates, specific gravity.
15. hs-CRP: To be done at Cycle 1 Day 1 prior to first IP administration, and 6 and 24 hours post-infusion in each cycle.

16. 12-Lead ECG: To be performed Day 1 (just before starting infusion and end of infusion) in each cycle, Day 8 (Cycles 1 and 2) and Day 14 (Cycle 2), and as clinically indicated. The final measurements will be performed at the EOT visit.
17. Holter Monitoring: To be placed on the patient 2 hours before starting the infusion and remain on the patient until 24 hours after the infusion (Cycles 1 and 2).
18. SAR650984 Administration: At the start of each treatment cycle, the patient's weight will be determined. The following clinical assessments are required: blood pressure, heart rate, temperature, and respiration rate required just before starting infusion, end of infusion, and 1, 2, 4, and 24 hours post-infusion in each cycle and as clinically indicated.
19. Cytokines (TNF-α, IL-1-β, IL-6, IFN-γ): Baseline sample to be drawn prior to first IP administration at Cycle 1, then at 6 and 24 hours post-infusion in each cycle. Samples to be shipped directly to Singulex (Refer to lab manual).
20. RO: See details regarding sampling times on Pharmacokinetics/Pharmacodynamics Flowchart Accelerated Phase. Samples to be shipped directly to Biocytex (Refer to lab manual).
21. PK, Anti-Drug Antibodies: See details regarding sampling times on Pharmacokinetics/Pharmacodynamics Flowchart Accelerated Phase. Samples to be shipped to Covance (Refer to lab manual).
22. Subsequent Cycles: After completing two cycles, patients may receive additional administrations of SAR650984 at Investigator's discretion.
23. End of Treatment (EOT): Assessments to be performed 30 days (+/-5 days) after last IP administration.
24. Follow-up Period: Patients will be followed beyond 30 days if IP-related AE and/or unresolved toxicity. PK and ADA samples required 60 days (+/-5 days) after last IP administration.
25. If disease assessment bone marrow biopsy/aspiration required at screening is completed within 7 days prior to IP administration, RO in bone marrow can be measured at that time.
26. RO in bone marrow for MM patients is optional for Cohorts 1-3.

1.10 STUDY FLOWCHART FOR PHASE 1 BASIC DOSE ESCALATION PHASE (SAR650984 ADMINISTRATION EVERY 2 WEEKS - FOR COHORTS 6-10)

Evaluation[1]	Screening/Baseline	Treatment Cycle 1					Treatment Cycle 2				Subsequent cycles[22]		End of treatment (EOT)[23]	Follow-up period[24]
	D-15 to D1	D1[2]	D2	D3	D8[27]	D14[27]	D1[2] (D15)	D2	D8[27]	D14[27]	D1[2] (D15)	D2	30 days (+/-5 days) after last IP administration	>30 Days
Informed Consent/Inclusion/Exclusion Criteria	X													
Demography/Medical/Surgical and Disease History[3]	X													
Physical Examination[4]	X	X			X	X	X		X	X	X		X	
Weight/Height (height at baseline only)	X	X				X	X			X	X		X	
Vital Signs[5]	X	X	X		X	X	X	X	X	X	X	X	X	
Chest X-ray, Spirometry, Diffusion Capacity[6]		X					X				X		X	
Performance Status (Karnofsky)	X	X			X	X	X		X	X	X		X	
CD38 Expression[7]	X													
Serumβ2-microglobulin (CLL, MM only)	X					X				X	X (end of even-numbered cycles)		X	
Immunoglobulins: IgG, IgA, IgM (MM only)	X					X				X	X (end of even-numbered cycles)		X	
Disease Assessment[8] † (baseline within 28 days)	X†									X	X (end of even-numbered cycles)		X	
Pregnancy Test[9] ‡ (baseline within 7 days)	X‡	X					X			X	X		X	
Blood Chemistry[10]	X	X[11]	X[12]		X	X	X[11]	X[12]	X	X	X		X	
Hematology[13]	X	X			X	X	X		X	X	X		X	
PSA, Pituitary Hormones (GH, FSH/LH, ACTH, TSH)		X					X			X	X		X	
Coagulation (PT/INR, PTT)	X	X			X	X	X		X	X	X		X	

Evaluation[1]	Screening/Baseline	Treatment Cycle 1					Treatment Cycle 2				Subsequent cycles[22]		End of treatment (EOT)[23]	Follow-up period[24]
	D-15 to D1	D1[2]	D2	D3	D8[27]	D14[27]	D1[2] (D15)	D2	D8[27]	D14[27]	D1[2] (D15)	D2	30 days (+/-5 days) after last IP administration	>30 Days
Urinalysis[14]	X	X			X	X	X		X	X	X		X	
hs-CRP[15]		X	X				X	X			X	X		
12-Lead ECG[16]		X			X		X		X	X	X		X	
Holter Monitoring[17]		X	X				X	X						
SAR650984 Administration[18]		X					X				X			
Central Labs:														
Cytokines (TNF-α, IL-1-β, IL-6, IFN-γ)[19]		X	X				X	X			X	X		
RO in blood (ALL, AML, CLL only) (Basic)[20]		X	X	X			X			X	X			
RO in bone marrow (MM only) (Basic)[20, 26]		X[25]								X			X	
PK (Basic)[21]		X	X	X	X		X			X	X		X	X (60 days (+/-5 days) after last IP administration)
ADA[21]		X		X			X			X	X		X	X (60 days (+/-5 days) after last IP administration)
AE/SAE Assessment	Continuously throughout the study period													X (related AE, all SAE)
Prior/Concomitant Medication	Continuously throughout the study period													X (related AE, all SAE)

1. **Evaluation:** Assessments should be performed prior to IP administration unless otherwise indicated. Results should be reviewed by the Investigator prior to the administration of the next dose. A Cycle is 14 days.

2. **D1:** Day 1 of Cycle 1 refers to the day the patient receives the first IP administration. Day 1 of each subsequent cycle corresponds to Day 15 (+/-1 day) of the previous cycle. Before Cycle 1, blood chemistry, hematology, coagulation, and urinalysis assessments not required if acceptable screening assessment is performed within 1 day prior to first IP administration; before subsequent cycles, assessments not required if acceptable assessment is performed on D14 of previous cycle. If necessary treatment with SAR650984 may be slightly delayed (max 7 days) for subsequent cycles following Cycle 2 Day 14 while awaiting results of disease assessment parameters.
3. **Demography:** Includes age, gender and race. **Medical/Surgical History:** Includes relevant history of previous/associated pathologies, other than the tumor. **Disease History:** Includes date of initial diagnosis, stage and extent of the disease, previous anti-tumor therapy (type and response to), disease status at inclusion (primary refractory, refractory to last therapy, or recurrent). In addition, results of additional procedures (such as karyotype, FISH, etc) performed as part of standard of care to assess the current disease status may also be collected.
4. **Physical Examination:** Consists of examination of major body systems, including neurological, digestive exam, extramedullary myeloma localizations, respiratory, hepatomegaly, splenomegaly, lymphadenopathy. Only clinically relevant findings will be reported in the CRF as AEs.
5. **Vital Signs:** Blood pressure, heart rate, temperature, and respiration rate required at screening, Day 1 (just before starting infusion, middle of infusion, end of infusion, and 1, 2, 4, 6, and 24 hours post-infusion) in each cycle, Day 8 and Day 14 (Cycles 1 and 2), and as clinically indicated. The final measurements will be performed at the EOT visit.
6. **Chest X-ray, Spirometry, Diffusion Capacity**: To be done within one week prior to IP administration for the first 2 cycles and then as clinically indicated. The final measurements will be performed at the EOT visit.
7. **CD38 Expression:** Archival samples may be used. If no archival sample, will be assessed at screening by flow cytometry and/or immunohistochemistry using malignant cells from peripheral blood, bone marrow and/or lymph node tissue depending on the disease type. When feasible, bone marrow and tissue samples will be obtained by Fine Needle Aspiration (FNA).
8. **Disease Assessment:** To be done at screening up to 28 days prior to first IP administration. Response is assessed on the basis of clinical, laboratory, radiologic, and pathologic (ie, bone marrow) findings at the end of Cycle 2 to determine if patient is eligible to continue treatment. Patients continuing after Cycle 2 should be evaluated for disease status at least every 4 weeks (end of every even-numbered cycle), whenever disease progression is suspected (eg, symptomatic deterioration), to confirm a partial or complete response (4-6 weeks after initial documentation of response), and at the EOT visit.
   - MM: Bone marrow biopsy/aspiration as clinically indicated, radiologic imaging of plasmocytoma as clinically indicated, bone skeletal survey as clinically indicated, M-protein quantification (serum and/or 24-hr urine), serum free light chains, or urinary light chain levels as clinically indicated
   - B-cell NHL: Bone marrow biopsy/aspiration as clinically indicated, lymph node biopsy as clinically indicated, radiologic tumor assessment (by X-ray, computed tomography [CT] scan, PET scan or magnetic resonance imaging [MRI]; ultrasound is not sufficient)
   - B-cell ALL: Bone marrow biopsy/aspiration as clinically indicated, Blood count with differential including blast count
   - AML: Bone marrow biopsy/aspiration as clinically indicated, Blood count with differential including blast count
   - CLL: Clinical examination, Bone marrow biopsy/aspiration as clinically indicated, Lymph node biopsy as clinically indicated, Radiologic imaging (CT scan) as clinically indicated, Blood count with differential
9. **Pregnancy Tests:** Women of child bearing potential must have a negative serum pregnancy test result within 7 days prior to first IP administration and at the EOT visit; negative urine pregnancy test required prior to each subsequent IP administration.
10. **Blood Chemistry:**
    - Liver function tests: SGOT (AST), SGPT (ALT), bilirubin (total and direct), alkaline phosphatase, lactate dehydrogenase (LDH)
    - Renal function: sodium, potassium, chloride, bicarbonate/carbon dioxide, calcium, magnesium, phosphate, uric acid, blood urea nitrogen (BUN), serum creatinine and estimated creatinine clearance (Cockcroft-Gault Formula).
    - Other: glucose, albumin, total protein, peptide C
    - Erythrocyte sedimentation rate (ESR)
11. Samples to be drawn immediately before the start of infusion, at the end of infusion, and 6 hours after the end of infusion.
12. Sample to be drawn 24 hours after the end of infusion on D1.
13. **Hematology:** Hemoglobin, hematocrit, RBC, WBC with differential, MCV, platelet counts, blast counts (AML/B-cell ALL). If Grade 4 neutropenia, assess ANC every 2-3 days until ANC $\geq$ 0.5 x 10^9/L and at least weekly thereafter until ANC $\geq$1.0 x 10^9/L.
14. **Urinalysis:** blood, protein, glucose, pH, ketones, bilirubin, leucocytes, nitrates, specific gravity.
15. **hs-CRP**: To be done at Cycle 1 Day 1 prior to first IP administration, and 6 and 24 hours post-infusion in each cycle.

16. **12-Lead ECG:** To be performed Day 1 (just before starting infusion, middle of infusion and end of infusion) in each cycle, Day 8 (Cycles 1 and 2) and Day 14 (Cycle 2), and as clinically indicated. The final measurements will be performed at the EOT visit.
17. **Holter Monitoring:** To be placed on the patient 1-2 hours before starting the infusion and remain on the patient until 24 hours after the infusion (Cycles 1 and 2).
18. **SAR650984 Administration:** At the start of each treatment cycle, the patient's weight will be determined. The following clinical assessments are required: blood pressure, heart rate, temperature, and respiration rate required just before starting infusion, middle of infusion, end of infusion, and 1, 2, 4, and 24 hours post-infusion in each cycle and as clinically indicated.
19. **Cytokines (TNF-α, IL-1-β, IL-6, IFN-γ):** Baseline sample to be drawn prior to first IP administration at Cycle 1, then at 6 and 24 hours post-infusion in each cycle. Samples to be shipped directly to Singulex (Refer to lab manual).
20. **RO:** See details regarding sampling times on Pharmacokinetics/Pharmacodynamics Flowchart Section 1.5 . Samples to be shipped directly to Biocytex (Refer to lab manual).
21. **PK, Anti-Drug Antibodies:** See details regarding sampling times on Pharmacokinetics/Pharmacodynamics Flowchart Section 1.5 . Samples to be shipped to Covance (Refer to lab manual).
22. **Subsequent Cycles:** After completing two cycles, patients may receive additional administrations of SAR650984.
23. **End of Treatment (EOT):** Assessments to be performed 30 days (+/-5 days) after last IP administration.
24. **Follow-up Period:** Patients will be followed beyond 30 days for IP-related AE, all SAEs (regardless of relationship to study treatment) and/or unresolved toxicity. PK and ADA samples required 60 days (+/-5 days) after last IP administration. At 60 days, if patient is positive for ADA or the sample is inconclusive, additional ADA and PK samples are required every 30 days (±5 days) until sample is interpretable or negative. All IP-related AEs and all SAEs (regardless of relationship to study treatment) to be followed until ADA sample is negative.
25. If disease assessment bone marrow biopsy/aspiration required at screening is completed within 14 days prior to IP administration, RO in bone marrow can be measured at that time.
26. RO in bone marrow for MM patients is optional for Cohorts 1-3.
27. Day 8 and Day 14 +/-1 day

1.11 STUDY FLOWCHART FOR PHASE 1 BASIC DOSE ESCALATION PHASE (SAR650984 ADMINISTRATION EVERY WEEK - FROM COHORT 11)

Evaluation[1]	Screening/ Baseline	Treatment Cycle 1						Treatment Cycle 2				Treatment Cycle 3					Subsequent cycles[21]		End of treatment (EOT)[22]	Follow-up period[23]
	D-15 to D1	D1[2]	D2	D3	D4	D8[25]	D14[25]	D1[2] (D15)	D2	D8[25]	D14[25]	D1[2] (D15)	D2	D3	D4	D8	D1[2] (D15)	D8 D8	30 days (+/-5 days) after last IP administration	>30 Days
Informed Consent/Inclusion/Exclusion Criteria	X																			
Demography/Medical/Surgical and Disease History[3]	X																			
Physical Examination[4]	X	X				X	X	X		X	X	X				X	X	X	X	
Weight/Height (height at baseline only)	X	X					X	X			X	X					X		X	
Vital Signs[5]	X	X	X			X	X	X	X	X	X	X				X	X	X	X	
Chest X-ray, Spirometry, Diffusion Capacity[6]		X						X				X					X		X	
Performance Status (Karnofsky)	X	X				X	X	X		X	X	X				X	X	X	X	
Serumβ2-microglobulin	X						X				X						X (end of even-numbered cycles)		X	
Immunoglobulins: IgG, IgA, IgM	X						X				X						X (end of even-numbered cycles)		X	
Disease Assessment[7] † (baseline within 28 days)	X†										X						X (end of even-numbered cycles)		X	

Evaluation[1]	Screening/ Baseline	Treatment Cycle 1						Treatment Cycle 2				Treatment Cycle 3					Subsequent cycles[21]		End of treatment (EOT)[22]	Follow-up period[23]
	D-15 to D1	D1[2]	D2	D3	D4	D8[25]	D14[25]	D1[2] (D15)	D2	D8[25]	D14[25]	D1[2] (D15)	D2	D3	D4	D8	D1[2] (D15)	D8 D8	30 days (+/-5 days) after last IP administration	>30 Days
Pregnancy Test[8] ‡ (baseline within 7 days)	X‡	X						X			X	X					X		X	
Blood Chemistry[9]	X	X[10]	X[11]			X[10]	X	X[10]	X[11]	X[10]	X	X				X	X	X	X	
Hematology[12]	X	X				X	X	X		X	X	X				X	X	X	X	
PSA, Pituitary Hormones (GH, FSH/LH, ACTH, TSH)		X						X			X	X					X		X	
Coagulation (PT/INR, PTT)	X	X				X	X	X		X	X	X				X	X	X	X	
Urinalysis[13]	X	X				X	X	X		X	X	X				X	X	X	X	
hs-CRP[14]		X	X			X		X	X	X		X				X	X	X		
12-Lead ECG[15]		X				X		X		X	X	X				X	X	X	X	
Holter Monitoring[16]		X	X					X	X											
SAR650984 Administration[17]		X				X		X		X		X				X	X	X		
Central Labs:																				
Cytokines (TNF-α, IL-1-β, IL-6, IFN-γ)[18]		X	X			X		X	X	X		X				X	X	X		
RO in bone marrow[19]		X[24]									X								X	
PK (Basic)[20]		X	X	X	X	X		X		X		X	X	X	X	X	X	X	X	X (60 days (+/-5 days) after last IP administration)
ADA[20]		X		X		X				X						X		X	X	X (60 days (+/-5 days) after last IP administration)

Evaluation[1]	Screening/ Baseline	Treatment Cycle 1						Treatment Cycle 2				Treatment Cycle 3					Subsequent cycles[21]		End of treatment (EOT)[22]	Follow-up period[23]
	D-15 to D1	D1[2]	D2	D3	D4	D8[25]	D14[25]	D1[2] (D15)	D2	D8[25]	D14[25]	D1[2] (D15)	D2	D3	D4	D8	D1[2] (D15)	D8 D8	30 days (+/-5 days) after last IP administration	>30 Days
AE/SAE Assessment	Continuously throughout the study period																			X (related AE, all SAE)
Prior/Concomitant Medication	Continuously throughout the study period																			X (related AE, all SAE)

1. **Evaluation:** Assessments should be performed prior to IP administration unless otherwise indicated. Results should be reviewed by the Investigator prior to the administration of the next dose. A Cycle is 14 days.
2. **D1:** Day 1 of Cycle 1 refers to the day the patient receives the first IP administration. Day 1 of each subsequent cycle corresponds to Day 15 (+/-1 day) of the previous cycle. Before Cycle 1, blood chemistry, hematology, coagulation, and urinalysis assessments not required if acceptable screening assessment is performed within 1 day prior to first IP administration; before subsequent cycles, assessments not required if acceptable assessment is performed on D14 of previous cycle. If necessary treatment with SAR650984 may be slightly delayed (max 7 days) for subsequent cycles following Cycle 2 Day 14 while awaiting results of disease assessment parameters.
3. **Demography:** Includes age, gender and race. **Medical/Surgical History:** Includes relevant history of previous/associated pathologies, other than the tumor. **Disease History:** Includes date of initial diagnosis, stage and extent of the disease, previous anti-tumor therapy (type and response to), disease status at inclusion (primary refractory, refractory to last therapy, or recurrent). In addition, results of additional procedures (such as karyotype, FISH, etc) performed as part of standard of care to assess the current disease status may also be collected.
4. **Physical Examination:** Consists of examination of major body systems, including neurological, digestive exam, extramedullary myeloma localizations, respiratory, hepatomegaly, splenomegaly, lymphadenopathy. Only clinically relevant findings will be reported in the CRF as AEs.
5. **Vital Signs:** Blood pressure, heart rate, temperature, and respiration rate required at screening, Day 1 and Day 8 (just before starting infusion, middle of infusion, end of infusion, and 1, 2, 4 and 6 hours post-infusion) in each cycle, Day 2, Day 8 and Day 14 (Cycles 1 and 2), and as clinically indicated. The final measurements will be performed at the EOT visit.
6. **Chest X-ray, Spirometry, Diffusion Capacity**: To be done within one week prior to IP administration on Day 1 for the first 2 cycles and then as clinically indicated. The final measurements will be performed at the EOT visit.
7. **Disease Assessment:** To be done at screening up to 28 days prior to first IP administration. Response is assessed on the basis of clinical, laboratory, radiologic, and pathologic (ie, bone marrow) findings at the end of Cycle 2 to determine if patient is eligible to continue treatment. Patients continuing after Cycle 2 should be evaluated for disease status at least every 4 weeks (end of every even-numbered cycle), whenever disease progression is suspected (eg, symptomatic deterioration), to confirm a partial or complete response (4-6 weeks after initial documentation of response), and at the EOT visit. Bone marrow biopsy/aspiration as clinically indicated, radiologic imaging of plasmocytoma as clinically indicated, bone skeletal survey as clinically indicated, M-protein quantification (serum and/or 24-hr urine), serum free light chains, or urinary light chain levels as clinically indicated. If necessary treatment with SAR650984 may be slightly delayed (max 7 days) for subsequent cycles while awaiting results of disease assessment parameters.
8. **Pregnancy Tests:** Women of child bearing potential must have a negative serum pregnancy test result within 7 days prior to first IP administration and at the EOT visit; negative urine pregnancy test required prior to each subsequent IP administration on Day 1.
9. **Blood Chemistry:**
   - Liver function tests: SGOT (AST), SGPT (ALT), bilirubin (total and direct), alkaline phosphatase, lactate dehydrogenase (LDH)
   - Renal function: sodium, potassium, chloride, bicarbonate/carbon dioxide, calcium, magnesium, phosphate, uric acid, blood urea nitrogen (BUN), serum creatinine and estimated creatinine clearance (Cockcroft-Gault Formula).
   - Other: glucose, albumin, total protein, peptide C
   - Erythrocyte sedimentation rate (ESR)

10. Samples to be drawn immediately before the start of infusion, at the end of infusion, and 6 hours after the end of infusion.
11. Sample to be drawn 24 hours after the end of infusion on Day 1.
12. **Hematology:** Hemoglobin, hematocrit, RBC, WBC with differential, MCV, platelet counts, blast counts (AML/B-cell ALL). If grade 4 neutropenia, assess ANC every 2-3 days until ANC $\geq$0.5 x 10^9/L and at least weekly thereafter until ANC $\geq$1.0 x 10^9/L.
13. **Urinalysis:** blood, protein, glucose, pH, ketones, bilirubin, leucocytes, nitrates, specific gravity.
14. **hs-CRP**: To be done at Cycle 1 Day 1 prior to first IP administration, on Day 1 and Day 8 at 6 hours post-infusion in each cycle and Day 2 (24 hours post-infusion) in Cycle 1 and 2 only.
15. **12-Lead ECG:** To be performed Day 1 and Day 8 (just before starting infusion, middle of infusion and end of infusion) in each cycle, and Day 14 (Cycle 2), and as clinically indicated. The final measurements will be performed at the EOT visit.
16. **Holter Monitoring:** To be placed on the patient 1-2 hours before starting the Day 1 infusion and remain on the patient until 24 hours after the infusion (Cycles 1 and 2).
17. **SAR650984 Administration:** At the start of each treatment cycle, the patient's weight will be determined. The following clinical assessments are required: blood pressure, heart rate, temperature, and respiration rate required just before starting infusion, middle of infusion, end of infusion, and 1, 2, and 4 hours post-infusion in each cycle and as clinically indicated.
18. **Cytokines (TNF-α, IL-1-β, IL-6, IFN-γ):** Baseline sample to be drawn prior to first IP administration on Cycle 1 Day 1, then at 6 hours post-infusion on Day 1 and Day 8 of each cycle, and Day 2 (24 hours post-infusion) of Cycle 1 and 2. Samples to be shipped directly to Singulex (Refer to lab manual).
19. **RO:** See details regarding sampling times on Pharmacokinetics/Pharmacodynamics Flowchart Section 1.6. Samples to be shipped directly to Biocytex (Refer to lab manual).
20. **PK, Anti-Drug Antibodies:** See details regarding sampling times on Pharmacokinetics/Pharmacodynamics Flowchart Section 1.6. If patient modifies to an every 2 week schedule (see Section 6.4), the D8 PK and ADA sample should be collected on D1 just before IP administration. Samples to be shipped to Covance (Refer to lab manual).
21. **Subsequent Cycles:** After completing two cycles, patients may receive additional administrations of SAR650984.
22. **End of Treatment (EOT):** Assessments to be performed 30 days (+/-5 days) after last IP administration.
23. **Follow-up Period:** Patients will be followed beyond 30 days for IP-related AE, SAEs (regardless of relationship to study treatment) and/or unresolved toxicity. PK and ADA samples required 60 days (+/-5 days) after last IP administration. At 60 days, if patient is positive for ADA or the sample is inconclusive, additional ADA and PK samples are required every 30 days (±5 days) until sample is interpretable or negative. All IP-related AEs and all SAEs (regardless of relationship to study treatment) to be followed until ADA sample is negative.
24. If disease assessment bone marrow biopsy/aspiration required at screening is completed within 14 days prior to IP administration, RO in bone marrow can be measured at that time.
25. Day 8 and Day 14 +/-1 day.

1.12 STUDY FLOWCHART FOR PHASE 1 BASIC DOSE ESCALATION PHASE (SAR650984 ADMINISTRATION EVERY 2 WEEKS - FROM COHORT 12)

Evaluation[1]	Screening/Baseline	Treatment Cycle 1						Treatment Cycle 2				Subsequent cycles[21]	End of treatment (EOT)[22]	Follow-up period[23]
	D-15 to D1	D1[2]	D2	D3	D4	D8[25]	D14[25]	D1[2] (D15)	D2	D8[25]	D14[25]	D1[2] (D15)	30 days (+/-5 days) after last IP administration	>30 Days
Informed Consent/Inclusion/Exclusion Criteria	X													
Demography/Medical/Surgical and Disease History[3]	X													
Physical Examination[4]	X	X				X	X	X		X	X	X	X	
Weight/Height (height at baseline only)	X	X					X	X			X	X	X	
Vital Signs[5]	X	X	X			X	X	X	X	X	X	X	X	
Chest X-ray, Spirometry, Diffusion Capacity[6]		X						X				X	X	
Performance Status (Karnofsky)	X	X				X	X	X		X	X	X	X	
Serumβ2-microglobulin	X						X				X	X (end of even-numbered cycles)	X	
Immunoglobulins: IgG, IgA, IgM	X						X				X	X (end of even-numbered cycles)	X	
Disease Assessment[7] † (baseline within 28 days)	X†										X	X (end of even-numbered cycles)	X	
Pregnancy Test[8] ‡ (baseline within 7 days)	X‡	X						X			X	X	X	

Evaluation[1]	Screening/Baseline	Treatment Cycle 1						Treatment Cycle 2				Subsequent cycles[21]	End of treatment (EOT)[22]	Follow-up period[23]
	D-15 to D1	D1[2]	D2	D3	D4	D8[25]	D14[25]	D1[2] (D15)	D2	D8[25]	D14[25]	D1[2] (D15)	30 days (+/-5 days) after last IP administration	>30 Days
Blood Chemistry[9]	X	X[10]	X[11]			X	X	X[10]	X[11]	X	X	X	X	
Hematology[12]	X	X				X	X	X		X	X	X	X	
PSA, Pituitary Hormones (GH, FSH/LH, ACTH, TSH)		X						X			X	X	X	
Coagulation (PT/INR, PTT)	X	X				X	X	X		X	X	X	X	
Urinalysis[13]	X	X				X	X	X		X	X	X	X	
hs-CRP[14]		X	X					X	X			X		
12-Lead ECG[15]		X				X		X		X	X	X	X	
Holter Monitoring[16]		X	X					X	X					
SAR650984 Administration[17]		X						X				X		
Central Labs:														
Cytokines (TNF-α, IL-1-β, IL-6, IFN-γ)[18]		X	X					X	X			X		
RO in bone marrow[18]		X[24]									X		X	
PK (Basic)[19]		X	X	X	X	X		X				X	X	X (60 days (+/-5 days) after last IP administration)
ADA[19]		X		X				X				X	X	X (60 days (+/-5 days) after last IP administration)

Evaluation[1]	Screening/Baseline	Treatment Cycle 1						Treatment Cycle 2				Subsequent cycles[21]	End of treatment (EOT)[22]	Follow-up period[23]
	D-15 to D1	D1[2]	D2	D3	D4	D8[25]	D14[25]	D1[2] (D15)	D2	D8[25]	D14[25]	D1[2] (D15)	30 days (+/-5 days) after last IP administration	>30 Days
AE/SAE Assessment	Continuously throughout the study period													X (related AE, all SAEs)
Prior/Concomitant Medication	Continuously throughout the study period													X (related AE, all SAEs)

1. **Evaluation:** Assessments should be performed prior to IP administration unless otherwise indicated. Results should be reviewed by the Investigator prior to the administration of the next dose. A Cycle is 14 days.
2. **D1:** Day 1 of Cycle 1 refers to the day the patient receives the first IP administration. Day 1 of each subsequent cycle corresponds to Day 15 (+/-1 day) of the previous cycle. Before Cycle 1, blood chemistry, hematology, coagulation, and urinalysis assessments not required if acceptable screening assessment is performed within 1 day prior to first IP administration; before subsequent cycles, assessments not required if acceptable assessment is performed on D14 of previous cycle. If necessary treatment with SAR650984 may be slightly delayed (max 7 days) for subsequent cycles following Cycle 2 Day 14 while awaiting results of disease assessment parameters.
3. **Demography:** Includes age, gender and race. **Medical/Surgical History:** Includes relevant history of previous/associated pathologies, other than the tumor. **Disease History:** Includes date of initial diagnosis, stage and extent of the disease, previous anti-tumor therapy (type and response to), disease status at inclusion (primary refractory, refractory to last therapy, or recurrent). In addition, results of additional procedures (such as karyotype, FISH, etc) performed as part of standard of care to assess the current disease status may also be collected.
4. **Physical Examination:** Consists of examination of major body systems, including neurological, digestive exam, extramedullary myeloma localizations, respiratory, hepatomegaly, splenomegaly, lymphadenopathy. Only clinically relevant findings will be reported in the CRF as AEs.
5. **Vital Signs:** Blood pressure, heart rate, temperature, and respiration rate required at screening, Day 1 (just before starting infusion, middle of infusion, end of infusion, and 1, 2, 4 and 6 hours post-infusion) in each cycle, Day 2, Day 8 and Day 14 (Cycles 1 and 2), and as clinically indicated. The final measurements will be performed at the EOT visit.
6. **Chest X-ray, Spirometry, Diffusion Capacity**: To be done within one week prior to IP administration for the first 2 cycles and then as clinically indicated. The final measurements will be performed at the EOT visit.
7. **Disease Assessment:** To be done at screening up to 28 days prior to first IP administration. Response is assessed on the basis of clinical, laboratory, radiologic, and pathologic (ie, bone marrow) findings at the end of Cycle 2 to determine if patient is eligible to continue treatment. Patients continuing after Cycle 2 should be evaluated for disease status at least every 4 weeks (end of every even-numbered cycle), whenever disease progression is suspected (eg, symptomatic deterioration), to confirm a partial or complete response (4-6 weeks after initial documentation of response), and at the EOT visit. Bone marrow biopsy/aspiration as clinically indicated, radiologic imaging of plasmocytoma as clinically indicated, bone skeletal survey as clinically indicated, M-protein quantification (serum and/or 24-hr urine), serum free light chains, or urinary light chain levels as clinically indicated. If necessary treatment with SAR650984 may be slightly delayed (max 7 days) for subsequent cycles while awaiting results of disease assessment parameters.
8. **Pregnancy Tests:** Women of child bearing potential must have a negative serum pregnancy test result within 7 days prior to first IP administration and at the EOT visit; negative urine pregnancy test required prior to each subsequent IP administration.
9. **Blood Chemistry:**
   - Liver function tests: SGOT (AST), SGPT (ALT), bilirubin (total and direct), alkaline phosphatase, lactate dehydrogenase (LDH)
   - Renal function: sodium, potassium, chloride, bicarbonate/carbon dioxide, calcium, magnesium, phosphate, uric acid, blood urea nitrogen (BUN), serum creatinine and estimated creatinine clearance (Cockcroft-Gault Formula).
   - Other: glucose, albumin, total protein, peptide C

- Erythrocyte sedimentation rate (ESR)

10. Samples to be drawn immediately before the start of infusion, at the end of infusion, and 6 hours after the end of infusion.
11. Sample to be drawn 24 hours after the end of infusion on D1.
12. **Hematology:** Hemoglobin, hematocrit, RBC, WBC with differential, MCV, platelet counts, blast counts (AML/B-cell ALL). If grade 4 neutropenia, assess ANC every 2-3 days until ANC $\geq$0.5 x 10^9/L and at least weekly thereafter until ANC $\geq$1.0 x 10^9/L.
13. **Urinalysis:** blood, protein, glucose, pH, ketones, bilirubin, leucocytes, nitrates, specific gravity.
14. **hs-CRP**: To be done at Cycle 1 Day 1 prior to first IP administration, 6 and 24 hours post-infusion, Cycle 2 at 6 and 24 hours post-infusion and then at 6 hours post-infusion in each cycle.
15. **12-Lead ECG:** To be performed Day 1 (just before starting infusion, middle of infusion and end of infusion) in each cycle, Day 8 (Cycles 1 and 2) and Day 14 (Cycle 2), and as clinically indicated. The final measurements will be performed at the EOT visit.
16. **Holter Monitoring:** To be placed on the patient 1-2 hours before starting the infusion and remain on the patient until 24 hours after the infusion (Cycles 1 and 2).
17. **SAR650984 Administration:** At the start of each treatment cycle, the patient's weight will be determined. The following clinical assessments are required: blood pressure, heart rate, temperature, and respiration rate required just before starting infusion, middle of infusion, end of infusion, and 1, 2 and 4 hours post-infusion in each cycle and as clinically indicated.
18. **Cytokines** (TNF-α, IL-1-β, IL-6, IFN-γ): Baseline sample to be drawn prior to first IP administration at Cycle 1, then at 6 and 24 hours post-infusion (Cycle 1 and 2) and then at 6hours post-infusion in each cycle. Samples to be shipped directly to Singulex (Refer to lab manual).
19. **RO**: See details regarding sampling times on Pharmacokinetics/Pharmacodynamics Flowchart Section 1.7. Samples to be shipped directly to Biocytex (Refer to lab manual).
20. **PK, Anti-Drug Antibodies**: See details regarding sampling times on Pharmacokinetics/Pharmacodynamics Flowchart Section 1.7. Samples to be shipped to Covance (Refer to lab manual).
21. **Subsequent Cycles:** After completing two cycles, patients may receive additional administrations of SAR650984.
22. **End of Treatment (EOT):** Assessments to be performed 30 days (+/-5 days) after last IP administration.
23. **Follow-up Period:** Patients will be followed beyond 30 days for IP-related AE, SAEs (regardless of relationship to study treatment) and/or unresolved toxicity. PK and ADA samples required 60 days (+/-5 days) after last IP administration. At 60 days, if patient is positive for ADA or the sample is inconclusive, additional ADA and PK samples are required every 30 days (±5 days) until sample is interpretable or negative. All IP-related AEs and all SAEs (regardless of relationship to study treatment) to be followed until ADA sample is negative.
24. If disease assessment bone marrow biopsy/aspiration required at screening is completed within 14 days prior to IP administration, RO in bone marrow can be measured at that time.
25. Day 8 and Day 14 +/-1 day

1.13 STUDY FLOWCHART FOR PHASE 2, STAGE 1A

Evaluation[1]		Screening /Baseline	Cycle 1-3[2]		Subsequent cycles[2, 3]		End of treatment (EOT)	Post treatment Follow-up period	
		D-21 to D1	D1[2] (±3 days)	D15 (±3 days)	D1 (±3 days)	D15 (±3 days)	Up to 30 days after last IP admin	At 60 days (±5 days) after last IP admin[45]	Every 3 months (±14 days) after last IP admin
Informed Consent/Inclusion/Exclusion Criteria		X							
Patient randomization (Stage 1 only)/registration		X							
Demography, Medical/Surgical and Disease History[4]		X							
Physical Examination[5]		X	X	X	X		X		
Weight/Height[6]		X	X (weight only)	X (weight only)	X (weight only)	X (weight only)	X (weight only)		
Vital Signs[7]		X	X	X	X	X	X		
Performance Status (Karnofsky)		X	X	X	X	X	X		
ePRO: QLQ-C30/ MY20[8]			X		X		X		
ePRO: EQ-5D[9]			C1 only		Every 3 cycles (ie, C4, C7, etc)		X		
12-Lead ECG[10]		X							
Chest X-ray[11]		X							
Laboratory Assessments:									
Pregnancy Test[12]		X					X		
Hepatitis B virus (HBV) serology			X[13]						
Central Labs[14]	Blood Chemistry[15]	X	X[17]	X	X	X	X		
	Hematology[16]	X	X[17]	X	X	X	X		
	Coagulation[18]	X							
	Urinalysis[19]	X							
	Cytokines[20] (TNF-α, IL-1-β, IL-6, IFN-γ)		C1 only						
	SAR650984 Safety Labs[21]		X	X	X	X			
	Serum β2-microglobulin[22]	X	C2, C3 only		X		X		
	Immunoglobulins[22]	X	C2, C3 only		X		X		

Evaluation[1]		Screening /Baseline	Cycle 1-3[2]		Subsequent cycles[2, 3]		End of treatment (EOT)	Post treatment Follow-up period	
		D-21 to D1	D1[2] (±3 days)	D15 (±3 days)	D1 (±3 days)	D15 (±3 days)	Up to 30 days after last IP admin	At 60 days (±5 days) after last IP admin[45]	Every 3 months (±14 days) after last IP admin
Central Labs[13]	PK[23]		X	X	X	X	X	X	
	ADA[24]		X	C1 only	X		X	X	
PD/Exploratory studies:									
Central Labs[14]	Bone marrow for:								
	- CD38 RD[25]	X							
	- FISH[26]	X							
	- Genomics/CD38 mRNA[27]	X					X		
	- Immune phenotyping[28]	X							
	- CD38 RO[29] - (Stage 1, selected sites only)	X	C2 only				X		
	- MRD assessment[30]	X							
	Blood for:								
	- Soluble CD38[31]		C1, C3 only				X		
	- Immune phenotyping[32]		C1, C3 only				X		
	- Immune genetic determinants[33]		C1 only						
	- Optional pharmacogenetic sample - (Stage 2 only)[34]		C1 only						
Disease Assessment[35]:									
Central Labs[14]	Serum M-Protein[36]	X	C2, C3 only		X		X		X[39]
	sFLC[37]	X	C2, C3 only		X		X		X[39]
Urine M-Protein (24-hr urine)[38]		X	C2, C3 only		X		X		X[39]
Bone Marrow for disease assessment[40]		X					X		X[39]

Evaluation[1]	Screening /Baseline	Cycle 1-3[2]		Subsequent cycles[2, 3]		End of treatment (EOT)	Post treatment Follow-up period	
	D-21 to D1	D1[2] (±3 days)	D15 (±3 days)	D1 (±3 days)	D15 (±3 days)	Up to 30 days after last IP admin	At 60 days (±5 days) after last IP admin[45]	Every 3 months (±14 days) after last IP admin
Skeletal survey, CT/MRI scan[41]	X					X		X[39]
SAR650984 Administration: 3 mg/kg Q2W or 10 mg/kg Q2W[42]		**X**	**X**	**X**	**X**			
SAR650984 Administration: 10 mg/kg Q2W for C1-2 then 10 mg/kg Q4W[42]		**X**	**C1, C2 only**	**X**				
AE/SAE Assessment[43]	Continuously throughout study period						X (related AE only)	
Prior/Concomitant Medication	Continuously throughout study period						X (related AE only)	
New anticancer therapy						X	X	X
Survival Status[44]						X	X	X

1. **Evaluation:** Assessments should be performed prior to IP administration unless otherwise indicated.
2. **Cycle:** A cycle is 28 days. The D1 ±3 day window applies to Cycle 2 and 3 only.
3. **Subsequent Cycles:** Patients on the Q4W schedule are only required to attend the D1 visit.
4. **Demography:** Includes age, gender and race. **Medical/Surgical History:** Includes relevant history of previous/associated pathologies, other than multiple myeloma. **Disease History:** Includes date of initial diagnosis, stage and extent of the disease, previous anti-tumor therapy (type, duration and response to), disease status at inclusion (refractory to last therapy, or recurrent). In addition, results of additional procedures (such as karyotype, FISH, etc) performed as part of standard of care to assess the current disease status may also be collected.
5. **Physical Examination:** Consists of examination of major body systems, including neurological, digestive exam, plasmacytoma assessment, respiratory, hepatomegaly, splenomegaly, lymphadenopathy. Only clinically relevant findings will be reported in the electronic case report form (eCRF) as AEs.
6. **Weight/Height:** Height is required at baseline only. Weight is required at screening, prior to starting infusion in each cycle and at the EOT visit.
7. **Vital Signs:** Blood pressure, heart rate, temperature, and respiration rate required at screening, D1 and D15 (just before starting infusion, middle of infusion, end of infusion) in each cycle and as clinically indicated. The final measurements will be performed at the EOT visit.
8. **ePRO (electronic Patient-Reported Outcomes EORTC QLQ-C30 and MY20):** To be completed by the patient at the center prior to discussing with them their health/disease status, before the administration of study drug, and if possible prior to other study-related procedures on D1 of every cycle and at the EOT visit.
9. **ePRO (EQ-5D):** To be completed by the patient at the center prior to discussing with them their health/disease status, before the administration of study drug, and if possible prior to other study-related procedures on D1 Cycle 1 then D1 of every 3rd cycle starting Cycle 4 (ie, C4, C7, C10, etc.) and at the EOT visit.
10. **12-Lead ECG:** To be performed at screening and then as clinically indicated.
11. **Chest X-ray**: To be performed at screening and then as clinically indicated.
12. **Pregnancy Test:** Women of child bearing potential must have a negative serum pregnancy test result within 7 days prior to first IP administration and at the EOT visit.
13. Includes HBsAg, anti-HBsAb, and anti-HBcAb (total and IgM) and HBV DNA in case of positive anti-HBsAg (see Section 6.8). Once at any time if HBV status unknown before treatment started and to be repeated if clinically indicated for patients still under treatment at the time of amended protocol 14.
14. **Central Labs:** Refer to lab manual for sample collection and shipping information.

15. **Blood Chemistry:** To be done at screening, on D1 and D15 of every cycle prior to pre-medication and IP administration, at the EOT visit and as clinically indicated. Blood chemistry includes: SGOT (AST), SGPT (ALT), bilirubin (total and direct), alkaline phosphatase, lactate dehydrogenase (LDH), sodium, potassium, chloride, bicarbonate/carbon dioxide, calcium, corrected serum calcium, magnesium, phosphate, uric acid, blood urea nitrogen (BUN), serum creatinine and estimated creatinine clearance (Cockcroft-Gault Formula), glucose, albumin and total protein.
16. **Hematology:** To be done at screening, on D1 and D15 of every cycle prior to pre-medication and IP administration, at the EOT visit and as clinically indicated. Hematology includes: Hemoglobin, hematocrit, RBC, WBC with differential, MCV and platelet counts. If grade 4 neutropenia, assess ANC every 2-3 days until ANC ≥ 0.5 x 10^9/L and at least weekly thereafter until ANC ≥1.0 x 10^9/L.
17. Blood chemistry and hematology assessments are not required to be repeated prior to D1 Cycle 1 if the screening labs were performed within 3 days prior to first IP administration.
18. **Coagulation:** To be done at screening and then as clinically indicated. Coagulation includes: Prothombin time (PT) or international normalized ration (INR) and activated partial thromboplastin time (PTT).
19. **Urinalysis:** To be done at screening and then as clinically indicated. Urinalysis includes: blood, protein, glucose, pH, ketones, bilirubin, leucocytes, nitrates and specific gravity.
20. **Cytokines (TNF-α, IL-1-β, IL-6, IFN-γ):** Baseline sample to be drawn prior to first IP administration on D1 of Cycle 1.
21. **SAR650984 Safety labs:** Should a SAR650984 infusion reaction of Grade ≥2 occur, additional blood sampling during the AE is required for analysis of cytokines, markers of complement activation (C3, C4, CH50), serum tryptase and blood chemistry.
22. **Serum β2-microglobulin and Immunoglobulins (IgG, IgA, IgM, IgD and IgE):** To be performed at screening, prior to each IP administration on D1 of every cycle (starting C2) and at the EOT visit.
23. **Pharmacokinetics (PK):** Refer to Pharmacokinetics/Pharmacodynamics Flowchart (Section 1.8).
24. **ADA (Anti-Drug Antibodies):** To be performed on D1 of every cycle prior to each IP administration, D15 of Cycle 1, at the EOT visit and at 60 days (±5 days) after last IP administration. At 60 days, if patient is positive for ADA or the sample is inconclusive, additional ADA and PK samples are required every 30 days (±5 days) until sample is interpretable or negative.
25. **Bone marrow biopsy/aspirate for CD38 RD:** To be performed at screening.
26. **Bone marrow biopsy/aspirate for FISH:** To be performed at screening.
27. **Bone marrow biopsy/aspirate for genomics/CD38 mRNA:** To be performed at screening and at the EOT visit for patients with PD.
28. **Bone marrow biopsy/aspirate for immune phenotyping:** To be performed at screening.
29. **Bone marrow biopsy/aspirate for CD38 RO:** To be performed at screening, on D1 of Cycle 2 prior to IP administration and at the EOT visit. CD38 RO will only be performed on patients in Stage 1 enrolled at selected sites trained in the CD38 RO assay.
30. **Bone marrow biopsy/aspirate for MRD assessment:** To be performed at screening and time of CR confirmation.
31. **Blood sample for soluble CD38:** To be performed on D1 of Cycle 1 prior to IP administration, D1 of Cycle 3 prior to IP administration and at the EOT visit for patients with PD.
32. **Blood sample for immune phenotyping:** To be performed on D1 of Cycle 1 prior to IP administration, D1 of Cycle 3 prior to IP administration and at the EOT visit.
33. **Blood sample for immune genetic determinants:** To be performed on D1 of Cycle 1 prior to IP administration.
34. **Blood sample for optional pharmacogenetic sample**: To be collected on D1 of Cycle 1 prior to IP administration for patients enrolled in Stage 2 only.
35. **Disease assessment:** At screening, all lab assessments to be performed within 7 days prior to first IP administration and all radiologic assessments to be performed within 21 days prior to first IP administration. Local lab results for M-protein and sFLC to be used to determine eligibility criteria. Response is assessed on the basis of clinical and laboratory findings on D1 of every cycle (starting C2, prior to IP administration), whenever disease progression is suspected (eg, symptomatic deterioration) and at the EOT visit.
36. **Serum M-Protein:** To be performed at screening, D1 of every cycle (starting C2, prior to IP administration) and at the EOT visit. Screening sample should be split for local (to determine eligibility) and central (for baseline response) lab analysis.
37. **Serum free light chains (sFLC):** To be performed at screening, D1 of every cycle (starting C2, prior to IP administration) and at the EOT visit. Screening sample should be split for local (to determine eligibility) and central (for baseline response) lab analysis.
38. **Urine M-Protein (24-hr urine):** To be performed at screening, D1 of every cycle (starting C2, prior to IP administration) and at the EOT visit.
39. Disease assessments during follow-up period are only required for patients who have discontinued study treatment for reasons other than disease progression and have not yet started treatment with another anti-cancer therapy. Patients will be followed every month for progression during this period. Disease assessments required every month include evaluation of serum M-protein, serum free light chains and urine M-protein. A bone marrow, skeletal survey and CT/MRI are only required if clinically indicated to confirm response or progression according to IMWG criteria. Disease assessments not required once patient starts treatment with another anti-cancer therapy.
40. **Bone marrow (biopsy/aspiration):** To be performed at screening, to confirm a sCR, CR, disease progression, at the EOT visit and as clinically indicated.

41. **Skeletal survey (including skull, all long bones, pelvis and chest) and CT/MRI scan:** Skeletal survey and CT/MRI to be performed at screening on all patients. Repeat skeletal surveys are only required as clinically indicated or to confirm response or progression according to the IMWG criteria. If a plasmacytoma is present at study entry, repeat radiologic assessment (CT or MRI) is required at least every 2 cycles (C3, C5, C7 etc) to evaluate/confirm response. Imaging may be performed more frequently as clinically indicated to confirm response or progression according to IMWG criteria. All imaging will be sent to a central imaging lab.
42. **SAR650984 Administration:** At the start of each treatment cycle, the patient's weight will be determined.
43. **AE/SAE assessment**: All AEs, including events of new onset as well as worsening of baseline signs and symptoms are to be reported from the signing of the informed consent to 30 days following the last administration of study treatment. After the 30 day follow-up all ongoing related AEs and SAE (regardless of relationship) and new related non-serious AEs and SAEs are to be followed to resolution or stabilization. For patients who have a positive ADA sample, all IP-related AEs to be followed to resolution or stabilization.
44. **Survival status:** Patients will also be followed for survival every 3 months from the date of last IP administration until death. Every effort will be made to follow all patients. If survival follow-up is missed and is not obtained at the time of the scheduled interval, it should be obtained immediately. For subsequent survival follow-up, the patient should be contacted at the original scheduled survival follow-up interval. If the patient is unable to visit the clinical center, the follow-up may be done via phone from the Investigator or designee to the patient or the patient's caregiver or a family member.
45. Applicable when ADA where collected at 60 days after last IP administration.

1.14 STUDY FLOWCHART FOR PHASE 2, STAGE 1B

Evaluation[1]	Screening/ Baseline	Cycle 1[2]				Subsequent cycles [2, 3]		End of treatment (EOT)	Post treatment Follow-up period[38]	
	D-21 to D1	D1	D8	D15	D22	D1 (D1 Cn= D29 Cn-1)	D15	Up to 30 days after last IP admin	At 60 days (±5 days) after last IP admin[44]	Every 3 months (±14 days) after last IP admin
Informed Consent/Inclusion/Exclusion Criteria	X									
Patient randomization (Stage 1 only)/ registration	X									
Demography, Medical/Surgical and Disease History[4]	X									
Physical Examination[5]	X	X	X	X	X	X	X	X		
Weight/Height[6]	X	X (weight only)	X (weight only)	X (weight only)	X (weight only)	X (weight only)	X (weight only)	X (weight only)		
Vital Signs[7]	X	X	X	X	X	X	X	X		
Performance Status (Karnofsky in Stage 1)	X	X	X	X	X	X	X	X		
ePRO: QLQ-C30/ MY20[8]		X				X		X		
ePRO: EQ-5D[9]		X				Every 3 cycles (ie, C4, C7, etc)		X		
12-Lead ECG[10]	X									
Chest X-ray[11]	X									
Laboratory Assessments:										
Pregnancy Test[12]	X					X		X		
Hepatitis B virus (HBV) serology		X[13]								
Laboratory Assessment: central labs[14]										
Blood Chemistry[15]	X	X[17]	X	X	X	X	X	X		

Evaluation[1]	Screening/ Baseline	Cycle 1[2]				Subsequent cycles [2, 3]		End of treatment (EOT)	Post treatment Follow-up period[38]	
	D-21 to D1	D1	D8	D15	D22	D1 (D1 Cn= D29 Cn-1)	D15	Up to 30 days after last IP admin	At 60 days (±5 days) after last IP admin[44]	Every 3 months (±14 days) after last IP admin
Hematology[16]	X	X[17]	X	X	X	X	X	X		
Coagulation[18]	X									
Urinalysis[19]	X									
Cytokines[20]TNF-α, IL-1-β, IL-6, IFN-γ)		X								
SAR650984 Safety Labs[21]		X	X	X	X	X	X			
Serum β2-microglobulin[22]	X					X		X		
Immunoglobulins: IgG, IgA, IgM[22]	X					X		X		
PK[23]		X	X	X	X	X	X	X		
ADA[24]		X		X		X		X	X	
PD/Exploratory studies: Central Labs[14]										
Bone marrow for:CD38 RD[25]	X									
FISH[26]	X									
Genomics[27]	X							X		
Immune phenotyping(Bone marrow)[28]	X									
CD38 RO[29] (Stage 1,selected sites only)	X					C2 only		X		
MRD assessment[30]	X									
Blood for: Soluble CD38[31]		X				C3 only		X		

Evaluation[1]		Screening/ Baseline	Cycle 1[2]				Subsequent cycles [2, 3]		End of treatment (EOT)	Post treatment Follow-up period[38]	
		D-21 to D1	D1	D8	D15	D22	D1 (D1 Cn= D29 Cn-1)	D15	Up to 30 days after last IP admin	At 60 days (±5 days) after last IP admin[44]	Every 3 months (±14 days) after last IP admin
Immune phenotyping(Blood)[32]			X				C3 only		X		
Immune genetic determinants[33]			X								
Disease Assessment [34]											
Central Lab[14]	Serum M-Protein[35]	X					X		X		X[38]
	sFLC[36]	X					X		X		X[38]
Urine M-Protein (24-hr urine) [37]		X					X		X		X[38]
Bone Marrow for disease assessment[39]		X							X		X[38]
Skeletal survey, CT/MRI scan[40]		X							X		X[38]
SAR650984 Administration: STAGE 1b: 20 mg/kg QW for C1, then Q2W [41]			X	X	X	X	X	X			
AE/SAE Assessment[42]				Continuously throughout study period						X (related AE only, all SAEs)	
Prior/Concomitant Medication				Continuously throughout study period						X (related AE only, all SAEs)	
New anticancer therapy									X	X	X
Survival Status[43]									X	X	X

1. **Evaluation:** Assessments should be performed prior to IP administration unless otherwise indicated.
2. **Cycle:** A cycle is 28 days.
3. **Subsequent Cycles:** Patients on the Q4W schedule are only required to attend the D1 visit.
4. **Demography:** Includes age, gender and race. **Medical/Surgical History:** Includes relevant history of previous/associated pathologies, other than multiple myeloma; smoking status, respiratory function history will be checked. **Disease History:** Includes date of initial diagnosis, stage of the disease, previous anti-tumor therapy (drug names, reason for discontinuation, duration and response to), disease status at inclusion (refractory to last therapy, or relapse). In addition, results of additional procedures (such as karyotype, FISH, etc) performed as part of standard of care at the site to assess the current disease status may also be collected.
5. **Physical Examination:** Consists of examination of major body systems, including neurological, digestive exam, plasmacytoma assessment, respiratory, hepatomegaly, splenomegaly, lymphadenopathy. Only clinically relevant findings will be reported in the electronic case report form (eCRF) as AEs. Before cycle1 physical examination should be performed within 7 days before study treatment

administration and repeated within 3 days before administration if abnormal. For further cycles, assessment can be performed the day of the infusion (before infusion the day of study treatment administration or the day before)

6. **Weight/Height:** Height is required at baseline only. Weight is required at screening, prior to starting infusion in each cycle and at the EOT visit.
7. **Vital Signs:** Blood pressure, heart rate, temperature, and respiration rate. For Phase 1 Stage 1, vital signs are required at screening, before starting infusion, middle of infusion, end of infusion on D1, D8, D15 and D22 of Cycle 1 and D1 and D15 of each subsequent cycle. The final measurements will be performed at the EOT visit
8. **ePRO (electronic Patient-Reported Outcomes EORTC QLQ-C30 and MY20):** To be completed by the patient at the center prior to discussing with them their health/disease status, before the administration of study drug, and if possible prior to other study-related procedures on D1 of every cycle and at the EOT visit.
9. **ePRO (EQ-5D):** To be completed by the patient at the center prior to discussing with them their health/disease status, before the administration of study drug, and if possible prior to other study-related procedures on D1 Cycle 1 then D1 of every 3rd cycle starting Cycle 4 (ie, C4, C7, C10, etc) and at the EOT visit.
10. **12-Lead ECG:** To be performed at screening and then as clinically indicated.
11. **Chest X-ray**: To be performed at screening and then as clinically indicated.
12. **Pregnancy Test:** Women of child bearing potential must have a negative serum pregnancy test result within 7 days prior to first IP administration and at the EOT visit.
13. Includes HBsAg, anti-HBsAb, and anti-HBcAb (total and IgM) and HBV DNA in case of positive anti-HBsAg (see Section 6.8). Once at any time if HBV status unknown before treatment started and to be repeated if clinically indicated for patients still under treatment at the time of amended protocol 14.
14. **Central Labs:** Refer to lab manual for sample collection and shipping information. Samples for all the parameters listed in the flowchart will be sent to a central laboratory. When indicated in the flow chart, blood samples for hematology, biochemistry and disease assessment tests (see footnote 34) will be split for central and local laboratory evaluations. For efficacy laboratory tests (eg, serum and urine M-protein, sFLC) and for safety laboratory data during the study treatment period, local results will be used for the decision to treat or not the patient at the site level. For statistical analysis, central laboratory results will be used. All local laboratory tests done for safety or efficacy purposes will be reported in the e-CRF.
15. **Blood Chemistry:** To be done at screening, then prior to pre-medication and IP administration on D1, D8, D15 and D22 of Cycle 1 and on D1 and D15 of every subsequent cycle, at the EOT visit and as clinically indicated. Blood chemistry includes: SGOT (AST), SGPT (ALT), bilirubin (total and direct), alkaline phosphatase, lactate dehydrogenase (LDH), sodium, potassium, chloride, bicarbonate/carbon dioxide, ionized calcium and corrected serum calcium, magnesium, phosphate, uric acid, blood urea nitrogen (BUN), serum creatinine and estimated creatinine clearance (Cockcroft-Gault Formula), fasting glucose, albumin and total protein.
16. **Hematology:** To be done at screening, then prior to pre-medication and IP administration on D1, D8, D15 and D22 of Cycle 1 and D1 and D15 of every subsequent cycle, at the EOT visit and as clinically indicated. Hematology includes: Hemoglobin, hematocrit, RBC, WBC with differential, MCV and platelet counts. If grade 4 neutropenia, assess ANC every 2-3 days until ANC ≥ 0.5 x 10^9/L and at least weekly thereafter until ANC ≥1.0 x 10^9/L.
17. **Blood chemistry and hematology:** assessments are required to be performed within 7 days prior to first IP administration, to be repeated within 3 days of first dose if abnormal. Both local and central assessment will be performed, but local laboratory results for hematology and biochemistry will be used for safety management and the decision to treat or not the patient at C1D1 and each subsequent administration.
18. **Coagulation:** To be done at screening and then as clinically indicated. Coagulation includes: Prothombin time (PT) or international normalized ration (INR) and activated partial thromboplastin time (PTT).
19. **Urinalysis:** To be done at screening and then as clinically indicated. Urinalysis includes: blood, protein, glucose, pH, ketones, bilirubin, leucocytes, nitrates and specific gravity.
20. **Cytokines (TNF-α, IL-1-β, IL-4, IL-6, IFN-γ):** Baseline sample to be drawn prior to first IP administration on D1 of Cycle 1.
21. **SAR650984 Safety labs:** Should a SAR650984 infusion reaction of Grade ≥2 occur, additional blood sampling during the AE is required for analysis of cytokines, markers of complement activation (C3, C4, CH50), serum tryptase and markers of potential Tumor Lysis Syndrome (TLS) (uric acid, lactate dehydrogenase [LDH], BUN/creatinine, Potassium, Sodium and calcium)
22. **Serum β2-microglobulin and Immunoglobulins (IgG, IgA, IgM, IgD and IgE):** To be performed at screening, prior to each IP administration on D1 of every cycle (starting C2) and at the EOT visit.
23. **Pharmacokinetics (PK):** Refer to Pharmacokinetics/Pharmacodynamics Flowchart (Section 1.8).
24. **ADA (Anti-Drug Antibodies):** To be performed on D1 of every cycle prior to each IP administration, D15 of Cycle 1, at the EOT visit and at 60 days (±5 days) after last IP administration. At 60 days, if patient is positive for ADA or the sample is inconclusive, additional ADA and PK samples are required every 30 days (±5 days) until sample is interpretable or negative.
25. **Bone marrow biopsy/aspirate for CD38 RD:** To be performed at screening.
26. **Bone marrow biopsy/aspirate for FISH:** To be performed at screening.
27. **Bone marrow biopsy/aspirate for genomics/CD38 mRNA:** To be performed at screening and at the EOT visit in patients who have responded to the study treatment but subsequently develop progressive disease.

28. **Bone marrow biopsy/aspirate for immune phenotyping:** To be performed at screening.
29. **Bone marrow biopsy/aspirate for CD38 RO:** To be performed at screening, on D1 of Cycle 2 prior to IP administration and at the EOT visit. CD38 RO will only be performed on patients in Stage 1 enrolled at selected sites trained in the CD38 RO assay.
30. **Bone marrow biopsy/aspirate for MRD assessment:** To be performed at screening and at CR confirmation.
31. **Blood sample for soluble CD38:** to be performed on D1 of Cycle 1 prior to IP administration, D1 of Cycle 3 prior to IP administration and at the EOT visit for patients with PD.
32. **Blood sample for immune phenotyping:** To be performed on D1 of Cycle 1 prior to IP administration, D1 of Cycle 3 prior to IP administration and at the EOT visit.
33. **Blood sample for immune genetic determinants:** To be performed on D1 of Cycle 1 prior to IP administration.
34. **Disease assessment:** All lab assessments for M-protein and sFLC to be performed at screening (within 21 days prior to first IP administration) for eligibility and within 7 days prior to first IP administration and all radiologic and bone marrow assessments to be performed within 21 days prior to first IP administration.Response to study treatment is assessed on the basis of clinical and laboratory findings on D1 of every cycle (starting C2, prior to IP administration), whenever disease progression is suspected (eg, symptomatic deterioration) and at the EOT visit.
35. **Serum M-Protein:** To be performed at screening, D1 of every cycle and at the EOT visit. Samples should be split for local and central lab analysis. (for eligibility, treatment decision and analysis - see foot note 13 and 16).
36. **Serum free light chains (sFLC):** To be performed at screening, D1 of every cycle and at the EOT visit. Samples should be split for local and central lab analysis. For eligibity, treatment decision and analysis - see foot note 13 and 16.
37. **Urine M-Protein (24-hr urine):** to be performed at screening, D1 of every cycle and at the EOT visit.
38. **Disease assessments during follow-up period** are only required for patients who have discontinued study treatment for reasons other than disease progression and have not yet started treatment with another anti-cancer therapy. Patients will be followed every month for progression during this period. Disease assessments required every month include evaluation of serum M-protein, serum free light chains and urine M-protein. A bone marrow, skeletal survey and CT/MRI are only required if clinically indicated to confirm response or progression according to IMWG criteria. Disease assessments not required once patient starts treatment with another anti-cancer therapy
39. **Bone marrow (biopsy/aspiration):** To be performed at screening, to confirm a sCR, CR, (and to confirm disease progression in Phase 1 Stage 1 only), at the EOT visit and as clinically indicated.
40. **Skeletal survey (including skull, all long bones, pelvis and chest) and appropriate PET-CT/MRI scan** to be performed at screening on all patients. Repeated skeletal surveys are only required as clinically indicated or to assess/confirm response or progression according to the IMWG criteria. If a plasmacytoma is present at study entry, a repeat radiologic assessment (PET-CT or MRI) is required every 2 cycles (C3, C5, C7 etc) and when clinically indicated (eg, suspicion of progression, confirmation of CR)) and to confirm a response according to the IMWG criteria (Appendix E). All imaging will be sent to the central imaging lab. The same method should be used throughout the study.
41. **SAR650984 Administration:** At the start of each treatment cycle, the patient's weight will be determined.
42. **AE/SAE assessment**: All AEs, including events of new onset as well as worsening of baseline signs and symptoms are to be reported from the signing of the informed consent to 30 days following the last administration of study treatment. After the 30 day follow-up all ongoing related and new related non-serious AEs and new SAEs regardless of relationship are to be followed to resolution or stabilization. For patients who have a positive ADA sample, all IP-related AEs and all SAEs (regardless of relationship to study treatment) to be followed to resolution or stabilization until ADA sample is negative.
43. **Survival status:** Patients will also be followed for survival every 3 months from the date of last IP administration until death. Every effort will be made to follow all patients. If survival follow-up is missed and is not obtained at the time of the scheduled interval, it should be obtained immediately. For subsequent survival follow-up, the patient should be contacted at the original scheduled survival follow-up interval. If the patient is unable to visit the clinical center, the follow-up may be done via phone from the Investigator or designee to the patient or the patient's caregiver or a family member.
44. Applicable when ADA where collected at 60 days after last IP administration.

1.15 STUDY FLOWCHART FOR PHASE 2, STAGE 2

Evaluation[1]	Screening/ Baseline	Cycle 1[2]				Subsequent cycles[2]		End of treatment (EOT)	Post treatment Follow-up period[42]	
	D-21 to D1	D1	D8	D15	D22	D1(±3 days)	D15 (±3 days)	Up to 30 days after last IP admin	At 60 days (±5 days) after last IP admin[43]	Every 3 months (±14 days) after last IP admin
Informed Consent/Inclusion/Exclusion Criteria	X									
Patient randomization registration[3]	X									
Demography, Medical/Surgical and Disease History[4]	X									
Physical Examination[5]	X	X	X	X	X	X	X	X		
Weight/Height[6]	X	X (weight only)	X (weight only)	X (weight only)	X (weight only)	X (weight only)	X (weight only)	X (weight only)		
Vital Signs[7]	X	X	X	X	X	X	X	X		
ECOG Performance Status	X	X	X	X	X	X	X	X		
12-Lead ECG[8]	X									
Chest X-ray[9]	X									
Hepatitis B virus (HBV) serology		X[10]								
Local Laboratory Assessments										
Blood type, Complete blood phenotyping and antibody screening[11]	X					C2D1 only)				
Blood Chemistry[12]	X	X	X	X	X	X	X	X		
Hematology[13]	X	X	X	X	X	X	X	X		
Coagulation[14]	X									
Urinalysis[15]	X									
Pregnancy Test[16]	X					X		X	X	X
Markers of potential TLS[17]		If clinically indicated								

Evaluation[1]		Screening/ Baseline	Cycle 1[2]				Subsequent cycles[2]		End of treatment (EOT)	Post treatment Follow-up period[42]	
		D-21 to D1	D1	D8	D15	D22	D1(±3 days)	D15 (±3 days)	Up to 30 days after last IP admin	At 60 days (±5 days) after last IP admin[43]	Every 3 months (±14 days) after last IP admin
Central Laboratory Assessment											
Serum β2-microglobulin[18]		X									
PK[19]			X	X	X	X	X	X	X		
ADA[20]			X		X		X		X	X	
PD/Exploratory studies: Central Labs[21]											
FISH (Bone Marrow aspiration)[22]		X									
Genomics (Bone marrow)[23]		X							X		
Immune phenotyping (bone marrow aspirate)[24]		X									
MRD assessment (Bone marrow aspirate)[25]		X									
Immune phenotyping (Blood)[26]			X				C3 only		X		
Immune genetic determinants (Blood)[27]			X								
Adaptive immune response (humoral and cellular response) (Blood)[28]			X				C2, C4, C7,C10 only		X		
Adaptive immune response (including TCR repertoire) (Blood)[29]			X				C3 and C5				
Laboratory Disease Assessment[30]											
Central and Local Labs[29]	Serum M-Protein[31]	X	X				X		X		X[42]
	Urine M-Protein (24-hr urine)[32]	X	X				X		X		X[42]
	sFLC[33]	X	X				X		X		X[42]
	Immunoglobulins: IgG, IgA, IgM, IgD and IgE[34]	X	X				X		X		
Bone Marrow for disease assessment[35]		X							X		X[42]

Evaluation[1]	Screening/ Baseline	Cycle 1[2]				Subsequent cycles[2]		End of treatment (EOT)	Post treatment Follow-up period[42]	
	D-21 to D1	D1	D8	D15	D22	D1(±3 days)	D15 (±3 days)	Up to 30 days after last IP admin	At 60 days (±5 days) after last IP admin[43]	Every 3 months (±14 days) after last IP admin
Skeletal survey, low dose whole body CT scan[36]	X							X		X[42]
PET-CT/MRI for plasmacytoma[37]	X							X		X[42]
Treatment										
SAR650984 infusion[38]		X	X	X	X	X	X			
Dexamethasone (Isadex arm only)[39]		X	X	X	X	D1 and D8	D15 and D22			
AE/SAE Assessment[40]	Continuously throughout study period								X (related AE only, all SAEs)	
Prior/Concomitant Medication[41]	Continuously throughout study period								X (related AE only, all SAEs)	
New anticancer therapy								X	X[42]	X[42]
Survival Status[42]								X	X[42]	X[42]

1. **Evaluation:** Assessments should be performed prior to IP administration unless otherwise indicated.
2. **Cycle:** A cycle is 28 days.
3. **Randomization:** To take place once the consented patient has completed all the necessary screening procedures and is deemed eligible (based on myeloma specific results from central laboratory and hematology/biochemistry local laboratory results) for study entry by the investigator or designee. All eligible patients must be randomized by contacting IVRS. Efforts should be done to start treatment within 3 working days even if a maximum up to 5 working days can be allowed.
4. **Demography:** Includes age, gender and race. **Medical/Surgical History:** Includes relevant history of previous/associated pathologies, other than multiple myeloma; smoking status, respiratory function history will be checked. **Disease History:** Includes date of initial diagnosis, stage of the disease, type of disease at diagnosis and at study entry (heavy and light chain component), previous anti-tumor therapy (drug names, include stem cell transplant, start and end date, reason for discontinuation, duration and best response), disease status at inclusion (refractory to last therapy, or relapsed). In addition, results of additional procedures (such as karyotype, FISH, etc) performed as part of standard of care at the site to assess the current disease status may also be collected.
5. **Physical Examination:** To be performed at screening (≤7 days prior to randomization), prior to study treatment administration on Day 1, Day 8, Day 15 and Day 22 of Cycle 1, Day 1 and Day 15 of each subsequent cycles and at the EOT visit. Consists of examination of major body systems, including neurological, digestive exam, plasmacytoma assessment, respiratory, hepatomegaly, splenomegaly, lymphadenopathy. Only clinically relevant findings will be reported in the electronic case report form (eCRF) as AEs.
6. **Weight/Height:** Height is required at baseline only. Weight is required at screening, prior to starting infusion in each cycle and at the EOT visit.
7. **Vital Signs:** include Blood pressure, heart rate, temperature, and respiration rate To be performed at screening (≤7 days prior to randomization), before starting infusion, middle of infusion, end of infusion on Day 1, Day 8, Day 15 and Day 22 of Cycle 1, before starting infusion on Day 1 and Day 15 of each subsequent cycles and at the EOT visit..
8. **12-Lead ECG:** To be performed at screening and then as clinically indicated.

9. **Chest X-ray**: To be performed at screening and then as clinically indicated. Screening chest X-ray is for determination of eligibility only and not to be submitted as part of the independent radiographic review, unless clinically indicated as per the Investigator.
10. Includes HBsAg, anti-HBsAb, and anti-HBcAb (total and IgM) and HBV DNA in case of positive anti-HBsAg (see Section 6.8). Once at any time if HBV status unknown before treatment started and to be repeated if clinically indicated for patients still under treatment at the time of amended protocol 14.
11. **Blood type, Complete blood phenotyping and antibody screening**: Antibody screening test: Blood typing and complete blood phenotyping (C,c; E,e; Kell. Kidd; Duffy; S,s is recommended, if not available follow site's standard) if not already done, and antibody screening (Indirect Coombs Test, Indirect Antiglobulin Test [IAT]) to be obtained prior to Cycle 1 Day 1 study treatment administration . IAT to be repeated at Cycle 2 Day 1; if the test is not performed at this visit, it can be done at a next blood sampling. Results of IAT will be recorded in eCRF. Antibody screen information made before any blood transfusion and blood transfusions are to be recorded in the eCRF if performed during the study treatment. Transfusions are to be recorded in the eCRF. A blood type card will be provided to the patient indicating he (she) is receiving an anti-CD38 treatment and the site will notify its blood bank that the patient is receiving an anti-CD38 treatment (see Appendix K).
12. **Blood Chemistry:** To be done at screening, and to be repeated if it is not within 7 days prior to first IP administration, then prior to pre-medication and IP administration on D1, D8, D15 and D22 of Cycle 1 and on D1 and D15 of every subsequent cycle, at the EOT visit and as clinically indicated. Blood chemistry includes: SGOT (AST), SGPT (ALT), bilirubin (total and direct), alkaline phosphatase, lactate dehydrogenase (LDH), sodium, potassium, chloride, bicarbonate/carbon dioxide, ionized calcium and corrected serum calcium, magnesium, phosphate, uric acid, blood urea nitrogen (BUN), serum creatinine and estimated creatinine clearance (Cockcroft-Gault Formula), fasting glucose, albumin and total protein. The estimated Glomerular Filtration Rate will be calculated according the Modification of diet in Renal Disease (MDRD) equation (see Appendix B)
13. **Hematology:** To be done at screening, and to be repeated if it is not within 7 days prior to first IP administration, then prior to pre-medication and IP administration on D1, D8, D15 and D22 of Cycle 1 and D1 and D15 of every subsequent cycle, at the EOT visit and as clinically indicated. Hematology includes: Hemoglobin, hematocrit, RBC, WBC with differential, MCV and platelet counts. If grade 4 neutropenia, assess ANC every 2-3 days until ANC $\geq$ 0.5 x 10^9/L and at least weekly thereafter until ANC $\geq$1.0 x 10^9/L.
14. **Coagulation:** To be done at screening and then as clinically indicated. Coagulation includes: Prothrombin time (PT) or international normalized ration (INR) and activated partial thromboplastin time (PTT).
15. **Urinalysis:** To be done at screening and then as clinically indicated. Urinalysis includes: blood, protein, glucose, pH, ketones, bilirubin, leucocytes, nitrates and specific gravity.
16. **Pregnancy Test:** Women of child bearing potential must have a negative serum pregnancy test result within 7 days prior to first IP administration, serum or urine pregnancy test using a threshold of 20mIU/hCG sensitivity test will be done at D1 of each cycle, at the EOT visit and monthly for 5 months after the last administration of SAR650984.
17. **Tumor Lysis Syndrome (TLS) markers**: to be done in case of suspicion of TLS (uric acid, creatinine, potassium, phosphate, calcium and corrected calcium) and LDH.
18. **Serum β2-microglobulin**: To be performed at screening.
19. **Pharmacokinetics (PK):** Refer to Pharmacokinetics/Pharmacodynamics Flowchart (Section 1.8).
20. **ADA (Anti-Drug Antibodies):** Refer to Pharmacokinetics/Pharmacodynamics Flowchart (Section 1.8). ADA samples to be done up to Cycle 10 included. After Cycle 10, no ADA samples. If ADA + at Cycle 10, one additional sampling time for ADA evaluation should be collected 3 months later. For patients with less than 10 cycles will have ADA sample at EOT visit and if positive should have one additional sample in 3 months. For patients with less than 10 cycles at the cut-off date, both PK and ADA samples collection will be stopped from the cut-off date. If last ADA before cut-off date is positive, one additional sampling time for ADA evaluation should be collected 3 months later. No further ADA will be sampled, even if this 3-month sample is positive.
21. **Central Lab:** Refer to laboratory manual for sample collection and shipping information.
22. **Bone marrow aspirate for FISH:** To be performed at screening.
23. **Bone marrow aspirate for genomics/CD38 mRNA:** To be performed at screening
24. **Bone marrow aspirate for immune phenotyping:** To be performed at screening.
25. **Bone marrow aspirate for MRD assessment:** To be performed at screening and at CR confirmation.
26. **Blood sample for immune phenotyping:** To be performed on D1 of Cycle 1 prior to IP administration, D1 of Cycle 3 prior to IP administration and at the EOT visit.
27. **Blood sample for immune genetic determinants:** To be performed on D1 of Cycle 1 prior to IP administration.
28. **Blood sample for adaptive immune response (humoral and cellular response):** To be performed on D1 of Cycle 1 prior to IP administration, D1 of Cycle 2 prior to IP administration, D1 of Cycle 4 prior to IP administration, D1 of Cycle 7 prior to IP administration, D1 of Cycle 10 prior to IP administration and in disease progression patients at EOT to assess humoral and cellular immune responses.. Humoral response will be assessed in all patients. Cellular response will be assessed in patients at selected sites.
29. **Blood sample for adaptive immune response (TCR repertoire assessment):** To be performed on D1 of Cycle 1 prior to IP administration, D1 of Cycle 3 prior to IP administration and D1 of Cycle 5 prior to IP administration

30. **Laboratory Disease assessment:** (central and local laboratory for each planned time point): At screening, all lab assessments to be performed within 21 days prior to randomization. Eligibility will be assessed based on central laboratory results. Results for central serum and urine M-protein must be available before the patient may be randomized. In the absence of central lab results, sites may use local laboratory results for eligibility. Central laboratory results may not be available due to (but not limited to) the following reasons: samples were not able to be analyzed by central lab (for various reasons) or lab-dependent decisions needed for patient treatment had to be made before the availability of central lab results. All lab assessments to be performed **again** prior first study treatment administration on Cycle 1 Day 1 and response evaluation will be calculated compared to Cycle 1 Day 1 assessments. An additional serum sample will be collected at all time-points to evaluate the potential interference of isatuximab in the M protein assessment (central laboratory).
    Response will be assessed on the basis of clinical and laboratory findings on Day1 of every cycle, to confirm response and whenever disease progression is suspected. Investigator decision to continue study treatment or not will be taken based on local laboratory results. Efficacy analyses will be done according to IRC assessment, which will use central laboratory data.
    For patients who discontinue study treatment for reasons other than disease progression serum M-protein, urine M-protein (plus or minus sFLCs if needed to confirm CR) to be performed monthly (central and local laboratory) during the follow-up period until progression.
31. **Serum M-Protein immunoelectrophoresis (SPEP) and immunofixation:** To be performed at screening and again at Cycle 1 Day 1 prior to study treatment administration, then at Day 1 (-1 day) of every subsequent cycle prior to study treatment administration, and at the EOT visit. After C1D1 immunofixation to be done if SPEP is negative
32. **Urine M-Protein (24-hour urine) immunoelectrophoresis (UPEP) and immunofixation:** To be performed at screening, Cycle 1 Day 1 and Day 1 of every subsequent cycle and to be completed prior to study treatment administration and at the EOT visit. If urine M-protein is negative at baseline and Cycle 1 Day 1, this assessment is to be repeated every 3 cycles only (Cycle 4, Cycle 7, Cycle 10, etc) and to confirm CR on blood labs. After Cycle 1 Day 1, immunofixation to be done if UPEP is negative in patients whose disease is evaluable in urine.
33. **Serum free light chains (sFLC, quantification and ratio involved/non-involved):** To be performed at screening, Cycle 1 Day 1, and Day 1 of every subsequent cycle (central lab analysis to be triggered if M protein is undetectable and immunofixation negative).
34. **Immunoglobulins (IgG, IgA, IgM, IgD and IgE):** To be performed at screening, Cycle 1 Day 1 and Day 1 of every subsequent cycle prior to study treatment administration and at the EOT visit (IgD or E only if the heavy chain component of the disease is known to be E or D).
35. **Bone marrow for disease assessment (biopsy/aspiration):** To be performed at screening, to confirm a sCR, CR, (and to confirm disease progression), at the EOT visit and as clinically indicated.
36. **Bone disease assessment:** Skeletal survey (including skull, spine, all long bones, pelvis and chest) or low-dose whole-body CT scan at baseline (within 21 days prior to randomization), then once a year and anytime during the study if clinically indicated. The same modality (skeletal survey or low-dose whole-body CT) should be used throughout the study for each individual patient. All imaging to be sent for central review
37. **Extramedullary disease (plasmacytoma) assessment (including bone plasmacytoma):** If known extramedullary disease at baseline, PET-CT scan or MRI is to be done at baseline and to be repeated every 12 weeks (±1 week), and if clinically indicated. If suspected extramedullary disease (plasmacytoma) at baseline, PET-CT/MRI to be done at baseline to centrally confirm its presence and in case of confirmation to be repeated every 12 weeks (±1 week) and if clinically indicated. To be done in case of suspicion of progression or if clinically indicated in a patient with no previous positive image for extramedullary disease. The same modality (PET-CT or MRI) should be used throughout the study for each individual patient. All imaging to be sent for central review.
38. **SAR650984 Administration:** At the start of each treatment cycle, the patient's weight will be determined.
39. **Dexamethasone**: If the patient is in Isa/Dex arm of the study, starting Cycle 2, patient will take dexamethasone at home and record dosing information in the home diary.
40. **AE/SAE assessment**: All AEs, including events of new onset as well as worsening of baseline signs and symptoms are to be reported from the signing of the informed consent to 30 days following the last administration of study treatment. After the 30 day follow-up all ongoing related and new related non-serious AEs and new SAEs regardless of relationship are to be followed to resolution or stabilization. All IP-related AEs and all SAEs (regardless of relationship to study treatment) to be followed to resolution or stabilization.
41. **Prior medications** (which are not prior anti-myeloma therapy) administered within 21 days prior to randomization will be collected.
42. **Follow-up:** Patients who discontinue study treatment **due to PD**: follow-up visit will be done every 3 months from the date of last study treatment administration until death: AEs according to footnote 40 (at EOT and 60 days [±5 days] after last study treatment administration), second primary malignancy, further anti-myeloma therapy, and survival status will be collected. Every effort will be made to follow all patients. If survival follow-up is missed and is not obtained at the time of the scheduled interval, it should be retrieved immediately. For subsequent survival follow-up, the patient FU visit should be scheduled at the original scheduled survival follow-up interval. If the patient is unable to visit the clinical center, the follow-up may be done via phone from the Investigator or designee to the patient or the patient's caregiver or a family member, but this should be exception and any effort should be done to schedule follow-up visit at clinical center.
    Patients who discontinue the study treatment **without PD** will be followed every month (at EOT and 60 days [±5 days] after last study treatment administration), second primary malignancy, laboratory disease assessment (local and central laboratory), radiological assessment every 12 weeks (±1 week) in case of extramedullary disease (plasmacytoma) at baseline until confirmation of PD (even for patients who would initiate further anti-myeloma therapy without PD). After PD patient will be followed every 3 months as described just above.
43. Applicable when ADA where collected at 60 days after last IP administration.

1.16 STUDY PK FLOWCHART FOR PHASE 2 STAGE 2

Study Phase	Cycle 1							Cycle 2-3			Cycle 4				Subsequent Cycles		EOT	Follow-up	
Day	D1			D8	D15		D22	D1		D15	D1			D15	D1	D15	30 days after last study treatment admin (±5 days)	60 days after last study treatment admin (±5 days)[f]	Monthly (±5 days) for approximately 12 months
Time (decimal hours)	0h[a] Start Infusion	EOI[b]	EOI +1h[c]	0h[a] Start Infusion	0h[a] Start Infusion	EOI[b]	0h[a] Start Infusion	0h[a] Start Infusion	EOI[b]	0h[a] Start Infusion	0h[a] Start Infusion	EOI[b]	EOI +1h[c]	0h[a] Start Infusion	0h[a] Start Infusion	0h[a] Start Infusion			
Indicative clock time	8 am	12 pm	1 pm	8 am	8 am	12 pm	8 am	8 am	12 pm	8 am	8 am	12 pm	1 pm	8 am	8 am	8 am	8 am	8 am	8 am
Treatment																			
SAR650984 (IV infusion)	x------	----x		x	x------	----x	x	x------	----x	x	x------	----x		x	x	x			
Pharmacokinetics[d]																			
SAR650984	P00	P01	P02	P03	P04	P05	P06	P00	P01	P02	P00	P01	P02	P03	P00[a]	P01[a]	PF0[e]		
Pharmacodynamics[d]																			
ADA (Anti-Drug Antibody) (Immunogenicity)	P00[a]				P01[a]			P00[a]			P00[a]				P00[a]		PF0[e]	PF1[e]	PFx[e]

EOI = End of Infusion; ADA = Anti-Drug Antibody (immunogenicity); P = Plasma; Y = Bone Marrow;
* 1 Cycle = 28 days

a Sample collected just before IP administration. Sample to be collected up to and including C10. If a patient does not complete 10 cycles, EOT sample should be collected.

b Sample collected just before actual end of infusion (EOI). A time window of [-10 min; +10 min] around the actual end of infusion will be allowed for end of infusion sample.

c Sample collected 1 hour after the actual end of infusion

d Refer to laboratory manual for sample collection, processing and shipping

e For patients with less than 10 cycles should have ADA sample at EOT visit and if positive should have one additional sample in 3 months. For patients with less than 10 cycles at the cut-off date, both PK and ADA samples collection will be stopped from the cut-off date. If last ADA before cut-off date is positive, one additional sampling time for ADA evaluation should be collected 3 months later. No further ADA will be sampled, even if this 3-month sample is positive

f Applicable when ADA where collected at 60 days after last IP administration.

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3 LIST OF ABBREVIATIONS

ADCC	antibody-dependent cell mediated cytotoxicity
AE	adverse event
AESI	adverse event of special interest
ALT (SGPT)	alanine aminotransferase (or serum glutamate-pyruvate transferase)
ALL	acute lymphoblastic leukemia
AML	acute myelogenous/myeloid leukemia
AP	alkaline phosphatase
ASCT	autologous stem cell transplantation
AST (SGOT)	aspartate aminotransferase (or serum glutamate-oxaloacetate transferase)
AUC	area under the time concentration curve
BUN	blood urea nitrogen
C	cycle
CBR	clinical benefit rate
CDC	complement-dependent cytotoxicity
C_{eoi}	concentration at end of infusion
CHOP	cyclophosphamide/doxorubicin/vincristine/prednisone
CL	clearance
CLL	chronic lymphocytic leukemia
C_{max}	maximum concentration
CR	complete remission
CRF	case report form
CSF	colony-stimulating factor
CTCAE	Common Terminology Criteria for Adverse Events
CTLS	Clinical Tumor Lysis Syndrome
DRF	Discrepancy Resolution Form
D	day
DL	dose level
DLTs	dose limiting toxicities
DMC	Data Monitoring Committee
DOR	duration of response
ECOG	Eastern Cooperative Oncology Group
FcGR	Fc fragment of IgG receptor
FLC	free light chains
eGFR	estimated Glomerular Filtration Rate
G-CSF	granulocyte colony stimulating factor
GVHD	Graft versus host disease
GMCSF	Granulocyte-monocyte colony stimulating factor
H	Hour
HLA	human leukocyte antigen
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HRQOL	health-related quality of life

IEC	Independent Ethics Committee
IMiD	Immunomodulatory drug
INR	International Normalized Ratio
IP	investigational product
IRB	Institutional Review Board
IV	intravenous
IVRS	interactive voice response system
IWRS	interactive web response system
KIR	killer cell immunoglobulin–like receptor
LTLS	Laboratory Tumor Lysis Syndrome
LDH	lactate dehydrogenase
MAD	maximum administered dose
Min	minute
MR	minimal response
MRD	minimal residual disease
MM	Multiple myeloma
MTD	maximum tolerated dose
NCI	National Cancer Institute
NHL	Non-Hodgkin's lymphoma
NIMP	Non-investigational medicinal product
OS	overall survival
ORR	overall response rate
PD	pharmacodynamics
PFS	progression free survival
PK	pharmacokinetics
PO	per os
PR	partial remission
PTT	partial thromboplastin time
QW	every week
Q2W	every 2 weeks
Q4W	every 4 weeks
RD	receptor density
RO	receptor occupancy
SAE	serious adverse event
SD	selected dose
$t_{1/2}$	half-life
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
VGPR	very good partial response
WBC	white blood cell

4 INTRODUCTION AND RATIONALE

4.1 INTRODUCTION

SAR650984 is a naked humanized IgG1 monoclonal antibody directed against CD38, a receptor antigen expressed on hematopoietic cells. CD38 is involved in the homeostasis of the hematopoietic compartment as a modulator of cell survival and differentiation. It is both an enzyme, able to catalyze the formation of nucleotide metabolites involved in calcium signaling, and a receptor, which induces cell signaling through interaction with other receptors at the surface of the cell. CD38 antigen is expressed in a number of hematological malignancies from B-lymphocyte, T-lymphocyte and myeloid origin. The monoclonal antibody SAR650984 has 3 modes of action to kill target cells:

1. Antibody-dependent cell mediated cytotoxicity (ADCC).
2. Complement-dependent cytotoxicity (CDC).
3. Pro-apoptotic activity.

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

Moreover, of clinical importance is that CD38 was identified as a negative prognostic marker in some hematological malignancies. As a consequence, SAR650984 has the potential to treat a variety of hematological indications:

- Multiple myeloma (MM), with nearly all patients being $CD38^+$.
- Acute myeloid leukemia (AML) with 58% $CD38^+$ patients.
- Chronic lymphocytic leukemia (CLL) for which 20%-25% of $CD38^+$ patients have been associated with an aggressive prognosis.
- Non-Hodgkin's lymphoma (NHL) with 30%-80% $CD38^+$ patients depending on the subtype.
- Acute lymphocytic leukemia (ALL) with 90%-100% $CD38^+$ patients.

4.2 MULTIPLE MYELOMA (MM)

Multiple myeloma is a malignant plasma cell disease that is characterized by clonal proliferation of plasma cells in the bone marrow and the production of excessive amounts of a monoclonal immunoglobulin (usually of the IgG or IgA type or free urinary light chain [paraprotein, M-protein or M-component]) (6). It is a disease predominantly associated with advancing age with more than 80% of patients aged 60 years or older and a median age of onset around 68 years; only about 2% of cases are diagnosed in individuals under the age of 40 (8).

Patients with MM can experience bone pain, bone fractures, fatigue, anaemia, infections, hypercalcaemia and kidney problems (9). The disease course for multiple myeloma varies with

the aggressiveness of the disease and related prognostic factors. Median survival is approximately 3 years; however, some patients can live longer than 10 years (10). Treatment options and survival are based on the patient's disease status. Patients presenting with symptomatic active disease in good physical health will receive initial therapy with autologous stem cell transplantation (ASCT). To achieve cytoreduction of the disease before collecting stem cells, induction chemotherapy is administered. Induction treatment regimens include dexamethasone alone, thalidomide plus dexamethasone, and vincristine, Adriamycin® (doxorubicin), and dexamethasone (VAD; or modifications to this regimen); however, the later 2 regimens are associated with higher toxicity (9). Newer treatments with Velcade® (bortezomib) alone, bortezomib combinations, and Revlimid® (lenalidomide) plus dexamethasone show some promise as induction therapy, and these agent demonstrate higher response rates and lower toxicity (10, 11).

The current aim of MM therapy is to control disease as effectively as possible, to maximize quality of life and to prolong survival. Treatments for relapsed and/or refractory disease are often referred to as salvage therapy. The initial chemotherapy regimen (eg, melphalan plus prednisone or VAD) can be reinstituted for relapsed/refractory disease if the disease relapsed more than 6 months after the last therapy ended. The patients for whom stem cells were cryopreserved early in the disease course, and who are transplant candidates, can benefit from ASCT as salvage therapy (10, 11). Subsequent treatment decisions are based on whether the patient experiences an indolent or aggressive relapse. Patients with relapsed disease may continue taking 1 drug or treatment regimen as maintenance therapy until relapse or toxicity. In general, MM patients will receive an average of 4 to 8 different regimens during their lifespan utilizing agents such as proteasome inhibitors (eg, bortezomib and carfilzomib) and immune modulatory agents (eg, lenalidomide and pomalidomide). However, once a patient becomes refractory to those agents, survival is limited and newer treatment options are needed to treat patients after they have failed therapy transplant, chemotherapy, proteasome inhibitors, and immune modulatory agents. Despite the dramatic improvement in patient outcomes, MM remains an incurable disease. Thus, the treatment of patients who have received at least three different lines of therapy including a proteasome inhibitor and an immunomodulatory agent or who are double refractory to a proteasome inhibitor and an IMiD remains an unmet medical need.

Based on the fact that CD38 is the most strongly and uniformly expressed antigen identified on the malignant clonal populations of myeloma cells compared with its pattern of expression on normal cells suggests that this antigen may be a useful target for the in vivo depletion of tumor cells while sparing normal cells (12).

4.3 ACUTE MYELOGENOUS LEUKEMIA (AML)

Acute myelogenous leukaemia (AML) is considered to be one of the most common types of adult acute leukemias worldwide. There are approximately 12 000 new cases annually in the US and 10,000 in Europe. AML is a stem cell disorders characterized by uncontrolled proliferation and accumulation of non-functional clonal hematopoietic cells called myeloblasts and impaired production of normal hematopoiesis leading to neutropenia, thrombocytopenia, anemia and/or hyperleucocytosis. Occasionally, blasts may invade different tissues, including the liver, spleen, skin, lymph nodes, bone, gingival and central nervous system. Despite diagnostic and therapeutic improvements over the last decade, the outcome of patients with AML remains poor, with a 5-year survival rate of 20%-30% for patients <60 years and less than 10% for older patients (13, 14).

Much of the search for new agents focuses on tumor targeted therapies, which may not only maximize the antitumor efficacy, but also significantly reduce the toxicity on normal tissues. Gemtuzumab ozogamicin (Mylotarg®), is a humanized anti-CD33 monoclonal antibody conjugated to a cytotoxic antibiotic, calicheamycin. Mylotarg obtained an accelerated approval from the FDA as single agent therapy for patients with CD33 positive AML in first relapse who are 60 years of age or older and who are not considered candidates for other cytotoxic chemotherapy. In these patients Mylotarg single agent induced 26% responses (CR + CRp) (15). The main toxicities were severe, long myelosupression (neutropenia, thrombocytopenia), hypersensitivity reactions and hepatotoxicity. Mylotarg is not approved in Europe.

4.4 CHRONIC LYMPHOCYTIC LEUKEMIA (CLL)

Chronic Lymphocytic Leukemia (CLL) is the most common leukemia in the Unites States (US) and European Union (EU) accounting for 25% of adult leukemias. Over two-thirds of patients with CLL are older than 60 years and the incidence steadily increases in individuals over 50 years of age. The disease has a very diverse natural history and patients with lymphocytosis have a median survival greater than 10 years whereas patients with evidence of bone marrow failure manifested by anemia or thrombocytopenia have a median survival of 2 years or less (16).

Treatment is commonly reserved for symptomatic patients, since no treatment has yet shown to be curative nor is there objective evidence that a specific treatment prolongs survival. The NCI sponsored CLL Working Group proposed the following indications for initiating treatment: 1) weight loss of more than 10% over the preceding 6 months; 2) extreme fatigue attributable to progressive disease; 3) fever or night sweats without evidence of infection; 4) worsening anemia (Rai Stage III) or thrombocytopenia (Rai Stage IV); 5) massive lymphadenopathy (>10 cm) or rapidly progressive lymphocytosis (lymphocyte doubling time <6 months); or 6) prolymphocytic or Richter's transformation (17)

Three purine analogues are currently used in CLL: fludarabine, pentostatin, and cladribine. Fludarabine remains by far the best-studied compound of the three in CLL. Fludarabine monotherapy produces superior overall response (OR) rates compared with other treatment regimens containing alkylating agents or corticosteroids. (18, 19, 20). In three Phase 3 studies in treatment-naïve CLL patients, fludarabine induced more remissions and more complete

remissions (CR) (7%-40%) than other conventional chemotherapies, such as CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone), CAP (cyclophosphamide, doxorubicin, prednisone), or chlorambucil. Despite the superior efficacy of fludarabine, only a trend for longer overall survival could be observed, and this trend was not statistically significant. (20, 21, 22).

Rituximab, an anti-CD20 monoclonal antibody, as a single agent is less active in CLL than in follicular lymphoma, unless very high doses are used. (23, 24, 25). Combinations of rituximab with chemotherapy have proven to be very efficacious therapies for CLL. There is preclinical evidence for synergy between rituximab and fludarabine (25). The majority of rituximab combination studies in CLL have focused on combinations with fludarabine or fludarabine-based regimens.

Alemtuzumab is a recombinant, fully humanized, monoclonal antibody against the CD52 antigen.

Monotherapy with alemtuzumab has produced response rates of 33% to 53%, with a median duration of response ranging from 8.7 to 15.4 months, in patients with advanced CLL who were previously treated with alkylating agents and had failed or relapsed after second-line fludarabinetherapy. (26, 27, 28). In addition, alemtuzumab has proven effective even in patients with poor prognostic factors, including high-risk genetic markers such as deletions of chromosome 11 or 17 and p53 mutations. (29, 30).

Expression of CD38 has been reported to be important in predicting prognosis in B-cell chronic lymphocytic leukemia (B-CLL). B-CLL patients with high levels of CD38 expression, defined as greater than or equal to 30% of neoplastic lymphocytes expressing CD38, had a significantly poorer OS than those with low levels of CD38 expression (31). An antibody that target the malignant CD38 + cells in B-CLL patient might offer a therapeutic benefit in this high risk population.

4.5 NON- HODGKIN'S LYMPHOMA (NHL)

Non-Hodgkin's lymphoma is the 10th most frequent cancer worldwide (32). Approximately 301 000 new cases diagnosed each year, and approximately 171 800 deaths each year due to non-Hodgkin's lymphoma are reported worldwide. Diffuse Large B-cell Lymphoman (DLBCL) represents almost 30% of all cases of non-Hodgkin's lymphoma (NHL). Follicular lymphoma (FL) is the second most frequent lymphoma subtype worldwide, representing approximately 15%-20% of all NHL cases. The cyclophosphamide/doxorubicin/vincristine/prednisone (CHOP) regimen is associated with durable remissions in approximately 35% of patients with DLBCL (33) and improved clinical outcome in the majority of patients with FL (34). The addition of rituximab to the CHOP regimen (R-CHOP) was associated with superior overall survival compared to CHOP alone in randomized clinical trials of young and elderly patients with DLBCL (35, 36, 37) and in another randomized clinical trial in patients with advanced-stage FL (38).

In the Feugier et al study (36) where long term results are reported, the median event free survival was 3.8 years versus 1.1 years in elderly patients with B-cell lymphoma treated with R-CHOP compared to CHOP alone, and the 5 year overall survival (OS) was 58% versus 45%. However, even if recent treatments increase durable remission and improved OS survival, novel agents and therapeutic strategies are still needed for the treatment of this disease.

4.6 ACUTE LYMPHOBLASTIC LEUKEMIA (ALL)

ALL is a heterogeneous malignant neoplasm of the lymphoid precursors with distinct morphologic, cytogenetics, and molecular entities, some of which have important clinical implication. ALL represents less than 1% of adult cancers, but it represents 25% of all childhood cancers (39).

Decisions regarding treatment modalities for adults with ALL have become increasingly dependent upon patient and disease-specific characteristics. Immunophenotype, cytogenetics, and molecular evaluation are needed for predicting prognosis and for selecting the best therapeutic choice for patients (40)

Historically, the standard induction treatment of adult ALL generally includes a glucocorticoid, vincristine, and an anthracycline. However, progress has been made in moving towards more age-specific and biologically driven treatment. Agents directed at gene mutations, signal transduction pathways, and specific cell surface antigens are providing the future platform for new treatment modalities based on specificity versus intensity. While 3-year survival estimates over the last decade for all adults with ALL range from 30% to 40%, recent studies using age and biologically risk adapted approaches suggest that significant improvements in survival may be achieved. The use of kinase inhibitors such as imatinib in Philadelphia + ALL is one such example of leukemia-adapted therapy (39).

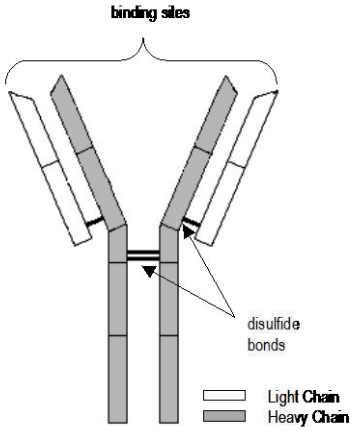
MAb therapy also represents a promising treatment approach in ALL. The target specificity, different mechanisms of action and side effect profile compared to chemotherapy make mAbs an attractive adjunct to standard chemotherapy. ALL blast cells express a variety of specific antigens such as CD20, CD19, CD22, CD33, CD52 (41) and CD38 (42) that may serve as targets for treatment with mAbs. Rituximab, a CD20 specific mAb, has been successfully integrated in therapy of mature B-ALL with survival rates increased above 80% with the combination of short intensive chemotherapy and rituximab. The combination of hyper-CVAD regimen with rituximab in B-precursor ALL was feasible, and a favorable outcome of CD20+ ALL was reported. Studies with alemtuzumab, a CD52 specific mAb, are also ongoing in a number of different settings (41).

4.7 COMPOUND DESCRIPTION

SAR650984 is the humanized version of mu38SB19, a murine anti-CD38 antibody, raised by immunizing mice with a murine pre-B cell overexpressing cell surface human CD38. The humanized version bears the constant regions of human IgG1 and displays the same affinity for CD38 as the murine version. SAR650984 selectively binds to human CD38 with an affinity of 2×10^{-10} M.

4.7.1 Chemical name and structure

SAR650984 is a naked humanized IgG1 derived-monoclonal antibody (mAb) binding selectively the human CD38 membrane protein. SAR650984 is expressed in Chinese Hamster Ovarian (CHO) cell line.

INN:	isatuximab
CAS registry number	Not available
Laboratory code number:	SAR650984
Synonymous names	hu38SB19
Schematic representation:	
Molecular mass:	SAR650984 is a humanized IgG1 mAb with a molecular weight of approximately 150 kDa (glycosylated form). The SAR650984 protein structure is comprised of two kappa light chains each with molecular weight of approximately 23 kDa and two IgG1 heavy chains each with a molecular weight of approximately 49 kDa (deglycosylated form) linked through disulfide bridges. Each light chain consists of 215 amino acid residues and each heavy chain consists of 451 amino acid residues.

4.7.2 Dosage form, route of administration, and dosing regimen (frequency and duration)

SAR650984 will be supplied for parenteral administration as a sterile, non-pyrogenic, injectable, solution for infusion. A refrigerated (2°C-8°C) 5 mg/mL solution (C1P1F1) for infusion is intended for Phase 1 and 2 clinical studies. A new refrigerated (2°C-8°C) 20 mg/mL solution (C1P2F2) for infusion was first introduced in TED14154 study and will be used in the Phase 2 Stage 2 of TED10893 study (Section 8.1.1), and may be for patients who are still on study treatment after cutoff date of Phase 2 Stage 1.

4.7.3 Pharmacology

SAR650984 targets CD38, an antigen expressed in hematological malignancies and represents a new treatment entity displaying, in vitro, three key biological properties: ADCC, CDC and apoptosis. SAR650984 demonstrated in vivo antitumor activity as a single agent and in combination with reference treatments on several CD38-positive tumor models. In addition, SAR650984 demonstrated antitumor activity against primary patient cells ex vivo supporting its clinical evaluation in CD38+ multiple myeloma, non-Hodgkin's lymphoma and leukemia patients.

4.7.4 Toxicology

Several techniques and in vitro assays were used to identify a relevant animal species. CD38 sequence analysis between the human and other animal species showed that only the CD38 sequence from Chimpanzee, Rhesus monkey, and Cynomolgus monkey displayed a percentage of identity with human CD38 sequence >92%. As a result, SAR650984 binding affinity was evaluated in 4 monkey species (baboon, Cynomolgus monkey, Rhesus and African green monkey) but demonstrated no binding. Moreover, IHC cross-reactivity studies conducted with SAR650984 on tissues from 13 animal species (mouse, rat, hamster, Guinea pig, rabbit, ferret, minipig, dog, Cynomolgus monkey, Rhesus monkey, marmoset, baboon and Chimpanzee) identified the Chimpanzee as the only species with a similar SAR650984 tissue binding pattern as observed in human tissues. However, due to ethical considerations, traditional toxicology studies cannot be conducted in the Chimpanzee.

Two monkey surrogate antibodies (ch38SB25 and chOKT10) were generated and investigated to potentially collect nonclinical safety information. Both surrogate antibodies bound Cynomolgus monkey CD38+ cells with affinities similar to that of SAR650984 to human CD38+ cells. However, ch38SB25 and chOKT10 demonstrated differences in tissue cross-reactivity (namely the vascular staining observed in multiple tissues of monkeys and not in human) and absence of pro-apoptotic activity in human tumor cell lines. As a result, toxicology findings in preclinical studies with these antibodies would be of very limited predictive value for safety evaluation of SAR650984 in human.

In vitro assays using SAR650984 on normal human PBMCs did not demonstrate any significant effects on cytokine release, cellular activation, or depletion (despite some induction of apoptosis in purified NK cells in 2 of 3 donors tested). However, it cannot be excluded that in a clinical setting SAR650984 could modulate cell survival, differentiation of both lymphoid and myeloid cells, and cytokine release in cancer patients. Therefore, appropriate monitoring of patients will be conducted in the clinical study.

In conclusion, given the absence of a relevant animal species for in vivo toxicity studies and the absence of a true surrogate antibody with complete pharmacological activity, single and/or repeated-dose in vivo toxicology studies in primates with SAR650984 or with the available surrogate antibodies were not expected to provide the necessary information to determine a safe starting dose for this FIM study nor to identify potential target organs for toxicity in human. Therefore, the Sponsor has selected the starting dose of 0.0001 mg/kg for the FIM study in patients based on the Minimal Anticipated Biological Effect Level (MABEL) approach using 10% of the theoretical occupancy (on normal B and T lymphocytes) (see Section 4.7.3).

4.7.5 Metabolism and pharmacokinetics in animal

Not applicable and not determined.

4.7.6 Clinical experience

Please refer to the Investigator Brochure for details on the clinical experience to date.

4.8 RATIONALE

4.8.1 Study rationale

The CD38 antigen is expressed in a number of hematological malignancies of B-lymphocyte, T-lymphocyte and myeloid origin. Moreover, CD38 was identified as a negative prognostic marker of clinical importance in some hematological malignancies. As a consequence, monoclonal antibodies to CD38 have the potential to treat a variety of hematological indications including MM, B-cell NHL, CLL, AML and B-cell ALL.

SAR650984 has shown promising activity in MM patients in the Phase 1 dose escalation part of this study. Therefore, the study has been amended to include a Phase 2 part in order to further evaluate the efficacy and safety of SAR650984 as a single agent or in combination with dexamethasone in patients with relapsed or relapsed/refractory multiple myeloma.

4.8.2 Design rationale

Phase 1

Modified methodology published by Eisenhauer (43) has been chosen for selecting the number of patients by dose level (DL) and the dose escalation plan, according to the dose limiting toxicity(ies) (DLTs) observed.

The rationale of the dose escalation scheme is to rapidly increase the dose when no related adverse events (AEs) are reported in order to minimize the number of patients treated at sub-therapeutic doses. The general approach is to begin with an accelerated dose escalation phase when no treatment-emergent, drug-related non-hematological AEs (≥ Grade 1 AE) including fever are observed (with exception of Grade 1 nausea, vomiting, diarrhea, fatigue, asthenia, anorexia, anemia, alkaline phosphatase (AP) elevation, or local [injection site] reactions. In the event of a Grade 1 or higher treatment-emergent, IP related non-hematological AE including fever, the cohort will be expanded to 3 patients and a semi-log escalation will be used between 2 DLs for all future doses. All successive cohorts will then include 3 patients per DL. A Grade 2 or higher treatment-emergent, IP related nausea, vomiting, diarrhea, fatigue, asthenia, anorexia, anemia, AP elevation and local (injection site) reactions will result in an expansion of that cohort to 3 patients and all successive cohorts will include 3 patients and to switch to semi-log dose escalation. In the event that a potential DLT (as defined in Section 9.1.1) is reported during this accelerated dose escalation scheme, up to 6 patients will be assessed at this DL. If less than 2 out of 6 patients experienced an IP related DLT at this DL, the dose escalation will proceed with 3 patients per DL

and with semi-log dose escalation. When a DLT considered related to IP is observed in a patient, all patients who are still receiving drug whatever the DL shall be monitored for evidence of a similar sub-toxic effect in the same organ system.

As a principle, in this study, any AE will be considered as potentially IP related in absence of clear evidence to the contrary. The causal relationship of potential DLTs or other AEs will be reviewed by the Study Committee (for the Phase 1 part) and by the Data Monitoring Committee (for the Phase 2 part), as well as by competent authorities, as appropriate.

During the Phase 1 part, patients who begin treatment at the same DL will be considered a cohort.

As part of Amendment 6, additional cohorts have been included to the Phase 1 part to evaluate additional dose levels and administration schedules. PK analysis suggests a nonlinear receptor mediated clearance at lower doses and a relatively short half-life between 8 to 18 days at the 5 mg/kg dose Q2W. Given this data, increasing the dosing frequency to every week (QW) to attain a steady state concentration closer to the mouse tumor growth inhibition model effective concentration of 129 ug/mL is desirable. In addition, increasing the dose to 20 mg/kg Q2W may also achieve the desired steady state concentration. A 20 mg/kg loading dose may hasten the time to reach this desired concentration earlier rather than waiting for steady state with the 10 mg/kg QW. Of note, based on updated pharmacokinetic characterization of isatuximab in 2019, the plasma half-life has been re-estimated to 28 days.

In order to establish a recommended Phase 2 dose (RP2D) and schedule for further studies, Cohorts 11 (10 mg/kg every week) and 12 (20 mg/kg every 2 weeks) will be evaluated in parallel since they have a similar monthly dose intensity. These cohorts will accrue 3 patients each. An additional 3 patients will be accrued to each of these cohorts if less than 2 out of the initial 3 patients experience an IP related DLT. An additional 6 patients (up to 12 patients per cohort) may be accrued if required, in order to establish a recommended dose and schedule. Cohorts 11 (10 mg/kg every week) and 12 (20 mg/kg every 2 weeks) will be restricted to patients with relapsed/refractory MM who have failed prior therapy with an immunomodulatory drug (IMiD) and proteasome inhibitor (as defined in Section 7.2).

After completion of Cohort 12, in order to further define the recommended dose for future studies, two expansion cohorts are planned to assess the safety and preliminary disease response in specific MM populations (1) standard risk MM patients and (2) high risk MM patients (optional, as defined in Section 7.2). Each expansion cohort will accrue up to 18 patients each. In November 2013, the dose selected for the expansion cohorts was 10 mg/kg based on the analysis of safety, efficacy and PK data of Cohorts 1-12.

In June 2014, PK analysis of patients enrolled in the standard risk expansion cohort showed that some patients treated at 10 mg/kg Q2W presented biphasic elimination profiles. These data suggest that SAR650984 exhibits nonlinear pharmacokinetics with target-mediated clearance dominating the elimination phase at low concentrations (10-20 µg/mL), which leads to low exposure and high interpatient variability at this dose and schedule. In order to overcome the mediated clearance disposition and reach the desired higher concentration, 20 mg/kg QW will be evaluated in Cohort 13. Cohort 13 was opened for enrollment following approved by the Study Committee and before the implementation of Amendment 10.

Phase 2

As part of Protocol Amendment 8, the Phase 2 part of the study was added to evaluate the efficacy and safety of SAR650984 as a single agent in patients with relapsed or relapsed/refractory MM.

Stage 1

- Stage 1a:

  The Stage 1a part is to commence after the Phase 1 standard risk expansion cohort has completed enrollment.

  Since responses were seen at different dose levels starting from 1 mg/kg Q2W (Section 4.8.4) Stage 1a was designed to further evaluate the activity and safety of SAR650984 at the following dose/schedules:

  - Arm 1: 3 mg/kg Q2W (every 2 weeks (Day 1 and 15 of each 28-day cycle)).
  - Arm 2: 10 mg/kg Q2W (Day 1 and 15 of each 28-day cycle).
  - Arm 3: 10 mg/kg Q2W for 2 cycles (Day 1 and 15 of Cycle 1 and 2), then 10 mg/kg Q4W (every 4 weeks (Day 1 of each 28-day cycle)).

- Stage 1b:

  As part of Amendment 10, Stage 1b (Arm 4) has been included to evaluate a 20 mg/kg QW for 1 cycle, followed by 20 mg/kg Q2W. This arm has been added following the analysis of the PK data of patients in the standard risk cohort (see Phase 1 section above). Since Stage 1b has been added after enrollment has started into Stage 1a, enrollment in Stage 1b will commence after completion of Cohort 13 (6 evaluable patients followed for safety for at least 4 weeks) and enrollment into Stage 1a is completed, whichever is last.

  - Arm 4[2]: 20 mg/kg QW for 1 cycle (Day 1, 8, 15 and 22 of Cycle 1), then 20 mg/kg Q2W (Day 1 and 15 of each 28-day cycle)

Stage 2

Phase 2 Stage 2 will further evaluate the activity and safety of SAR650984 at the dose and schedule selected from Stage 1a and 1b, alone or in combination with dexamethasone. Although the objective of the study is not to compare the efficacy and safety of the ISA and ISAdex arms, patients in Stage 2 will be randomly assigned in 1 of the 2 arms using an Interactive Voice Response System (IVRS) to not introduce any bias in the enrollment of the patients in the 2 arms.

[2] The planned dose for arm 4 is 20 mg/kg, however during the Phase 1, if 20 mg/kg QW is the MAD then a lower dose (such as 15 mg/kg QW) would be evaluated in this arm.

4.8.3 Phase 1 dose, regimen, and treatment duration rationale

In this FIM study, the starting dose of 0.0001 mg/kg was selected based on 10% of the theoretical CD38 receptor occupancy on normal B and T lymphocytes as part of MABEL (The "Minimal Anticipated Biological Effect Level") approach.

- The calculation of MABEL is an integrated approach (EMEA guidance http://www.emea.europa.eu/pdfs/human/swp/2836707enfin.pdf) using all in vitro and in vivo information available from pharmacokinetic/pharmacodynamic (PK/PD) data.

SAR650984 activity is linked to 3 mechanisms of action: ADCC, CDC and apoptosis activities. Therefore, each component of SAR650984 activity as well as receptor occupancy was studied to evaluate individual MABEL, using different test systems. In the in vitro models, the MABEL was defined as the effective concentrations that induced 20% of the maximal effect (EC_{20} values). In the in vivo model, the MABEL was defined by the trough concentration at steady-state at the lowest active dose.

The MABEL based on the concentration observed on in vitro most sensitive model (eg, ADCC) leads to an extremely low dose in patients (0.000005 mg/kg) and <0.5% of receptor occupancy.

Considering that:

- There was no cytokine release from PBMC up to 10 µg/mL (equivalent to 0.20 mg/kg in humans) of SAR650984 concentration, which is the concentration corresponding to in vivo MABEL.
- There was no effect of SAR650984 on PBMC proliferation up to 10 µg/mL (0.20 mg/kg).
- The high in vitro ADCC activity of SAR650984 might not be representative of the physiological condition, since normal serum levels of IgG1 have been shown to compete for access of immune effector cells.
- The monitoring of CD38 receptor occupancy on normal cells can be used as a tool for safety monitoring during dose escalation.

The recommended starting dose is based on 10% of the predicted CD38 receptor occupancy measured from normal cells. This dose is 2000 fold less than the predicted human dose of 0.2 mg/kg (lowest in vivo active dose based on animal model) demonstrating no significant in vitro effect on normal PBMC cytokine production, apoptosis and proliferation.

Further dose escalation in the clinic may be guided by higher levels of receptor occupancy.

4.8.4 Phase 2 dose selection rationale

A total of 45 patients were treated with SAR650984 in the Phase 1 dose escalation phase (Cohorts 1-12) of the study. SAR650984 has shown a favorable safety profile in hematological malignancies. Evaluation of PK parameters using both non-compartmental and individual modeling approaches show that there is a high variability of exposure and CL within a given dose level and SAR650984 has a non linear PK behavior with dose increases. CL was demonstrated to

decrease as doses were increased with lowest change occurring between 10 and 20 mg/kg (a 5% decrease). Evaluation of CD38 RO reached the Emax for the highest dose levels (10 mg/kg Q2W, 10 mg/kg QW and 20 mg/kg Q2W). Please refer to the SAR650984 Investigator Brochure for additional details of the safety, PK and PD observed in the Phase 1 part of the study.

At the time of Amendment 8, analysis of the safety, PK and CD38 RO data demonstrated there was no significant difference between these dose levels, therefore 10 mg/kg Q2W was selected as the RP2D for the Phase 1 expansion cohorts. Clinical activity has been observed at dose levels ≥1 mg/kg Q2W in the Phase 1 part of the study.

Stage 1a (Amendment 8):

In order to further confirm the dose and schedule for future studies, Stage 1a of the Phase 2 part of the study will evaluate the 10 mg/kg Q2W alongside 3 mg/kg. The dose levels were selected based on PK and RO analyses which demonstrated high variability at the 3 mg/kg level but more constant clearance and RO at the 10 mg/kg level. In addition, a schedule of 10 mg/kg Q2W for 8 weeks (2 cycles) followed by 10 mg/kg every 4 weeks (Q4W) will also be evaluated. This alternative schedule was selected based on PK simulations which demonstrated that SAR650984 trough concentrations would be above 129 µg/mL (the concentration required to maintain for tumor eradiation in mice) after administering 10 mg/kg Q2W for 8 weeks. Thereafter, an administration of 10 mg/kg Q4W could be sufficient to maintain SAR650984 above this threshold concentration.

Stage 1b (Amendment 10):

After Amendment 8 was implemented, analysis of the PK parameters in patients in the 10 mg/kg Q2W standard risk expansion cohort demonstrated a high level of variability in exposure and nonlinear clearance suggesting that a higher dose and more intense “loading” schedule may be required to reach the desired steady state faster. Therefore, in Amendment 10, Stage 1b was included to evaluate a 20 mg/kg QW for 1 cycle, then 20 mg/kg Q2W dose schedule. The selection of the dose and schedule was based upon PK simulations.

The dose and schedule for Stage 2 will be determined based on response rate along with safety, PK, PD, and overall efficacy reported for Stage 1a and 1b (see Section 13.5).

Stage 2 (Amendment#11)

From July 2014 to April 2015, a total of 97 patients were treated in Stage 1 of TED10893 study at doses ranging from 3 mg/kg to 20 mg/kg at four different doses and/or schedules of administration. As planned in the protocol (see Section 13.5), an interim analysis of efficacy, safety, PK and PD data of the Phase 2 Stage 1 part was performed to define the dose of SAR650984 to be used in Phase 2 Stage 2. A summary of the most frequent TEAEs (≥30% of patients) is presented in Table 1. Overall, SAR650984 appeared to be well tolerated at all dose levels tested. At doses ≥10 mg/kg, preliminary data show no difference in terms of type, incidence and severity of TEAEs. Infusion associated reactions occurred in approximately half of patients and were of Grade 1/2 for all patients except for 2 patients treated at 10 mg/kg Q2W.

Preliminary efficacy data show a dose response effect between the 3 mg/kg Q2W (ORR <10%) and the doses ≥10 mg/kg (ORR ≥20% in all arms). At doses ≥10 mg/kg, response rate was ranging from 20% to 29%, without clear dose response between the 10 mg/kg and the 20 mg/kg arms.

A preliminary PK/PD analysis to evaluate the relationship between ORR and PK parameters was performed using generalized additive model with pooled Phase 1 and Phase 2 Stage 1 data. This analysis showed that C_{trough} at Week 4 (CT4W) was a significant predictor of tumor response. The probability of response to treatment increases as CT4W increases up to a plateau. This plateau was reached for CT4W values following a weekly administration at 20 mg/kg, indicating that frequent administration together with a high dose in the first cycle is needed to optimize the response (4 weekly administrations at 20 mg/kg). In addition, modeling and simulations of exposure-response to SAR650984 based on M-protein concentration-time profile would induce a higher response to treatment in term of reduction in M-protein at 8 or 12 weeks following 20 mg/kg QW for 4 weeks followed 20 mg/kg Q2W compared to lower doses (ie, 10 mg/kg QW for 4 weeks followed 10 mg/kg Q2W).

Taking the PK/PD analysis together, 20 mg/kg weekly (QW) for 1 cycle followed by 20 mg/kg every 2 weeks (Q2W) would allow an optimal response to treatment.

Therefore, based on safety, efficacy and PK/PD modeling and simulation, the selected dose and schedule of administrations for Stage 2 are: 20 mg/kg weekly (QW) for 1 cycle (4-week treatment) followed by 20 mg/kg every 2 weeks (Q2W) for subsequent cycles.

Table 1 - TED10893 - Phase 2 (Stage 1): Summary of the most frequent TEAEs by system organ class and preferred term regardless relationship to study treatment - All treated population (preliminary results)

	3mg/kg Q2W (N=23)		10mg/kg Q2W (N=24)		10mg/kg Q2W/Q4W (N=25)		20mg/kg QW/Q2W (N=25)	
Primary SOC Preferred Term	All Grades	Grade >=3	All Grades	Grade >=3	All Grades	Grade >=3	All Grades	Grade >=3
Any TEAEs	22 (95.7%)	16 (69.6%)	24 (100%)	18 (75.0%)	25 (100%)	14 (56.0%)	25 (100%)	12 (48.0%)
Infections and infestations	12 (52.2%)	7 (30.4%)	14 (58.3%)	7 (29.2%)	15 (60.0%)	2 (8.0%)	12 (48.0%)	4 (16.0%)
Upper respiratory tract infection	5 (21.7%)	2 (8.7%)	4 (16.7%)	0	7 (28.0%)	0	3 (12.0%)	0
Blood and lymphatic system disorders	10 (43.5%)	9 (39.1%)	3 (12.5%)	3 (12.5%)	6 (24.0%)	6 (24.0%)	10 (40.0%)	6 (24.0%)
Anaemia	9 (39.1%)	8 (34.8%)	1 (4.2%)	1 (4.2%)	5 (20.0%)	5 (20.0%)	7 (28.0%)	4 (16.0%)
Thrombocytopenia	4 (17.4%)	4 (17.4%)	0	0	0	0	8 (32.0%)	5 (20.0%)
Metabolism and nutrition disorders	10 (43.5%)	4 (17.4%)	10 (41.7%)	3 (12.5%)	6 (24.0%)	1 (4.0%)	7 (28.0%)	3 (12.0%)

	3mg/kg Q2W (N=23)		10mg/kg Q2W (N=24)		10mg/kg Q2W/Q4W (N=25)		20mg/kg QW/Q2W (N=25)	
Primary SOC Preferred Term	All Grades	Grade >=3	All Grades	Grade >=3	All Grades	Grade >=3	All Grades	Grade >=3
Nervous system disorders	8 (34.8%)	1 (4.3%)	10 (41.7%)	2 (8.3%)	11 (44.0%)	0	8 (32.0%)	1 (4.0%)
Headache	4 (17.4%)	0	3 (12.5%)	0	8 (32.0%)	0	4 (16.0%)	0
Respiratory, thoracic and mediastinal disorders	13 (56.5%)	4 (17.4%)	15 (62.5%)	3 (12.5%)	18 (72.0%)	1 (4.0%)	19 (76.0%)	1 (4.0%)
Dyspnoea	7 (30.4%)	1 (4.3%)	5 (20.8%)	1 (4.2%)	7 (28.0%)	1 (4.0%)	7 (28.0%)	0
Cough	3 (13.0%)	1 (4.3%)	8 (33.3%)	0	5 (20.0%)	0	9 (36.0%)	0
Gastrointestinal disorders	14 (60.9%)	2 (8.7%)	11 (45.8%)	0	18 (72.0%)	2 (8.0%)	11 (44.0%)	1 (4.0%)
Nausea	7 (30.4%)	0	8 (33.3%)	0	11 (44.0%)	0	6 (24.0%)	0
Diarrhoea	5 (21.7%)	0	5 (20.8%)	0	8 (32.0%)	1 (4.0%)	5 (20.0%)	0
Vomiting	1 (4.3%)	0	3 (12.5%)	0	7 (28.0%)	0	6 (24.0%)	0
Constipation	7 (30.4%)	0	2 (8.3%)	0	2 (8.0%)	0	1 (4.0%)	0
Musculoskeletal and connective tissue disorders	10 (43.5%)	2 (8.7%)	15 (62.5%)	3 (12.5%)	10 (40.0%)	2 (8.0%)	10 (40.0%)	2 (8.0%)
Back pain	3 (13.0%)	1 (4.3%)	7 (29.2%)	2 (8.3%)	3 (12.0%)	1 (4.0%)	5 (20.0%)	1 (4.0%)
General disorders and administration site conditions	16 (69.6%)	3 (13.0%)	16 (66.7%)	0	17 (68.0%)	2 (8.0%)	16 (64.0%)	1 (4.0%)
Fatigue	5 (21.7%)	0	5 (20.8%)	0	11 (44.0%)	0	8 (32.0%)	0
Chills	4 (17.4%)	0	5 (20.8%)	0	7 (28.0%)	0	3 (12.0%)	0
Chest discomfort	1 (4.3%)	0	4 (16.7%)	0	3 (12.0%)	0	6 (24.0%)	0
Investigations	8 (34.8%)	6 (26.1%)	4 (16.7%)	1 (4.2%)	7 (28.0%)	3 (12.0%)	7 (28.0%)	1 (4.0%)
Injury, poisoning and procedural complications	10 (43.5%)	0	15 (62.5%)	2 (8.3%)	17 (68.0%)	2 (8.0%)	16 (64.0%)	1 (4.0%)
Infusion related reaction	9 (39.1%)	0	11 (45.8%)	2 (8.3%)	13 (52.0%)	0	14 (56.0%)	0

Extracted from : PGM=DEVOPS/SAR650984/TED10893_P2S1/DWG_2015_02/REPORT/PGM/ae_teae_socpt5_cr_s_t.sas
OUT=REPORT/OUTPUT/ae_teae_socpt5_cr_s_t_i.rtf (18NOV2015 - 17:00)

5 STUDY OBJECTIVES

5.1 PRIMARY

Phase 1

- To determine the maximum tolerated dose (MTD)/maximum administered dose (MAD) of SAR650984 according to the investigational product (IP) related dose-limiting toxicities (DLTs) observed in patients with CD38+-selected hematological malignancies.

Phase 2

- In Phase 2 Stage 1: To evaluate the activity of single agent SAR650984 at different doses/schedules and to select dose and regimen for Phase 2 Stage 2.
- In Phase 2 Stage 2: To further evaluate the activity in terms of overall response rate (ORR) of SAR650984 at the selected dose/schedule from Stage 1, as single agent (ISA arm) and in combination with dexamethasone (ISAdex arm) in patients with relapsed or relapsed/refractory multiple myeloma.

5.2 SECONDARY

Phase 1

- To characterize the global safety profile including cumulative toxicities.
- To evaluate the pharmacokinetic profile of SAR650984 in the proposed dosing schedule(s).
- To assess the pharmacodynamics, immune response, and preliminary disease response.

Phase 2 Stage 1

<u>To evaluate the followings objectives for SAR650984 as single agent:</u>

- Safety.
- Efficacy as measured by:
  - Duration of response (DOR).
  - Clinical benefit rate (CBR).
  - Progression free survival (PFS).
  - Overall survival (OS).
- Patient-reported changes in health-related quality of life, symptoms of multiple myeloma and generic health status.
- Pharmacokinetic profile of SAR650984.
- Immunogenicity of SAR650984.

- Investigate the relationship between CD38 receptor density and CD38 receptor occupancy (Stage 1 only) on multiple myeloma cells and parameters of clinical response.

Phase 2 Stage 2

To evaluate the followings objectives in each arm (Isa and ISAdex):

- Safety.
- Efficacy as measured by:
  - Duration of response (DOR).
  - Clinical benefit rate (CBR).
  - Progression free survival (PFS).
  - Overall survival (OS).
- Pharmacokinetic profile of SAR650984.
- Immunogenicity of SAR650984.

5.3 EXPLORATORY

Phase 2

- 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 (Stage 1 only).
- To investigate the relationship between immune genetic determinants, immune phenotype adaptive immune response and parameters of clinical response.

6 STUDY DESIGN

This is an open-label, international multi-center study conducted in 2 parts (Phase 1 and Phase 2).

6.1 DESCRIPTION OF THE PROTOCOL – PHASE 1 PART

The Phase 1 part is a dose escalation study of SAR650984 administered as single agent as an intravenous (IV) infusion every week or every 2 weeks to adult patients with selected CD38+ hematological malignancies that have progressed on or after standard therapy for which there is no effective standard therapy, or for which the patient is not suitable for standard therapy at the discretion of the treating physician.

In the Phase 1 part, a cycle is 14 days.

6.1.1 Starting dose and dose escalation design

The Phase 1 starting dose selection and dose escalation design are described in Diagrams Section 1.1 and Section 1.2.

The dose escalation decision will be based on the IP related DLTs observed in *C1 +C2* of each DL. However, cumulative toxicities observed on subsequent administrations should also be considered for the dose escalation process and the dose selection decision.

The administration of SAR650984 will start at the 0.0001 mg/kg dose (representing 10% of theoretical CD38 receptor occupancy (RO) on normal B and T lymphocytes).

Two dose escalation schemes will be used based upon AEs observed during the first two cycles of treatment (4 weeks). In this FIM study, potential DLTs are defined in Section 9.1.1.

6.1.1.1 Accelerated dose escalation step

One patient per DL unless Grade 1 or higher IP related non-hematological toxicity, and log dose escalation between DLs until 0.1 mg/kg (representing the dose with minimal antitumor activity in an animal model) unless the MAD reached.

Cohort 1: 0.0001 mg/kg,

Cohort 2: 0.001 mg/kg,

Cohort 3: 0.01 mg/kg,

Cohort 4: 0.03 mg/kg,

Cohort 5: 0.1 mg/kg,

- Patient(s) will receive two administrations (cycles) of SAR650984 (at 2 week interval) followed by a 2 week post-second dose administration observation period. The data obtained from this 4-week period will be used for acute safety monitoring and to make decisions regarding cohort expansion and/or dose escalation for the next cohort.

- PK and CD38 receptor occupancy data will be collected and may also be used for dose escalation decisions.
- After completing two cycles, patients may be considered for additional administrations of SAR650984 (at the same DL) every 2 weeks upon Investigator's decision provided that this dosing regimen is considered safe. Patients can continue treatment until unacceptable toxicity, disease progression, death, withdrawal of consent, Investigator's decision and/or availability of study drug. Additional PK, safety and disease response will be assessed.
- In the event of a Grade 1 or higher treatment-emergent, IP related non-hematological toxicity including fever, the cohort will be expanded to 3 patients and a semi-log escalation will be used between DLs for all future doses. All successive cohorts will then include 3 patients per DL. In addition, in the event of a Grade 2 or higher treatment-emergent nausea, vomiting, diarrhea, fatigue, asthenia, anorexia, AP elevation or local (injection site) reaction, the cohort will be expanded to 3 patients with a switch to semi-log dose escalation. All successive cohorts will also include 3 patients. In the event that a potential DLT is reported during the accelerated dose escalation scheme, up to 6 patients will be assessed at this DL. If <2 out of 6 patients experienced an IP related DLT at this DL, the dose escalation will proceed with 3 patients per DL. If ≥ 2 out of 6 patients experience an IP related DLT MAD reached and dose escalation is stopped.

A Study Committee will be set up, including at least the Principal Investigator(s) and Clinical Study Director from sanofi-aventis. When needed, ad hoc members will be included. Upon completion of enrollment in each cohort, Study Committee will review collected data and will make the decision to continue the enrollment in a subsequent DL cohort.

6.1.1.2 Basic dose escalation phase

Successive patient cohorts will include at least 3 evaluable patients if no potential DLT is reported, or up to 6 evaluable patients if a potential DLT is experienced by 1 of the first 3 patients, and semi-log dose escalation between DLs. In each cohort, at least 7 days must pass after dosing the first patient before dosing the second patient.

Cohort 6: 0.3 mg/kg every 2 weeks,

Cohort 7: 1 mg/kg every 2 weeks,

Cohort 8: 3 mg/kg every 2 weeks,

Cohort 9: 5 mg/kg every 2 weeks,

Cohort 10: 10 mg/kg every 2 weeks,

Cohort 11: 10 mg/kg every week,

Cohort 12: 20 mg/kg every 2 weeks,

Cohort 13: 20 mg/kg every week,

- Patients in cohorts 6-10 and 12 will initially receive two administrations of SAR650984 (at a 2 week interval) followed by a 2-week post-second dose administration observation period. Patients in Cohort 11 and 13 will initially receive four administrations of

SAR650984 (at a 1 week interval) followed by a 1-week post-fourth dose administration observation period. The data obtained from this 4-week period will be used for acute safety monitoring. PK and CD38 receptor occupancy data will be collected and may be used to make the dose escalation decision for the next cohort.

- After completing two cycles, patient(s) may continue to receive additional administrations of SAR650984 (at the same DL and schedule). If this dosing regimen is considered safe, patients can continue treatment until unacceptable toxicity, disease progression, death, withdrawal of consent, Investigator's decision and/or availability of study drug. Additional PK, safety and disease response will be assessed.
- Cohorts 11, 12 and 13 will initially accrue 3 patients each. Cohorts 11 and 12 will be evaluated in parallel since they have similar monthly dose intensity. An additional 3 patients will be accrued to each of these cohorts if 1 out of the initial 3 patients experience an IP related DLT. An additional 6 patients (up to 12 patients per cohort) may be accrued if required, in order to establish a recommended dose and schedule.

Patients enrolled in Cohort 13 will follow the every week schedule detailed in Section 1.6 (PK/PD Flowchart) and Section 1.11 (Study Flowchart) corresponding to Cohort 11 visit schedules.

- Additional (optional) cohort(s) beyond Cohort 13 may be evaluated (such as 15 mg/kg every week, evaluation of a loading dose followed by a weekly or every 2-week schedule, or evaluation of intermediate doses such as 7.5 mg/kg every week or 15 mg/kg every 2 weeks), however, the decision to proceed to these optional cohort(s) will be discussed with the Study Committee and based on the totality of safety and PK data.

A Study Committee will be set up, including at least the Principal Investigator(s) and Clinical Study Director from sanofi-aventis. When needed, ad hoc members will be added. Upon completion of enrollment in each cohort, Study Committee will review collected data and will make the decision to continue the enrollment in a subsequent DL cohort.

Dose escalation will stop when the MAD is reached. MAD is defined below in Section 6.1.2.

6.1.2 Maximum administered dose (MAD)/Maximum tolerated dose (MTD)/Recommended Phase 2 dose (RP2D)

The MAD is defined in Section 6.1.1.1 of this protocol.

The MTD is defined as the highest DL at which no more than 1 patient of a maximum of 6 patients experienced an IP related DLT. Usually, the MTD is one DL below the MAD. The RP2D is defined as the dose selected for the Phase 1 expansion cohort. The Study Committee will review the overall safety and PK/PD data observed up to and including Cohort 12 and will decide the dose and schedule for the Phase 1 expansion cohort.

Although the dose escalation process is guided by the safety evaluation any time after treatment, cumulative toxicities observed in subsequent administrations should also be considered for the dose escalation and dose selection decisions (ie, smaller increases in dose, expansion of a given DL, intermediate DL), upon agreement between the Investigator and sanofi-aventis.

6.1.3 Phase 1 expansion cohorts

Once the MTD or RP2D has been established based on Cohorts 1-12, the decision to proceed to the standard risk and high risk cohorts will be based on the overall safety and PK observed during dose escalation.

Two MM specific expansion cohorts are planned:

- Standard risk cohort (as defined in Section 7.2)
- (Optional) High risk cohort(as defined in Section 7.2)

Up to 18 additional patients per cohort (for a total accrual of 36 patients) will be accrued to further evaluate the safety, tolerability, PK and disease response at the selected SAR650984 dose and schedule. Patients enrolled in the expansion cohorts will follow the every 2 week schedule detailed in Section 1.7 (PK/PD Flowchart) and Section 1.12 (Study Flowchart) corresponding to Cohort 12 visit schedules.

6.2 DESCRIPTION OF THE PROTOCOL - PHASE 2 PART

The Phase 2 part is to commence after the Phase 1standard risk cohort has completed enrollment and will evaluate the efficacy and safety of SAR650984 as a single agent, in patients with multiple myeloma who have previously received an IMiD and a proteasome inhibitor and have relapsed or relapsed/refractory disease. In the Phase 2 part, a cycle is 28 days. The Phase 2 study will be conducted in 3 stages; Stage 1a dose finding to evaluate 3 dose levels, Stage 1b dose finding to evaluate 1 dose level and Stage 2 expansion to evaluate the selected Stage 1 dose:

- Stage 1a will determine the dose and schedule of single agent SAR650984 by evaluating the activity and safety of SAR650984 at 3 dose levels:
  - Arm 1: 3 mg/kg Q2W (Day 1 and 15 of each 28-day cycle).
  - Arm 2: 10 mg/kg Q2W (Day 1 and 15 of each 28-day cycle).
  - Arm 3: 10 mg/kg Q2W for 2 cycles (Day 1 and 15 of Cycle1 and 2), then 10 mg/kg Q4W (every 4 weeks (Day 1 of each 28-day cycle)).

Patients in Stage 1a will be randomly assigned to one of 3 treatment arms (Arm 1, 2 or 3), in a 1:1:1 ratio using an Interactive Voice Response System/Interactive Web Response System (IVRS/IWRS). Randomization will be stratified according to the patients prior multiple myeloma therapy; Stratum 1: prior treatment with pomalidomide and/or carfilzomib, Stratum 2: no prior treatment with pomalidomide and/or carfilzomib.

- Stage 1b will commence after Cohort 13 has completed the DLT-observation period and enrollment in Stage 1a is completed, whichever is last. The following dose/schedule will be evaluated if fewer than 1/3 or 2/6 patients experiences a DLT in Cohort 13:
  - Arm 4[3]: 20 mg/kg QW for 1 cycle (Day 1, 8, 15 and 22 of Cycle 1), then 20 mg/kg Q2W (Day 1 and 15 of each 28-day cycle).

[3] The planned dose for arm 4 is 20 mg/kg, however during the Phase 1, if 20 mg/kg QW is the MAD then a lower dose (such as 15 mg/kg QW) would be evaluated in this arm.

- Stage 2 will further evaluate the activity and safety of SAR650984 alone or in combination with dexamethasone.

In Phase 2 Stage 2, patients will be randomly assigned to one of the 2 treatment arms in a 2:1 ratio using an IVRS/IWRS. Enrollment will stop when the targeted number of patients is reached in both arms.

SAR650984 dose and schedule for Phase 2 Stage 2 is selected from the interim analysis of Phase 2 Stage 1a and 1b (see Section 13.5) is: 20mg/kg QW for 4 IV infusions followed by 20 mg/kg Q2W (in both arms). This dose was determined based on response rate along with safety, PK, PD and overall efficacy from Phase 1 and Stage 1a and b (see Section 13.5). For patients in ISAdex arm, dexamethasone will be administered at the dose of 40mg/day (20mg/day for ≥75 y.o patients) on Days 1, 8, 15, 22 of each cycle. Dexamethasone will be administered as IV or PO. As part of the pre-medication, dexamethasone will be administered before the SAR650984 infusion.

The Phase 2 Stage 2 part of the TED10893 will be initiated after completion of the dose escalation and dose expansion parts of TED14154 study aiming to evaluate the C1P2F2 formulation in patients with multiple myeloma and that preliminary safety and PK data are supporting the use of the C1P2F2 formulation in the Phase 2 Stage 2 part of the TED10893 study.

In addition, the data monitoring committee (DMC) will review preliminary safety data on the first 12 patients treated in the Phase 2 Stage 2 part of TED10893 with a cut-off date 1 month follow-up after randomization of the 12th patient.

For all stages of the Phase 2 part, the primary efficacy endpoint is overall response rate defined as the proportion of patients with

- Stringent complete response (sCR),
- Complete response (CR),
- Very good partial response (VGPR),
- Partial response (PR),
- Using the International Myeloma Working Group (IMWG) Uniform Response Criteria (1) in Stage 1 and the updated IMWG Response Criteria (2) in Stage 2.

6.3 RETREATMENT OF PATIENTS

In case of AEs, the patient must have recovered to grade ≤1 or to his (her) baseline status before being considered for the next administration of SAR650984. In case of clear clinical benefit a patient can continue the study treatment at the same DL until disease progression, unacceptable toxicity or patient's decision.

6.4 DOSE DELAYS/MODIFICATIONS

In Phase 1 part:

A dose delay of up to 2 weeks is permitted in order for a patient to recover to their baseline status (see Section 6.3) or to accommodate scheduling issues (eg, holidays, weather, etc). In case of a delay greater than 2 weeks due to an AE the patient will be withdrawn from the treatment as per study committee decision. Exceptions allowed by the study committee should be considered only for patients with clear objective clinical benefit.

Individual patients may be considered for treatment at a higher dose or different schedule than they were originally assigned. In order for a patient to be treated at a higher dose or different schedule, the patient must have tolerated the original dose or schedule for at least 12 weeks. In addition, the new dose level or schedule with which the patient is to be treated, must be a dose or schedule that has previously been determined to be safe. During the Phase 1 part, all intra-patient dose and schedule modifications will be discussed on a case-by-case basis and agreed between Sanofi and the Study Committee.

In Phase 2 Stage 1 part:

During the Phase 2 Stage 1 part only, all patients who have progressive disease while on treatment may be considered for treatment at a higher dose level (not to exceed 20 mg/kg on a Q2Wschedule). To be considered for a dose increase, the patient must have tolerated their original dose or schedule for at least 1 cycle.

During the Stage 1a part, patients treated at the 3 mg/kg dose level may be considered for treatment at a higher dose level (10 mg/kg or 20 mg/kg Q2W schedule). In order for a patient to be treated at the higher dose, the patient must have tolerated the 3 mg/kg dose for at least 12 weeks.

All intra-patient dose and schedule modifications will be discussed on a case-by-case basis and agreed between Sanofi and the treating Investigator.

In Phase 2 Stage 2 part:

No dose reduction is authorized for SAR650984. Dexamethasone dose reduction is planned in case of toxicity (see Table 7).

If a patient experiences several toxicities and there are conflicting recommendations, the most conservative dose adjustment recommended (dose reduction/omission appropriate to the most severe toxicity) should be followed. Once a dose has been decreased, intra-patient re-escalation back to the previous dose level is not permitted.

Cycle delay up to 14 days is allowed. If administration within 14 days following the planned date is not possible the patient will discontinue the study treatment. Exceptions can be considered only for patients with clear objective clinical benefit and after the discussion between investigator and sponsor.

SAR650984 infusion/dexamethasone administration delay up to 3 days within a cycle is allowed. If administration within cycle cannot be done within the 3 days following the planned date, SAR650984 infusion (at Cycle 1 only)/dexamethasone administration may be omitted, in which case, the Cycle 1 should be increased to 5 weeks to allow 4 of SAR650893 administration if possible.

No more than 2 dose reductions of dexamethasone and no more than 2 SAR650984 consecutive infusions omitted per patient are permitted.

In ISA arm, the patient will be withdrawn from the study treatment in case of SAR650984 discontinuation. In ISAdex arm, if one drug is prematurely discontinued, patient may continue other study treatment until disease progression, unacceptable toxicity, cut-off date or willingness to stop (whichever comes first).

6.5 GUIDELINES FOR THE MANAGEMENT OF POTENTIAL HYPERSENSITIVITY REACTIONS

Patient(s) should routinely receive premedications prior to SAR650984 infusion as detailed in Section 8.2.1 to reduce the risk and severity of hypersensitivity reactions commonly observed with monoclonal antibodies. Infusion associated reactions (IARs) are defined as related adverse events typically with onset within 24 hours from the start of the infusion. Please refer to the current edition of the IB for IARs manifestations reported in patients treated with isatuximab.

General guidelines for the management of IARs (excluding Phase 2 Stage 2) are provided in Table 2.

Table 2 - Infusion associated reactions management (excluding Phase 2 Stage 2)

Symptom severity	Intervention recommendation
Mild Grade 1 NCI CTCAE v. 4.03 eg, transient flushing or rash, drug fever <38°C (<100.4°F)	Continuation of SAR650984 infusion is per the judgment of the Investigator following close direct monitoring of the patient's clinical status. SAR650984 infusion may be stopped at any time if deemed necessary. If stopped, SAR650984 infusion may be resumed* only after patient recovery with slower infusion rate and with continued close monitoring. If the infusion is stopped, patients may receive additional premedication with IV diphenhydramine 25 mg IV (or equivalent) and/or IV methylprednisolone 100 mg (or equivalent) as needed.
Moderate Grade 2 NCI CTCAE v. 4.03 eg, cutaneous reaction, pruritus, flushing, rash, dyspnea, tachycardia, hypotension, anxiety, headache, myalgia, edema, nausea	Stop SAR650984 infusion; Give additional premedication with IV diphenhydramine 25 mg IV (or equivalent) and/ or IV methylprednisolone 100 mg (or equivalent) as needed. SAR650984 may be resumed* only after patient recovery, with slower infusion rate and with close monitoring
Severe Grade 3 NCI CTCAE v. 4.03 eg, symptomatic bronchospasm, generalized urticaria, systolic BP ≤80 mm Hg, angioedema, anaphylaxis	Stop SAR650984 infusion; Give additional premedication with diphenhydramine 25 mg IV (or equivalent) and/ or IV methylprednisolone 100 mg (or equivalent) and/or epinephrine as needed. Definitive treatment discontinuation

*The infusion should be completed within 7.5 hours (C1P1F1) or 16 hours (C1P2F2) from the end of infusion preparation or a new infusion should be prepared with the remaining dose to be administered the same day.

Patients who experience Grade 1 or Grade 2 IAR(s) may subsequently resume SAR650984 infusion under close monitoring and supportive care as needed. Patients may receive additional premedication per the judgment of the Investigator. Additional recommended premedications are: dyphenhydramine 25 mg IV (or equivalent) and methylprednisolone 100 mg IV (or equivalent). These patients must be informed of the potential risk of recurrent allergic reactions.

Once a Grade 2 IAR has improved to Grade ≤1, the infusion may be restarted at one half the original infusion rates. If symptoms do not recur after 30 minutes, the infusion rate may be increased in 50 mg/hour increments every 30 minutes, to a maximum of 400 mg/hour.

Patients with Grade 3 or 4 SAR650984 IAR must have SAR650984 permanently discontinued and appropriate supportive therapy should be administered. The infusion reaction and the therapy administered must be documented in the CRF.

Grade 3 and Grade 4 IARs must be reported as AESIs (see Section 10.6). Study personnel should consult the Medical Monitor for further guidance regarding re treatment of patients with infusion reactions and regarding issues of premedication management (eg, alternative medications for patients allergic or intolerant to premedication agents) or to determine if locally used equivalent medications are acceptable.

In Phase 2 Stage 2 part updated general guidelines on IAR management are provided in Table 3.

Infusion associated reactions (IARs) NCI CTCAE v. 4.03 term are defined as adverse events related to SAR650984 typically with onset within 24 hours from the start of the infusion.

Table 3 - IAR management (2) (Phase 2 Stage 2)

NCICTCAE v. 4.03 criteria definition	Intervention recommendation
Mild Grade 1 Infusion interruption or intervention not indicated	Continuation of SAR650984 infusion is per the judgment of the Investigator following close direct monitoring of the patient's clinical status. SAR650984 infusion may be stopped at any time if deemed necessary. If stopped, IAR will be classified as a Grade 2 as per NCI-CTCAE
Moderate Grade 2 Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for <=24 hrs)	Stop SAR650984 infusion. Give additional premedication with IV diphenhydramine 25 mg IV (or equivalent) and/or IV methylprednisolone 100 mg (or equivalent) as needed. SAR650984 may be resumed[a] only after patient recovery, with slower infusion rate and with close monitoring. Blood samples for additional safety labs will be collected.
Severe Grade 3 or 4 Grade 3: Prolonged (eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae Grade 4: life-threatening consequences; urgent intervention indicated	Stop SAR650984 infusion. Give additional premedication with diphenhydramine 25 mg IV (or equivalent) and/ or IV methylprednisolone 100 mg (or equivalent) and/or epinephrine as needed. Blood samples for additional safety labs will be collected. Definitive treatment discontinuation

a The infusion should be completed within 16hours (C1P2F2) from the end of infusion preparation or a new infusion should be prepared with the remaining dose to be administered the same day.

6.6 GUIDELINES FOR THE MANAGEMENT OF POTENTIAL TUMOR LYSIS SYNDROME

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

Table 4 - Tumor lysis syndrome management (excluding Phase 2 Stage 2)

Symptom	Recommended action
Laboratory Tumor Lysis Syndrome (LTLS): • ≥2 simultaneous abnormalities within 3 days prior to and up to 7 days after start of treatment. • Uric acid >8 mg/dL (>475.8 µmol/L). • Potassium >6.0 mmol/L. • Phosphorus >4.5 mg/dL (>1.5 mmol/L). • Corrected calcium <7.0 mg/dL (<1.75 mmol/L) orionized calcium <1.12 mg/dL (<0.3 mmol/L). • Clinical Tumor Lysis Syndrome (CTLS): meeting criteria for LTLS in addition to one of the following complications • Elevated creatinine. • Seizures. • Dysrhythmia.	Hold SAR650984 until all serum chemistries have resolved Ensure normal hydration; correct laboratory abnormalities, fluid overload, electrolyte or acide-based deviations Monitor for CTLS complications including renal function Reinstitute SAR650984 at full doses after resolution

In Phase 2 Stage 2 part updated general guidelines on TLS management are provided in Table 5 (44)

Table 5 - Tumor lysis syndrome management (2) (Phase 2 Stage 2)

Symptom	Recommended action
Laboratory TLS (LTLS) ≥2 simultaneous abnormalities within 3 days prior to and up to 7 days after treatment start Uric acid >8 mg/dL (>475.8 µmol/L) Potassium >6.0 mmol/L Phosphorus >4.5 mg/dL (>1.5 mmol/L) Corrected calcium <7.0 mg/dL (<1.75 mmol/L), ionized calcium <1.12 mg/dL (<0.3mmol/L) Clinical TLS: LTLS in addition to one of the following complications • Acute kidney injury: increase in the serum creatinine level of 0.3 mg/dL (26.5 µmol/L) or the presence of oliguria, defined as an average urine output of <0.5 mL/kg/hr for 6 hr. • Seizures, cardiac dysrhythmia, neuromuscular irritability (tetany, paresthesias, muscle twitching, carpopedal spasm, Trousseau's sign, Chvostek's sign, laryngospasm, bronchospasm), hypotension, or heart failure probably or definitely caused by hypocalcemia. • Dysrhythmias probably or definitely caused by hyperkaliemia.	Omit IMP until all serum chemistries have resolved. Ensure normal hydration, correct laboratory abnormalities, fluid overload, electrolyte or acid-base deviation Monitor TLS complications including renal functions. Reinstitute IMP at full doses after resolution

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

6.7 GUIDELINES FOR THE MANAGEMENT OF POTENTIAL ADVERSE EVENTS DUE TO DEXAMETHASONE

For patients randomized in the ISAdex arm, dose reductions levels and instructions for management of toxicities related to dexamethasone are provided in Table 6 and Table 7, respectively.

Table 6 - Dose reduction steps for dexamethasone

Starting dose of dexamethasone (IV/PO) Days 1, 8, 15, and 22	1ST Dose reduction	2ND Dose reduction	3RD Dose reduction
40 mg[a]/20 mg[b]	24 mg[a]/12 mg[b]	16 mg[a]/8 mg[b]	Discontinue dexamethasone

a in patients <75 y.o.
b in patients ≥75 y.o.

Table 7 - Dexamethasone adverse events management

Gastrointestinal	Dyspepsia, gastric or duodenal ulcer, gastritis Grade 1-2 (requiring medical management)	Treat with H2 blockers, sucralfate, or omeprazole. If symptoms persist despite above measures, decrease dexamethasone dose by 1 dose level
	> Grade 3 (requiring hospitalization or surgery)	Omit dexamethasone until symptoms adequately controlled. Restart and decrease one dose level of current dose along with concurrent therapy with H2 blockers, sucralfate, or omeprazole. If symptoms persist despite above measures, discontinue dexamethasone and do not resume.
	Acute pancreatitis	Discontinue dexamethasone and do not resume.
Cardiovascular	Edema > Grade 3 (limiting function and unresponsive to therapy or anasarca)	Diuretics as needed, and decrease dexamethasone dose by 1 dose level; if edema persists despite above measures, decrease dose another dose level. Discontinue dexamethasone and do not resume if symptoms persist despite second reduction.
Neurology	Confusion or Mood alteration > Grade 2 (interfering with function +/- interfering with activities of daily living)	Omit dexamethasone until symptoms resolve. Restart with one dose level reduction. If symptoms persist despite above measures, discontinue dexamethasone and do not resume.
Musculoskeletal	Muscle weakness > Grade 2 (symptomatic and interfering with function +/- interfering with activities of daily living	Decrease dexamethasone by one dose level. If weakness persists despite above measures decrease dose by one level. Discontinue dexamethasone and do not resume if symptoms persist.
Metabolic	Hyperglycemia > Grade 3 or higher	Treatment with insulin or oral hypoglycemics as needed. If uncontrolled despite above measures, decrease dose by one dose level until levels are satisfactory.

Dose reduction for persistent Grade 2 or Grade ≥3 AEs believed to be related to dexamethasone and not listed above are permitted. The AE must be documented in the eCRF. More aggressive dose reductions for lower grade adverse reaction than those listed above must first be discussed with the Clinical Study Director. If dexamethasone is discontinued due to toxicities, and if the patient is benefiting from treatment, SAR650984 can be continued as single agent until progression at the Investigator's discretion and in consultation with the Clinical Study Director.

6.8 GUIDANCE IN CASE OF HEPATITIS B REACTIVATION OCCURRING UNDER STUDY TREATMENT

Patient still on treatment at the time of amended protocol 14 will be tested for HBV serology and HBV viral DNA once at any time if HBV status was unknown before treatment started; test will be repeated if clinically indicated.

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

6.9 DURATION OF STUDY PARTICIPATION

6.9.1 Duration of study participation for each patient

For the Phase 1 part, study duration for an individual patient will include a screening period for up to 2 weeks, up to 4 weeks of SAR650984 administration (weekly or Q2W) unless discontinued earlier due to safety or disease progression, followed by a minimum of 30 days following the last use of study drug or more than 30 days in case of unresolved IP related AE, or up to initiation of another anticancer treatment. Patients with SD, or objective response (CR, PR) and no DLT at the end of 4 weeks of SAR650984 dosing maybe considered for continued treatment as long as clinical benefit is possible, or until PD or other reasons for discontinuation (see Section 11.2). Patients will be followed for a minimum of 30 days following the last use of study drug or more than 30 days in case of unresolved IP related AE, or up to initiation of another anticancer treatment. In addition, PK and ADA sample are required at 60 days after last IP administration and then, in the case of a positive ADA sample, every 30 days until the sample is negative.

For the Phase 2 part, the study duration for an individual patient will include a screening period for up to 3 weeks prior to the first administration of IP, then a treatment period and a follow-up period. Following the screening period, eligible patients will receive SAR650984 at their assigned dose and schedule. Treatment will continue until disease progression, unacceptable adverse

reactions or other reasons for discontinuation (see Section 11.2). Patients with documented disease progression at the end of treatment visit will receive follow-up visits at 30, 60 and 90 days after the last dose (in Phase 2 Stage 1 part) and in Phase 2 Stage 2 part, at 60 days after the last dose of study treatment (isatuximab or dexamethasone, whichever comes last), then will be followed every 3 months until death or cutoff date, whichever comes first. However, female patients of childbearing potential will have the serum pregnancy test every month for 5 months after the last administration of SAR650984. Patients without documented disease progression at the end of treatment visit and have not yet started treatment with another anti-cancer therapy will receive follow-up visits every month until initiation of another anti-cancer therapy, progression, death or cutoff date, whichever comes first. However, female patients of childbearing potential will have the serum pregnancy test every month for 5 months after the last administration of SAR650984. For all patients, any IP-related adverse events and all serious adverse events (regardless of their causal relationship to study treatment) ongoing at the time of study treatment discontinuation will be followed during the follow-up period until resolution or stabilization. During the follow-up period, all new serious adverse events related to study treatment will be collected and followed until resolution or stabilization.

6.9.2 Determination of end of clinical trial (all patients)

For the Phase 1 part, the final analysis cutoff date for primary statistical analysis will be 4 months after the date of the first dose of the last patient. Patients still on treatment at time of the cutoff date and who still continue benefiting from treatment with SAR650984 will have the option to continue treatment under this protocol (see Section 12.3).

For the Phase 2 Stage 1 part, the cutoff date for the primary analysis of ORR and for the secondary analysis will be 12 months after the date of the first dose of the last patient.

For Phase 2 Stage 2, the cutoff date for the primary analysis of ORR is 4 months after the date of the first dose of the last patient. Final analysis cutoff date for the updated analysis of ORR and final analysis of secondary endpoints is 12 months after the date of the first dose of the last patient.

Patients that are still on treatment at time of the final analysis cutoff date and continue benefiting from treatment with SAR650984 will have the option to continue treatment under this protocol (Section 12.3).

At the cut-off date, patients in follow-up will be discontinued from the study unless there are ongoing related adverse events or ongoing serious adverse events 30 days after last study treatment administration whatever the relationship to study treatment.

6.9.3 Interim analysis

Refer to Section 13.4.8.

6.9.4 Phase 1 Study Committee

A Study Committee will be set up to include at least the Principal Investigator and the sanofi-aventis Monitoring Team members. Decisions to initiate or continue the enrollment in subsequent cohorts will be taken after the appropriate data are collected and reviewed by the Study Committee. For this purpose, bi-weekly teleconferences will be held between Investigators and the sanofi-aventis Monitoring Team. A tracking form with all TEAEs (with their severity) will be distributed and jointly reviewed at each teleconference. Before escalating SAR650984 dose to the next DL, the TEAEs and especially the reported potential DLTs will be reviewed in order to determine their relationship to the IP. Dose escalation or dose decrease decisions will be based on the assessment of IP related DLTs, in agreement within the Study Committee. Any of these decisions will be documented in writing, communicated to all investigators in a timely manner and submitted to the Competent Health Authorities, as appropriate. As part of the study committee meeting, any AE that meets the protocol definition of a DLT will be identified and appropriate decisions implemented. Prompt communication with the FDA will occur when needed to determine the relevance of the event not being considered as a DLT based on the full protocol definitions.

6.9.5 Phase 2 Study Committees

Executive Steering Committee (ESC) (Phase 2 Stage 1 only): The ESC will include the Study Chairman, the designated main Investigators and Sponsor representatives. They will be responsible for:

- Supervising the progress of the trial toward its overall objectives.
- Reviewing relevant information that may affect the study conduct at regular intervals.
- Discussing the implementation of the recommendations of the independent DMC.

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

Data Monitoring Committee (DMC): The DMC will be comprised of 3 independent experts. They will be responsible for:

- Reviewing the conduct of the study.
- Reviewing the safety data.
- Reviewing the efficacy and safety results from the Stage 1 analysis.
- Reviewing early safety data from the first 12 patients treated in the Phase 2 Stage 2 part of the study.
- Advising the sponsor and the ESC on potential modifications or communications that may be necessary to ensure patient safety or to protect the scientific integrity of the trial.

In the above capacities, the DMC is advisory to the Sponsor. Detailed guidelines regarding the structure, function and decision-making mechanisms for this committee are described in the DMC charter.

Independent Adjudication Committee (IAC): The IAC will be comprised of independent Multiple Myeloma experts. They will be responsible for:

- Determine presence or absence of plasmacytomas and bone lesions at baseline.
- Objectively assessing clinical response as defined by the IMWG response criteria on an on-going basis in order to independently evaluate the drug effect of SAR650984 on disease status.
- The IAC will determine response using:
  - Serum and urine M-protein, free light chains (FLC), bone marrow biopsy/aspirate and corrected calcium.
  - Radiologic results for bone lesions and plasmacytoma assessment.

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

7 SELECTION OF PATIENTS

7.1 NUMBER OF PATIENTS

Phase 1: It is anticipated that approximately 85 patients will be required to establish the MTD and the preliminary safety of SAR650984.

Phase 2: Approximately 96 patients (24 patients per arm) will be enrolled in Stage 1a and 1b of the study.
Approximately 160 patients will be enrolled in Stage 2 of the study.

7.2 PHASE 1 INCLUSION CRITERIA

I 01. **A. For dose escalation Cohorts 1 to 10 and the Cohort 10 expansion**: Patients with confirmed selected CD38+ hematological malignancies (as outlined below) who have progressed on or after standard therapy or for whom there is no effective standard therapy (refractory/relapsed patients).

- Multiple myeloma (MM) patients with measurable M-protein (serum and/or 24-hr urine, or serum free light chains).
- Acute myeloid leukemia (AML) patients, all types except M3 based on FAB classification
- Chronic lymphocytic leukemia (CLL) patients.
- B-cell non-Hodgkin's lymphoma (NHL) patients. For lymphoma patients at least 1 measurable lesion should be present.
- Acute lymphoblastic leukemia (ALL) patients.

B. For dose escalation Cohorts 11, 12 and 13 (and additional optional cohorts): Patients with relapsed/refractory MM with measurable M-protein (serum M-protein of >0.5 g/dL and/or urine M-protein of >200 mg (24-hr urine)) or elevated serum free light chains (FLC >10 mg/dL with abnormal FLC ratio) who have progressed on or after standard therapy that includes an IMiD and a proteasome inhibitor.

For the standard risk expansion cohort: Patients with relapsed/refractory MM with measurable M-protein (serum M-protein of >0.5 g/dL and/or urine M-protein of >200 mg (24-hr urine)) or elevated serum free light chains (FLC >10 mg/dL with abnormal FLC ratio) who meet the following criteria:

- have progressed on or after at least 2 prior lines of standard therapy that includes an IMiD and a proteasome inhibitor

For the high risk expansion cohort: Patients with relapsed/refractory MM with measurable M-protein (serum M-protein of >0.5 g/dL and/or urine M-protein of >200 mg (24-hr urine) or elevated serum free light chains (FLC >10 mg/dL with abnormal FLC ratio) who have progressed on or after standard therapy that includes an IMiD and a proteasome inhibitor and who meet one of the following criteria:

- have relapsed within 6 months of autologous transplantation
- have 17p deletion, t (4, 14), t (14, 16), t (14, 20) or >3 copies of 1q21
- have a high-risk gene expression profiling (GEP) signature (if available)

I 02. Signed written informed consent.

7.3 PHASE 1 EXCLUSION CRITERIA

E 01. No previous treatment with any anti-CD38 is allowed

E 02. Patient less than 18 years old

E 03. Karnofsky performance status <60

E 04. Poor bone marrow reserve as defined by absolute neutrophils count <1.0 x 10^9/L or hemoglobin <9.0 g/dL or platelets <50 x 10^9/L

E 05. Poor organ function as defined by one of the following:

- Liver function tests
  - (AST, ALT, AP, bilirubin >2.5 x upper limit of normal [ULN] if no liver metastasis; >5 x ULN if liver metastases
  - >5 x ULN AP if bone involvement
- Serum creatinine >2 x ULN (>3 x ULN for multiple myeloma

E 06. Received any investigational drug within 30 days or 5 half-lives of the investigational drug, whichever is longer

E 07. Prior anticancer therapy (chemotherapy, targeted agents, radiotherapy, immunotherapy) within 21 days except for alkylating agents (eg, Melphalan) 28 days will be required. Hydroxyurea may be used up to 24 hours prior to the first drug infusion and leukophoresis may be used up to 1 week prior to the first drug infusion

E 08. Known intolerance to infused protein products, sucrose, histidine, polysorbate 80 or known hypersensitivity to any of the components of study therapy that is not amenable to pre-medication with steroids and H2 blockers

E 09. Allogeneic bone marrow transplant or an allogeneic peripheral blood stem cell transplant within 1 year prior to study entry or evidence of GVHD requiring >10 mg prednisone. Patients having undergone ASCT(s) may be included in the study. For AML patients, prior allogeneic stem cell transplantation or donor lymphocytes infusion within 3 months preceding the first dose of SAR650984

E 10. Any serious active disease (including clinically significant infection that is chronic, recurrent, or active) or co-morbid condition, which, in the opinion of the Investigator, could interfere with the safety, the compliance with the study or with the interpretation of the results

E 11. Any other severe underlying medical conditions including presence of laboratory abnormalities, which could impair the ability to participate in the study or the interpretation of its results

E 12. Concomitant or prior malignancy (other than the one under study) except adequately treated basal cell or squamous cell carcinoma of the skin, carcinoma in situ of the cervix, or other cancer for which the subject has been disease-free for ≥5 years

E 13. Concurrent treatment with other anti-cancer therapy not specified in the protocol

E 14. Central nervous system (CNS) metastatic disease

E 15. Pregnant or breast-feeding women

E 16. Female patients of childbearing potential and male subjects with female partners of childbearing potential who are not willing to avoid pregnancy by using an adequate method of contraception (2 barrier method or 1 barrier method with a spermicide or intrauterine device for 2 weeks prior to screening, during and 5 months after the last dose of trial medication). Adequate methods of contraception are provided as examples. Other acceptable and effective methods of birth control are also permitted (eg, abstinence).

E 17. Known HIV seropositivity, AIDS, hepatitis C or active hepatitis B infection

E 18. Autoimmune disease (eg, inflammatory bowel disease such as Crohn's disease, systemic lupus or multiple sclerosis)

E 19. No resolution of all specific toxicities (excluding alopecia) related to any prior anti-cancer therapy to Grade ≤1 according to the NCI CTC AE v.4.03

E 20. Any of the following within 6 months prior to enrollment: myocardial infarction, severe/unstable angina, or coronary/peripheral artery bypass graft surgery, clinically symptomatic and uncontrolled cardiovascular disease, or clinically significant cardiac arrhythmias (Grade 3-4)

E 21. Mental condition rendering the patient unable to understand the nature, scope and possible consequences of the study. Patient unlikely to comply with protocol eg, uncooperative attitude, inability to return for follow up visits, and unlikelihood of completing the study

7.4 PHASE 2 (STAGE 1 AND STAGE 2) INCLUSION CRITERIA

I 01. Patients must have a known diagnosis of multiple myeloma with evidence of measurable disease, as defined below:

- Serum M-protein ≥1 g/dL (≥0.5 g/dL in case of IgA disease in Stage 2), or urine M-protein ≥200 mg/24 hours.

OR

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

I 02. Patients must have received prior treatment with an IMiD (for ≥2 cycles or ≥2 months of treatment) and a proteasome inhibitor (for ≥2 cycles or ≥2 months of treatment).

I 03. Patients must have received at least three prior lines of therapy (as defined in Appendix C) for multiple myeloma. Induction therapy and stem cell transplant (± maintenance) will be considered as one line

OR

Patients whose disease is double refractory to an IMiD and a PI. For patients who have received more than one type of IMiD and PI, their disease must be refractory to the most recent one.

Refractory disease is defined as a disease that is progressive while being on treatment, or progressive within 60 days of the last administration of these therapies or never reached at least a MR with those drugs

I 04. Patients must have achieved an MR or better to at least one prior line of therapy.

I 05. Patients must have received an alkylating agent (≥2 cycles or ≥2 months) either alone or in combination with other MM treatments (history of stem cell transplant is acceptable). Treatment with high-dose melphalan for stem cell transplantation meets this requirement.

I 06. Patients must have evidence of disease progression on or after the most recent prior regimen based on IMWG criteria ((2) and Appendix E) (Phase 2 Stage 2)

I 07. Signed written informed consent and be willing and able to complete all study-related procedures, including completion of patient-reported endpoints

7.5 PHASE 2 (STAGE 1 AND STAGE 2) EXCLUSION CRITERIA

E 01. Patients less than 18 years old.

E 02. Patients with multiple myeloma IgM subtype.

E 03. Previous treatment with any anti-CD38 therapy.

E 04. Patients with concurrent plasma cell leukemia.

E 05. Patients with known or suspected amyloidosis.

E 06. Patients treated with approved or investigative anticancer therapeutic agents, excluding dexamethasone in Phase 2 Stage 2 but including steroid therapy (eg, prednisone >10 mg/day orally or equivalent for more than 7 consecutive days except for inhalation corticosteroids and patients being treated for adrenal insufficiency/replacement therapy), within 3 weeks or within five drug half-lives ($t_{1/2}$) prior to first dose, whichever time is greater.

E 07. Patients treated with systemic radiation therapy within 4 weeks prior to first dose or localized radiation therapy within 1 week prior to first dose.

E 08. Patients who have had major surgery within 3 weeks prior to first dose.

E 09. Prior autologous stem cell transplant within 12 weeks of the first dose of study treatment and/ or prior allogeneic transplant within 1 year or has evidence of active graft versus host disease (GVHD) requiring >10 mg prednisone daily.

E 10. Patients with a life expectancy of less than three months.

E 11. Karnofsky performance status <60.
In Stage 2 part patient with ECOG Performance status >2.

E 12. Patients with laboratory values of:

a) Total bilirubin ≥2.0 x upper limit of normal (excluding congenital conjugation disorders (Gilberts) with direct bilirubin <2 x upper limit of normal.

b) AST or ALT ≥3.0 x upper limit of normal.

c) Phase 2 Stage 1: Calculated or measured creatinine clearance <30 mL/minute (using Cockcroft and Gault formula [(140 - age) x mass (kg) / (72 x creatinine mg/dL)], multiply result by 0.85 if female).

Phase 2 Stage 2: serum creatinine >2xULN and/or estimated Glomerular Filtration Rate calculated according the Modification of diet in Renal Disease (MDRD) equation <15mL/min/1.73m2, (see formula in Appendix B), and/or on renal dialysis.

d) Absolute neutrophil count ≤1 000/mm^3 (use of colony-stimulating factors to achieve these counts is allowed).

e) Hemoglobin <8.0 g/dL (patients may receive red blood cell transfusion or receive supportive care such as erythropoietin and darbepoetin in accordance with institutional guidelines).

f) Platelet count ≤50,000/mm^3 (patients should be platelet transfusion independent for 2 weeks prior to screening lab values).

E 13. No resolution of all specific toxicities (excluding alopecia) related to any prior anti-cancer therapy to Grade ≤1 according to the NCI CTC AE v.4.03.

E 14. Patients with concurrent POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes).

E 15. Patients with congestive heart failure (New York Heart Association class III to IV), symptomatic ischemia, conduction abnormalities uncontrolled by conventional intervention, or myocardial infarction in the 6 months prior to first dose.

E 16. Patients with active infection requiring systemic antibiotics, antivirals or antifungals within 2 weeks prior to first dose (except when used for chronic prophylaxis).

E 17. Known intolerance to infused protein products, sucrose, histidine, polysorbate 80 or known hypersensitivity to any of the components of study therapy that is not amenable to pre-medication with steroids and H2 blockers.

E 18. Patients with known HIV.

E 19. Patients with active hepatitis B, or C infection.

E 20. Patients diagnosed or treated for a malignancy within the past 3 years except:

a) adequately treated basal cell or squamous cell skin cancer, or

b) carcinoma in situ of the cervix, or

c) prostate cancer with < Gleason Grade 6 and stable PSA.

E 21. Patients with myelodysplastic syndrome (MDS).

E 22. Patients with significant neuropathy (Grade 2 with pain or ≥ Grade 3) within 2 weeks prior to first dose.

E 23. Any clinically significant medical or psychiatric disease or condition that, in the Investigator's opinion, may interfere with protocol adherence, the ability to complete patient-reported measures or the ability to give informed consent.

E 24. Female patients of childbearing potential and male patients with female partners of childbearing potential who are not willing to avoid pregnancy by using an adequate method of contraception (2-barrier method or 1 barrier method with a spermicide or intrauterine device for 2 weeks prior to screening, during and 5 months after the last dose of trial medication) and/or who are unwilling or unable to be tested for pregnancy monthly for 5 months after the last administration of SAR650984. Adequate methods of contraception are provided as examples. Other acceptable and effective methods of birth control are also permitted (eg, abstinence).

E 25. Female patients who are pregnant or breast feeding.

E 26. (Phase 2 Stage 2) Patient is the Investigator or any Sub-investigator, research assistant, pharmacist, study coordinator, other staff or relative thereof directly involved in the conduct of the protocol.

8 TREATMENTS

8.1 INVESTIGATIONAL PRODUCT

8.1.1 Pharmaceutical form

8.1.1.1 Formulation for Phase 1 and Phase 2 Stage 1

The C1P1F1 drug product is presented as a concentrate for solution for infusion in vials containing 5 mg/mL (100 mg/20 mL) SAR650984 in 10 mM histidine, 10 % (w/v) sucrose, 0.005 % (w/v) polysorbate 80, pH 6.5 buffer. For administration to patients, the appropriate volume of SAR650984 will be diluted in an infusion bag of 0.9% sodium chloride solution. The final infusion volume corresponding to the dose of SAR650984 will be administered for period of time that will depend on dose administered and will be based on protein amount given per hour.

8.1.1.2 Formulation for Phase 2 Stage 1 and 2

The C1P2F2 drug product is presented as a concentrate for solution for infusion in vials containing 20 mg/mL (500 mg/25 mL) SAR650984 in 20 mM histidine, 10 % (w/v) sucrose, 0.02% (w/v) polysorbate 80, pH 6.0 buffer.

It is supplied for parenteral administration as a sterile, non-pyrogenic, injectable, colorless, 20 mg/mL concentrate for solution for infusion that may contain white to off-white particulates and is packaged in 30 mL glass vials fitted with elastomeric closure. Each vial contains a nominal content of 500 mg of SAR650984 P2F2. The fill volume has been established to ensure removal of 25 mL.

For administration to patients, the appropriate volume of SAR650984 will be diluted in an infusion bag of 0.9% sodium chloride solution. The final infusion volume corresponding to the dose of SAR650984 will be administered for period of time that will depend on dose administered and will be based on protein amount given per hour.

For those patients that are still on treatment after study cutoff date in Phase 2 Stage 1, they may be switched from C1P1F1 to C1P2F2.

For more details, please see the Investigator's brochure.

8.1.2 Dose of drug per administration

During Phase 1 SAR650984 will be administered by IV infusion every week or once every two weeks (Q2W) as determined by the assigned cohort in 14-day cycles.

During Phase 2 SAR650984 will be administered by IV infusion at the assigned dose and schedule (see Section 6.2) in 28-day cycles.

For both Phase 1 and Phase 2 parts, the dose administered should be calculated using actual body weight as measured at each cycle.

The rate of infusion for each of the planned dose levels in the Phase 1 is as follows:

0.0001 mg/kg---------- 0.042 mg/hr for a total of 3 mL
0.001 mg/kg ---------- 0.42 mg/hr for a total of 3 mL
0.01 mg/kg---------- 1.4 mg/hr
0.03 mg/kg---------- 4.2 mg/hr
0.1 mg/kg ---------- 7 mg/hr
0.3 mg/kg ---------- 10.5 mg/hr
1 mg/kg ---------- 17.5 mg/hr
3 mg/kg ---------- 52.5 mg/hr
5 mg/kg ---------- 87.5 mg/hr
10 mg/kg---------- 175 mg/hr
20 mg/kg---------- 250 mg/hr

First infusion: initiate infusion at a rate noted above. In the absence of infusion reaction, increase infusion rate by 50 mg/hour increments every 30 minutes, to a maximum of 400 mg/hour.

Subsequent infusions: initiate infusion at a rate noted above. In the absence of infusion reaction, increase rate by 100 mg/hour increments every 30 minutes, to a maximum of 400 mg/hour.

During Phase 2, the rate of infusion will be at 175 mg/hr and will follow the first and subsequent infusion rate increases as detailed above.

In Phase 2 Stage 2:

The rate of infusion for SAR650984 at 20 mg/kg is as follows:

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

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

In case of IAR of Grade ≥2, the administration should be interrupted, in case of IAR of Grade ≥3 SAR650984 should be permanently discontinued (see Table 3). Once the event has improved to Grade ≤1 the infusion may be restarted at one half the initial infusion rates. If symptoms do not recur after 30 minutes, the infusion rate may be increased in 50 mg/hour increments every 30 minutes, to a maximum of 400 mg/hour.

8.1.3 Duration of treatment:

Phase 1: Patient(s) in Cohorts 1 to 10 and 12 will receive administrations of SAR650984 at 2-week intervals. Patients in Cohort 11 and 13 will receive administration of SAR650984 at 1-week intervals.

Patients enrolled in the Phase 1 expansion cohorts (standard risk or the optional high risk cohorts) will receive SAR650984 at 10 mg/kg Q2W for continued treatment as long as clinical benefit is possible, or until PD or for other reasons (see Section 11.2).

Phase 2: Patients will receive administrations of SAR650984 at the assigned dose and schedule (or modified dose and schedule, see Section 6.4) for continued treatment as long as clinical benefit is possible, or until PD or for other reasons (see Section 11.2).

8.1.4 Dilution method

The SAR650984 concentrate for solution for infusion will be diluted in an infusion bag with 0.9% sodium chloride solution to achieve the appropriate drug concentration for infusion.

The low doses 0.0001 and 0.001 mg/kg will require serial dilution to achieve the necessary drug concentration for infusion. For all other doses, a single dilution will be sufficient.
Due to the low volume (3 mL) of administration, the 0.0001 and 0.001 mg/kg doses will be administrated by extemporaneous injection of bolus by syringe.

For all other doses, infusion via a central line is preferred if available according to the rate of infusion detailed above. Patients with local intolerance after peripheral IV infusion should receive next dose(s) using a central line. The final infusion volume corresponding to the dose of SAR650984 will be administered by IV infusion for the period of time that will depend on dose administered and on the protein amount administered per hour (detailed above).

Prior to dosing, each patient's dose will be individually prepared by the study pharmacist and labeled with protocol number, patient number, and treatment description.

A 0.2µm in-line filter is required for administration from the second dose (0.001 mg/kg).

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

Detail instruction for dilution of the SAR650984 concentrate for solution for infusion is provided in a Pharmacy Manual.

8.1.5 Stability under light

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

8.1.6 Dexamethasone (investigational product for patients randomized in the ISAdex arm - Phase 2 Stage 2 only)

8.1.6.1 Availability

Dexamethasone from available commercial supplies will be used for this study where applicable; otherwise, it will be re-labeled by the Sponsor according to Good Manufacturing Practice (GMP) guidelines before supplies are provided to the study sites.

When commercial supplies will be used please refer to package insert for further details as regards to formulation storage and handling procedures.

8.1.6.2 Accountability

A patient diary will be used to document all oral dexamethasone drug administration.

8.1.6.3 Administration

Dexamethasone, being part of both backbone treatment regimen and SAR650984 premedication, will be administered orally (PO) or and by intravenous infusion (IV) as follows:

- Patients of <75 year-old: 40 mg on D1, D8, D15, D22 of each cycle
- Patients of ≥75 year-old: 20 mg on D1, D8, D15, D22 of each cycle

On days of SAR650984 administration, dexamethasone will be given before the SAR650984 infusion (see Section 8.2.1).

For a regional or national emergency declared by a governmental agency that results in travel restrictions, confinement, or restricted site access, oral dexamethasone may be supplied at the site or from the PI/site/Sponsor to the participant via a Sponsor-approved courier company where allowed by local regulations and agreed upon by the participant during the time the measures are applied.

For dexamethasone dose adjustment, see Section 6.4 and Section 6.7.

8.2 NONINVESTIGATIONAL MEDICINAL PRODUCT

8.2.1 Premedication

In Phase 1 and Phase 2 Stage 1:

Patient(s) should routinely receive premedications prior to SAR650984 infusion to reduce the risk and severity of hypersensitivity reactions commonly observed with monoclonal antibodies. The recommended premedication agents are: diphenhydramine 25-50 mg IV (or equivalent), methylprednisolone 100 mg IV (or equivalent), ranitidine 50 mg IV (or equivalent) and acetaminophen 650-1000 mg po 15-30 minutes (but no longer than 60 minutes) prior to

SAR650984 infusion. General guidelines for the management of the infusion associated reactions are provided in Table 1. If an infusion associated reaction is observed, patients must also be informed of the potential risk of recurrent allergic reactions.

For the Phase 2 part, patients who do not experience an infusion associated reaction during the first 4 SAR650984 infusions may have the need for subsequent pre-medication reconsidered at the investigator's discretion in consultation with the sponsor to avoid unnecessary sedation.

In Phase 2 Stage 2:

Before each administration of SAR650984, all patients will receive prophylaxis for infusion associated reaction.

In ISA arm: The recommended premedication agents are: diphenhydramine 25-50 mg IV (or equivalent), methylprednisolone 100 mg IV (or equivalent), ranitidine 50 mg IV (or equivalent) and acetaminophen 650-1000 mg PO. The pre medication will be administered at least 15 to 30 minutes (but no longer than 60 minutes) prior to SAR650984 infusion.

In ISAdex arm, on the day of SAR650984 infusion, a total of 40 mg (or 20 mg for patients ≥75 years old) of dexamethasone will be administered as part of the pre-medication and the combination treatment.

The order of premedication administration is the following:

- When dexamethasone is administered orally: dexamethasone, acetaminophen, ranitidine, and then diphenhydramine.
- When dexamethasone/methylprednisolone is administered IV, acetaminophen, ranitidine, diphenhydramine and then dexamethasone/methylprednisolone.
- Patients who do not experience an infusion associated reaction in 4 consecutive SAR650984 infusions may have the need for subsequent pre-medication reconsidered at the investigator's discretion inconsultation with the sponsor to avoid unnessary sedation.

8.3 PACKAGING AND LABELING

The investigational product is packaged in 25 mL glass vials fitted with elastomeric closure for C1P1F1 and is packaged in 30 mL glass vials fitted with elastomeric closure for Phase 2 Stage 2 C1P2F2.

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

8.4 METHOD OF ASSIGNING PATIENTS TO TREATMENT GROUP

In Phase 1, there is no randomization.

In Phase 2, after each patient has completed the necessary screening visit procedures and is deemed eligible for study enrolment by the investigator, the study site will contact the IVRS/IWRS, to allow for patient randomization or registration for Stage 1a and Stages 1b and 2, respectively.

For Stage 1a, patients will be classified into 1 of 2 strata according to their prior multiple myeloma therapy:

- Stratum 1: Prior treatment with pomalidomide and/or carfilzomib.
- Stratum 2: No prior treatment with pomalidomide and/or carfilzomib.

Within each stratum, patients will be randomized to Stage 1a in a 1:1:1 ratio into one of the 3 treatment arms (Arm 1, 2 or 3). The patient randomization list will be generated by the IVRS/IWRS according to the randomization scheme provided by the study biostatistician.

Enrollment in Stage 1b will start after completion of Cohort 13 and enrollment in Stage 1a is completed, whichever is last.

Stage 2 will be initiated after the interim analysis of Stage 1. Patients will be registered and randomized using an Interactive Voice Response System/Interactive Web Response System (IVRS/IWRS).

8.5 STORAGE CONDITIONS

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

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

8.6 RESPONSIBILITIES

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

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

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

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

8.7 RETRIEVAL OF TREATMENTS AND/OR DESTRUCTION

All used treatments of SAR650984 will be destroyed at the study site after an accurate accountability has been performed and signed by the Investigator (or the pharmacist).

All unused IPs may be retrieved by sanofi-aventis. A detailed treatment log form of the returned Investigational Product will be established with the Investigator (or the pharmacist) and countersigned by the Investigator and the Monitoring Team.

The Investigator will not destroy the unused Investigational Product unless sanofi-aventis provides written authorization.

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

8.8 CONCOMITANT TREATMENT

All treatments being taken by the patient 7 days prior to registration onto the study, at any time during the treatment period and up to 30 days after the last dose are regarded as prior and concomitant treatments respectively, and the type, dose and route of administration must be documented on the appropriate pages of the CRF or e-CRF.

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

- Palliative radiotherapy may be given for control of pain for palliative intents. Sanofi-aventis should be notified to obtain prior approval prior to treatment if palliative radiotherapy is being considered, and prior to resuming therapy on the study. The irradiated area should be as small as possible and should never involve more than 20% of the bone-marrow in any given 3-week period. In all such cases, the possibility of tumor progression should be ruled out by physical and radiological assessments of the tumor. If the only evaluable lesions are to be irradiated, the patient will stop the study treatment. The irradiated area cannot be used as a parameter for response assessment.
- Supportive treatment as medically indicated for the patient’s well-being may be prescribed at the Investigator’s discretion. Every medication or treatment taken by the patient during the trial and the reason for its administration must be recorded on the CRF.

The following concomitant treatments are not permitted during this study:

- Concurrent treatment with other investigational drugs.
- Concurrent treatment with any other anticancer therapy not specified in this protocol, including immunotherapy, hormonal therapy, targeted therapy, steroid therapy or biological therapies.
- During the Phase 1 part, prophylactic use of hematopoietic growth factors (eg, G-CSF, GM-CSF, erythropoietin) during the first cycle. Prophylactic use of hematopoietic growth factors during the Phase 2 part is permitted.

8.9 POST-INVESTIGATIONAL PRODUCT

As per the discretion of the Investigator.

8.10 TREATMENT ACCOUNTABILITY AND COMPLIANCE

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

The person responsible for drug dispensing is required to maintain adequate records of the IP. These records (eg, drug movement form) include the date the IP is received from sanofi-aventis, dispensed for patient and destroyed or returned to sanofi-aventis. The packaging batch number (PR Nr) on the vial must be recorded on the drug accountability form.

The person responsible for drug administration to the patient will record precisely the date and the time of the drug administration.

8.11 CONTRACEPTIVE MEASURES

Females of child bearing potential or male subjects with female partners of childbearing potential shall be required to use effective contraceptive methods (double barrier method, intrauterine device, oral contraception or abstinence) starting 2 weeks before first IMP administration, while on therapy and for 5 months following the last dose of IMP. A woman is considered of childbearing potential (WOCBP), i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile. The following highly effective methods of contraception are accepted:

- Established use of oral, intravaginal, or transdermal combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation.
- Established use of oral, injectable, or implantable progestogen-only hormonal contraception associated with inhibition of ovulation.
- Placement of an intrauterine device (IUD) or intrauterine hormone-releasing system (IUS).

- Barrier methods of contraception: male condom with either cap, diaphragm or sponge with spermicide (double barrier methods). The use of double barrier methods should always be supplemented with the use of a spermicide. Female condom and male condom should not be used together.
- Male sterilization (provided that the partner is the sole sexual partner of the patient and that the sterilized partner has received medical assessment of the surgical success.)
- Sexual abstinence.

9 ASSESSMENT OF INVESTIGATIONAL PRODUCT

9.1 SAFETY

The primary objective of the Phase 1 part is to establish, based on IP related DLTs, the MTD or RP2D of SAR650984 when administered as an intravenous infusion every week or every 2 weeks to patients with advanced hematologic malignancies known to be refractory to standard available therapies or for which no standard therapy exists. A secondary objective of the Phase 2 part is to evaluate the safety of SAR650984 when administered as an intravenous infusion to patients with relapsed or relapsed/refractory multiple myeloma. The safety profile will be assessed from the findings of physical examination (preferably by the same physician), laboratory tests, etc, and will be based on incidence, severity (as graded by the NCI CTCAE v. 4.03), and cumulative nature of AEs as defined in Section 10.4.

The NCI CTC AE v 4.03 (45) can be accessed through the NCI website at http://ctep.info.nih.gov/reporting/ctc.html (45).

9.1.1 Dose limiting toxicities (DLTs) - Phase 1 part only

For the purposes of dose escalation and determination of the MTD/RP2D, only DLTs that occur during the first 28 days (Cycle 1 and Cycle 2) of treatment will be considered for decisions regarding dose escalation.

DLTs are defined as any Grade 3 or higher non-hematological toxicity (with the exception of allergic reaction/hypersensitivity), Grade 4 neutropenia and/or Grade 4 thrombocytopenia lasting longer than 5 days, attributed to SAR650984 and as defined by the NCI-CTCAE v.4.03.

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

Before escalating SAR650984 dose to the next DL, all safety data, and especially the reported potential DLTs will be reviewed to determine their relationship to the IP. Dose escalation or dose decrease decisions will be based on the assessment of IP related DLTs by the Safety Committee.

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

In case of existing usable prophylactic and/or curative treatment for a dose limiting non-hematologic AE (eg: diarrhea, hypersensitivity, nausea-vomiting, hyperglycemia), this treatment may be evaluated in an additional cohort of up to 6 patients treated at the same DL. Further dose escalation could be allowed if <33% of patients in this additional cohort experience DLT when receiving the prophylactic/corrective therapy. These prophylactic/corrective therapies will be systematically implemented in further DLs. In addition, in the expansion cohort at MTD, cumulative toxicities will be specifically detected, in order to confirm the feasibility of the MTD selected in the dose escalation step.

Although the dose escalation process is guided by the safety evaluation during the first two cycles of treatment, cumulative toxicities observed in subsequent administrations should also be considered for the dose escalation and the dose selection decisions (ie, smaller increases in dose, expansion of a given DL, intermediate DL), upon agreement within the Study Committee.

9.1.2 Adverse events

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

The NCI CTC AE v. 4.03 may be accessed through the NCI website at http://ctep.info.nih.gov/reporting/ctc.html (45).

9.1.3 Laboratory measurements

9.1.3.1 Phase 1 laboratory assessments

Blood chemistry, hematology, coagulation, urinalysis, cytokines and CRP will be performed at screening, during treatment and at the EOT visit (see Section 12.1 for assessment timings).

Blood Chemistry: SGOT (AST), SGPT (ALT), bilirubin (total and direct), alkaline phosphatase (AP), lactate dehydrogenase (LDH), sodium, potassium, chloride, bicarbonate/carbon dioxide, calcium, magnesium, phosphate, uric acid, blood urea nitrogen (BUN), serum creatinine and estimated creatinine clearance, glucose, albumin, total protein, peptide C, erythrocyte sedimentation rate (ESR)

Hematology: hemoglobin, hematocrit, RBC, WBC with differential, MCV, platelet count

Coagulation: PT/INR, PTT

Urinalysis: blood, protein, glucose, pH, ketones, bilirubin, leucocytes, nitrates, specific gravity

Cytokines: Tumor necrosis factor alpha (TNF-α), IL-6, IL-1B, IFN-γ

Hs/CRP

9.1.3.2 Phase 2 laboratory assessments

Blood chemistry, hematology, coagulation, urinalysis and cytokines will be performed at screening, during treatment and at the EOT visit (see Section 12.2 for assessment timings).

Blood Chemistry: SGOT (AST), SGPT (ALT), bilirubin (total and direct), AP, lactate dehydrogenase (LDH), sodium, potassium, chloride, bicarbonate/carbon dioxide, calcium, corrected serum calcium, magnesium, phosphate, uric acid, blood urea nitrogen (BUN), serum creatinine and estimated creatinine clearance, glucose, albumin and total protein

Hematology: hemoglobin, hematocrit, RBC, WBC with differential, MCV, platelet count

Coagulation: PT/INR, PTT

Urinalysis: blood, protein, glucose, pH, ketones, bilirubin, leucocytes, nitrates, specific gravity

Cytokines: Tumor necrosis factor alpha (TNF-α), IL-6, IL-1B, IFN-γ

Safety labs: Should a SAR650984 infusion reaction of Grade ≥2 occur, additional blood sampling during the AE is required for analysis of cytokines, markers of complement activation (C3, C4, CH50), serum tryptase and blood chemistry (Phase 1 and Phase 2 Stage 1 only)

9.1.4 Physical examinations

Please refer to Section 12.2 for assessment timings. Physical examination consists of examination of major body systems, plasmacytoma assessment, respiratory, hepatomegaly, splenomegaly, lymphadenopathy.

9.1.5 Vital signs

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

9.1.6 ECG

Please refer to Section 12 for assessment timings of the 12-lead ECG.

9.1.7 Other Clinical assessments

- Karnofsky performance status evaluation for Phase 1 and Phase 2 Stage 1, ECOG Performance status for Phase 2 Stage 2 part.
- Results of additional procedures (such as karyotype, FISH, etc) performed as part of standard of care to assess the current disease status may also be collected.

9.2 EFFICACY

9.2.1 Phase 1 criteria for response

Please refer to Appendix D for the response criteria for each disease type (MM, AML, CLL, NHL and ALL).

9.2.2 Phase 2 primary endpoint

ORR is defined as the proportion of patients with stringent complete response (sCR), complete response (CR), very good partial response (VGPR), and partial response (PR) based on responses as assessed by the Independent Adjudication Committee (IAC) using the International Myeloma Working Group (IMWG) Uniform Response Criteria (Stage 1[(1)] , Stage 2 [(2)] see Appendix E)

Response evaluation will include:

- M-protein quantification (serum and 24-hr urine)
- Serum free light chain levels
- Bone marrow biopsy/aspiration
- PET-CT or MRI or CT scan of plasmacytoma
- Bone skeletal survey or low dose whole body CT scan
- Corrected serum calcium

In the Stage 2 part, response evaluation will be performed on a monthly basis. Responses (≥ PR) and progression should be confirmed on 2 consecutive biology (serum and/or urine M protein) disease assessments according to study flow-chart. Confirmation of response or progression will be performed within 4 weeks (to confirm response or progressive disease, two discrete samplers are required: testing cannot be based upon the splitting of a single sample). Progression based on images does not need to be confirmed.

In case of plasmacytoma at baseline, response assessment will include radiological every 2 cycles until progression.

9.2.3 Phase 2 secondary endpoints

9.2.3.1 Secondary efficacy endpoints:

- DOR: defined as the time from the date of the first IAC determined response to the date of subsequent IAC determined PD or death, whichever happens earlier. In the absence of the confirmation of subsequent IAC determined disease progression or death before the analysis cut-off date, the DOR will be censored at the date of the last valid assessment, the analysis cut-off date or date of initiation of new anticancer treatment, whichever is earlier. DOR is determined only for patients who have achieved a response of ≥ PR. DOR will not be calculated for patients that do not achieve a response.
- CBR: defined as the proportion of patients with sCR, CR, VGPR, PR or MR according to IMWG criteria, as determined by the IAC.
- PFS: defined as the time interval from the date of first study treatment administration to the date of the first IAC-assessed disease progression or the date of death due to any cause, whichever comes first. In the absence of 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 assessment performed before the cut-off date or the date of initiation of new anticancer treatment, whichever is earlier.

- OS: 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 analysis cut-off date, OS will be censored at the last date the patient is known to be alive or at the study cut-off date, whichever is earlier.

9.2.3.2 Electronic patient reported outcomes (Phase 2 Stage 1a and 1b only)

Health-related quality of life (HRQOL) and symptoms of multiple myeloma will be obtained through the use of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) and its myeloma-specific module (MY-20). Generic health status will be measured through the use of the EQ-5D. These will be captured electronically throughout the study.

The EORTC-QLQ-C30 and QLQ-MY20 as well as the EQ-5D (Appendix G, Appendix H) that will be completed by the patients in the Phase 2 part, as specified in the study flowchart (Section 1.13). These HRQOL and health status measures must be completed through the electronic format before other assessments are performed or study drug is administered, or before any information regarding current health or state of disease has been communicated to the patient. The EORTC QLQ-C30 and QLQ-MY20 questionnaires will be completed on Day 1 Cycle 1 then D1 of every cycle and at the EOT visit. The EQ-5D questionnaire will be completed on Day 1 Cycle 1 then D1 of every 3rd cycle starting Cycle 4 (ie, Cycle 4, 7, 10, etc) and at the EOT visit.

- The EORTC QLQ-30 is a cancer-specific instrument that contains 30 questions and provides a multi-dimensional assessment of HRQOL. The validity and reliability of the EORTC-QLQ-C30 has been established in various types of cancers, including multiple myeloma (46, 47). The QLQ-C30 is composed of both multi-item scales and single-item measures. These include five functional scales (physical functioning, role functioning, emotional functioning, cognitive functioning, and social functioning), three symptom scales (fatigue, nausea and vomiting, and pain), a Global Health Status (GHS)/quality of life scale, and six single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). All of the scales and single-item measures range in score from 0 to 100. A high score for a functional scale/GHS represents a high/healthy level of functioning/QOL, but a high score for a symptom scale/item represents a high level of symptomatology/problems. The time recall period for this instrument is 1 week.
- The QLQ-MY20 multiple myeloma module (20-items; (48) has 4 independent subscales, 2 functional subscales (body image, future perspective), and 2 symptoms scales (disease symptoms and side-effects of treatment). This will be administered following, yet in conjunction with the EORTC QLQ-C30.

These are reliable and valid measures of HRQOL in patients with cancer and takes about 15 minutes to administer. The instruments consist of a total of 50 items and have been validated and used in many countries.

- Generic health status will be assessed via the EQ-5D (49) The EuroQol EQ-5D (Appendix H) provides a simple descriptive profile and an overall numeric estimate of health utility/health status which can be used for both clinical and economic evaluations of health care. It is validated for use in a wide range of health conditions and treatments.

EQ-5D essentially consists of 2 pages - the EQ-5D descriptive system and the Visual Analogue Scale VAS. The EQ-5D descriptive system comprises 5 items: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each item has 3 levels: no problem, some problems, and severe problems. The Visual Analogue Scale (VAS) records the respondent's self-rated health on a vertical visual analogue scale. The VAS 'thermometer' has endpoints of 100 (Best imaginable health state) at the top and 0 (Worst imaginable health state) at the bottom. This information can be used as a quantitative measure of health outcome as judged by the individual respondents. The questionnaire is self-administered and takes about 5 minutes to complete. The 5 dimensional 3-level system will be converted into a single index utility score: values for the 243 theoretically possible health states defined by the EuroQol classification are calculated using a regression model (49).

The minimum value for the single index utility score (UK based) is -0.594, which corresponds to a level 3 (severe problems) for mobility, self-care, usual activities, pain/discomfort and anxiety/depression. The maximum value for this index is 1.0, which corresponds to a full health (level 1 (no problem) for mobility, self-care, usual activities, pain/discomfort and anxiety/depression).

9.3 PHARMACOKINETIC EVALUATION

The following PK parameters will be calculated with PKDMS software (Pharsight), using non-compartmental methods from plasma of SAR650984 concentrations obtained after single dose administration and/or using population PK modeling after repeated dose administration (Phase 2). The parameters will include, but may not be limited to the following:

- Maximum observed concentration (C_{max}).
- Concentrations just before drug infusion (C_{trough}).
- AUC over the dosing interval (AUC_{1week} or AUC_{2week}).

9.3.1 Phase 1 pharmacokinetic evaluations

During the Accelerated Phase, PK samples will be collected prior to, during, and after administration of Cycle 1 Day 1, then on Days 2, 3, and 8, and on Cycle 2 prior to and after drug administration on Day 1, then on Days 2, 3, 8, and 14 and at the end of study.

During Basic Phase (Cohorts 6-10), PK samples will be collected prior, during and after administration on Cycle 1, Day 1, then on Days 2, 3, and 8, then on Day 1 (prior to drug administration) of subsequent cycles, at the end of study and at 60 days after last IP administration. If a patient is positive or inconclusive for ADA at 60 days, additional ADA and PK samples will be collected at 90 days after the last drug administration and then every 30 days until the patient has a negative ADA sample.

During Basic Phase (with an every week administration of SAR650984, from Cohort 11), PK samples will be collected prior, during and after administration on Day 1, then on Days 2, 3, 4 and

8 of Cycle 1 and Cycle 3, then Day 1 and Day 8 (prior to drug administration) on Cycle 2 and all other cycles, at the end of study and at 60 days after last IP administration. If a patient is positive or inconclusive for ADA at 60 days, additional ADA and PK samples will be collected at 90 days after the last drug administration and then every 30 days until the patient has a negative ADA sample.

During Basic Phase (with an every 2 week administration of SAR650984, from Cohort 12), PK samples will be collected prior, during and after administration on Day 1 Cycle 1, 2 and, then on Days 2, 3, 4, and 8, then on Day 1 (prior to drug administration) of subsequent cycles, at the end of study and at 60 days after last IP administration. If a patient is positive or inconclusive for ADA at 60 days, additional ADA and PK samples will be collected at 90 days after the last drug administration and then every 30 days until the patient has a negative ADA sample.

9.3.2 Phase 2 pharmacokinetic evaluations

During the Phase 2 part, PK samples will be collected as detailed in Section 1.8 and Section 1.16.

Blood concentrations of SAR950894 will be used for population PK analysis by non-linear mixed effects modeling. Additional details of the analysis plan and the results could be provided in a separate document. This analysis will involve an estimation of inter-patient PK variability, the population pharmacokinetic parameters estimates and the assessments of patho-physiologic covariate effects on CL and possibly on volume if warranted. Empirical Bayesian estimation of individual parameters and of individual exposure (AUCs) will also be performed. PK estimates will then be investigated as prognostic factors for clinical outcome including safety and efficacy endpoints, if possible.

9.3.3 Sampling time and sample blood volume for Phase 1 and Phase 2

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

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

The sampling times for blood collection can be found in the PK Flowcharts (For Phase 1: Section 1.4, Section 1.5, Section 1.6, Section 1.7 and for Phase 2: Section 1.8 and Section 1.16).

Details of the sampled blood volume during Cycle 1 and further cycles, as appropriate are summarized in Appendix I.

9.3.4 PK handling procedure

Detailed in the laboratory manual and summarized in Appendix I.

9.4 IMMUNE RESPONSE

Human anti-drug antibodies to SAR650984 will be assessed throughout the Phase 1 and Phase 2 parts of the study. Blood samples will be collected for ADA detection according to the flowcharts (see Section 1).

Phase 1: In case of positivity or inconclusive sample at 60 days post last IP administration, additional assessment of ADA will be performed at 90 days and then every 30 days until sample is negative.

Phase 2 Stage 1: In case of positivity or inconclusive sample at 60 days post last IP administration, additional assessment of ADA will be performed at 90 days and then every 30 days until sample is negative.

Phase 2 Stage 2: In case of positivity of the last sample, one additional sample should be assessed in 3 months. No additional samples will be performed.

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

9.5 PHARMACODYNAMIC ASSESSMENT

For the Phase 1 part, CD38 receptor occupancy (RO) and receptor density (RD) will be assessed from bone marrow aspirates at the time points detailed in Section 1.8.

For the Phase 2 part (Stages 1a and 1b only), CD38 RD from baseline bone marrow aspirates will be correlated with parameters of clinical response, including overall response rate, clinical benefit rate, duration of response, PFS and/or OS.

For the Phase 2, Stages 1a and 1b parts only, CD38 RO will be assessed from bone marrow aspirates at the time points detailed in Section 1.8.

9.6 PHASE 2 EXPLORATORY BIOMARKER STUDIES

Exploratory biomarker handling procedures detailed in the laboratory manual and summarized in Appendix K.

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

- Myeloma cell CD38 mRNA levels from baseline bone marrow aspirates will be correlated with parameters of clinical response.
- Correlation of minimal residual disease (MRD) in bone marrow samples from patients achieving a CR with parameters of clinical response will be assessed by flow cytometry and/or sequencing. Traditional methods to measure MRD include multiparametric flow cytometry. More recently next generation sequencing to amplify and sequence immunoglobulin gene segments present in myeloma clone has also been used as a quantitative method for MRD detection. Bone marrow samples will be collected at CR confirmation.

- Chromosomal abnormalities such as del17p, t (4; 14), t (14; 16), 1q gain and 1p deletion; have been associated with poor prognosis and high risk in multiple myeloma (50, 51, 52). Baseline bone marrow samples will be collected for FISH analyses. In addition, results of local FISH/cytogenetic tests performed the most recently prior to patient enrollment may also be collected through report or access to data.
- For genomics studies, DNA and/or RNA will be isolated from multiple myeloma cells and sequenced to identify somatic mutations present only in the myeloma cells (not in the patient's germline, or heritable genome). Sequencing studies may include whole exome or whole genome sequencing (for DNA), or whole transcriptome sequencing to quantify gene expression or identify expressed gene fusions, mutations or other tumor-specific transcripts. A source of normal DNA (non-tumor DNA), from blood leukocytes may also be sequenced. For the purposes of myeloma genomics, the normal (non-tumor) DNA sequence will be used only as a reference genome for the identification of myeloma-specific somatic mutations in a given patient. The normal (non-tumor) DNA sequence will not be used to determine risk or prognosis of multiple myeloma or other malignancies, or used in any other disease-specific research unless explicitly granted by separate pharmacogenetic consent.
- Sequencing will also be performed at EOT with tumor DNA in patients who have responded to the study treatment but subsequently develop progressive disease to identify acquired mutations that may elucidate potential resistance mechanism.Genomics analyses will be performed only in Phase 2 Stage 1 only.
- Correlation of immune genetic determinants (FcγR genes, HLA and KIR genotypes) with parameters of clinical response. This germline genetic analysis is a mandatory part of the protocol and will not be performed under separate pharmacogenetic consent. Blood samples collected on D1 of Cycle 1 will be used for this analysis.
- Correlation of adaptive immune response (TCR repertoire profiling) with parameters of clinical response. Blood samples collected on D1 of Cycle 1, D1 of Cycle 3 and on D1 of Cycle 5 will be used for this analysis. In addition, humoral (antibody) and cellular (T cell) response to a panel of multiple myeloma-related tumor antigenes following isatuximab administration will be assessed and correlated with clinical response. Blood samples will be collected on Day 1 of Cycles 1, 2, 4, 7, 10 and in disease progression patients at EOT. Cellular response analysis will be performed in patients who have positive humoral response. These analyses will be performed in Phase 2 Stage 2 only.
- Correlation of immune phenotype in bone marrow and/or peripheral blood with parameters of clinical response. Immune cell populations including B-cell, T-cell and NK-cell subsets will be characterized by multiparametric flow cytometry based on the expression of cell surface markers. The proportion of cells positive for a given marker or set of markers (eg, regulatory T cells [Tregs]) will be correlated with response to SAR650984. Bone marrow aspirate collected at baseline and blood samples collected at D1 of Cycle 1, D1 of Cycle 3 and EOT will be used for this analysis.
- Soluble CD38 level will be correlated with parameters of PK and clinical response. In Phase 2 Stage 1, blood samples collected at D1 Cycle 1, D1 of Cycle 3, and EOT in disease progression patients will be used for soluble CD38 analysis.

- Additional molecular analysis, not specified in the protocol but related to the drug action and/or effect of SAR650984, may be conducted on remaining samples pending evolving literature.

10 PATIENT SAFETY

10.1 SAFETY ENDPOINTS ASSESSED IN THIS TRIAL

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

The safety profile will be based on incidence, severity, and cumulative nature of TEAEs. TEAEs are defined as AEs that develop or worsen in grade or become serious during the on-treatment period.

Adverse events encountered before the start of SAR650984 treatment will be summarized separately. Adverse events will be coded to a "Lower Level Term (LLT)", "Preferred Term (PT)", "High Level Term (HLT)", "High Group Level Term (HGLT)" and associated primary "System Organ Class (SOC)" using MedDRA (Medical Dictionary for Regulatory Activities). AEs will be summarized with respect to the type, frequency, severity, seriousness, and relatedness. Laboratory abnormalities will be assessed according to the NCI CTCAE v.4.03.

Please also refer to Section 9.1.

10.2 SAFETY INSTRUCTIONS

The safety of the patients in this clinical trial is primarily dependent on the clinical Investigators' monitoring and assessment of their patients. For hypersensitivity reactions, please refer to Section 6.5.

10.3 ADVERSE EVENTS MONITORING

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

10.4 DEFINITIONS OF ADVERSE EVENT (AE) AND SERIOUS ADVERSE EVENT (SAE)

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

A SAE is any untoward medical occurrence that at any dose:

- Results in death or;
- Is life-threatening or;

Note: The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

- Requires inpatient hospitalization or prolongation of existing hospitalization or;
- Results in persistent or significant disability/incapacity or;
- Is a congenital anomaly/birth defect;
- Is a medically important event:

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above.

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

10.5 OBLIGATION OF THE INVESTIGATOR REGARDING SAFETY REPORTING

10.5.1 Adverse events

All AEs regardless of seriousness or causal relationship to the Investigational Product, spanning from the signature of the informed consent form (ie, occurring during the wash out period even in the absence of any administration of IP), up to the last visit planned in the protocol (ie, up to 30 days after the last IP administration), are to be recorded on the corresponding page(s) included in the Case Report Form.

All IP-related AEs and all SAEs (regardless of their causal relationship to study treatment) ongoing at the time of study treatment discontinuation need to be followed during the follow-up period until resolution or stabilization.

Whenever possible, diagnosis or single syndrome should be reported instead of symptoms (with the exception of IARs for which a main diagnosis IAR and individual symptoms should be reported).The Investigator should specify the date of onset, intensity, action taken with respect to Investigational Product, corrective treatment/therapy given, additional investigations performed, outcome and his/her opinion as to whether there is a reasonable possibility that the AE was caused by the Investigational Product.

Laboratory, vital signs or ECG abnormalities are to be recorded as Adverse Events only if they lead to treatment discontinuation and/or modification of treatment administration (delay, reduction, omission) or fulfill a seriousness criterion and/or are defined as an Adverse Event of Special Interest (AESI) (see Section 10.6).

10.5.2 Serious adverse events

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

- ENTER (within 24 hours) the information related to the Serious Adverse Event in the appropriate screens of the e-CRF; the system will automatically send the notification to the Monitoring Team after approval of the Investigator within the e-CRF or after a standard delay.
- There may be instances when copies of medical records for certain cases are requested by Sanofi. In such case, care should be taken to ensure that the patient's identity is protected and the patient's identifiers in the study are properly mentioned on any copy of a source document provided to the Company. For laboratory results, include the laboratory normal ranges.
- When cohorts of more than one patient begin accruing, the monitoring team will notify the study investigators of the occurrence of DLTs and SAEs within 24 hours.
- All further data updates should be recorded in the e-CRF as appropriate within 1 working day of knowledge. In addition, every effort should be made to further document each Serious Adverse Event that is fatal or life threatening within the week (7 days) following initial notification.
- A back-up plan is used (using paper flow) when the e-CRF system does not work.

10.5.3 Follow-up

- The Investigator should take all appropriate measures to ensure the safety of the patients, notably he/she should follow up the outcome of any AEs (clinical signs, laboratory values or other, etc) until the return to normal or consolidation of the patient's condition;
- In case of any Serious Adverse Event, the patient must be followed up until clinical recovery is complete and laboratory results have returned to normal, or until outcome has been stabilized. This may imply that follow-up may continue after the patient has left the Clinical Trial and that additional investigations may be requested by the Monitoring Team;
- In case of any Serious or Non Serious Adverse Event brought to the attention of the Investigator at any time after cessation of Investigational Product and considered by him/her to be caused by the Investigational Product with a reasonable possibility, this should be reported to the Monitoring Team.
- Follow-up information for any events entered in the pharmacovigilance database will be entered in the pharmacovigilance database at any time irrespective of the clinical database lock. GPE may also request follow-up on Individual Case Safety Reports received for entry in the pharmacovigilance database.

10.5.4 Treatment discontinuation due to non-serious adverse event

In the case of a treatment discontinuation due to a non-Serious Adverse Event:

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

10.6 ADVERSE EVENT OF SPECIAL INTEREST (AESI)

An AESI is an AE (serious or non-serious) of scientific and medical concern specific to SAR650984, for which ongoing monitoring and rapid communication by the Investigator to sanofi-aventis is required (see Section 10.5). Such adverse events may require further investigation in order to characterize and understand them. Adverse events of special interest may be added or removed during a study by protocol amendment.

The following adverse events are considered AESIs:

- Acute infusion associated reactions ≥ Grade 3 (IARs; “please refer to the current edition of the IB for IARs manifestations reported in patients treaded with isatuximab”). An IAR is an adverse event related to SAR650984 with onset within 24 hours from the start of the infusion. A main diagnosis and individual symptoms should be reported in the eCRF as AESIs in order to well characterize IARs.
- During Phase 1, all protocol-defined potential or IP related DLTs (as defined in Section 9.1.1) are considered AESIs, and as such, the Investigators will be required to report them to the Sponsor within 24 hours of the Investigator becoming aware of the adverse event. The Investigator will attach the DLT-specific CRF page to the DLT/AESI form.

When cohorts of more than one patient begin accruing, the monitoring team will notify the study investigators of the occurrence of DLTs and SAEs within 24 hours.

- Pregnancy occurring in a female patient entered in the clinical trial or in a female partner of a male patient entered in the clinical trial will be qualified as an SAE only if it fulfills one of the seriousness criteria (see Section 10.4). In the event of pregnancy in a female participant, treatment with the IP should be discontinued.

Follow-up of the pregnancy in a female patient or in a female partner of a male participant is mandatory until the outcome has been determined (see Section 10.7).

- Symptomatic overdose (serious or non-serious) of IP/Non-Investigational medinical product (NIMP) An overdose (accidental or intentional) with the IMP/NIMP is an event suspected by the Investigator or spontaneously notified by the patient (not based on systematic pills count) and defined as at least 30% above the intended administered dose.
- Of note, asymptomatic overdose has to be reported as a standard AE.

10.7 PREGNANCY

- Pregnancy of a female subject entered in a study (as well as pregnancy occurring in a female partner of a male subject entered in this study) will be recorded as an AE in all cases. It will be qualified as a SAE only if it fulfills SAE criteria.
- In the event of pregnancy in a female subject, Investigational Product should be discontinued and sanofi-aventis Monitoring Team should be informed immediately (within 24 hours), even if the event does not fulfill a seriousness criterion, using the AE form together with the SAE complementary form to be sent to the representative of the Monitoring Team whose name, address and fax number appear on page 2 of the clinical trial protocol.
- Follow-up of the pregnancy is mandatory until the outcome has been determined.

10.8 OVERDOSE

In case of accidental or intentional overdose (at least 30% above the intended administered dose at each cycle expressed in unit per body weight) with the IP, even not fulfilling a seriousness criterion is to be reported to the Sponsor immediately (within 24 hours) using the AE form together with the SAE complementary form to be entered in the e-CRF.

10.9 OBLIGATIONS OF SANOFI-AVENTIS

During the course of the study, sanofi-aventis will report in an expedited manner all SAEs that are both unexpected and at least reasonably related to the IP according to applicable regulations and as appropriate, to the Authorities, Independent Ethic Committes (IECs) /Institional Review Boards (IRBs) as appropriate and to the Investigators.

All AEs not listed as expected events in the Investigator's Brochure will be considered as unexpected.

Sanofi-aventis will report all safety observations made during the conduct of the trial in the CSR.

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

The Investigational Product should be continued whenever possible in accordance with the Investigator's judgment and patient consent. In case the IP is stopped, it should be determined if the stop can be made temporarily; permanent IP discontinuation should be a last resort. Any IP discontinuation should be fully documented in the CRF. In any case, the patient should remain in the study as long as possible.

Pregnancy will lead to definitive treatment discontinuation in all cases.

11.1 TEMPORARY TREATMENT DISCONTINUATION WITH INVESTIGATIONAL PRODUCT

From oncology perspectives, temporary treatment discontinuation may correspond to "retreatment of patients" and "dose-delays/modifications:" Section 6.3 and Section 6.4.

11.2 DEFINITIVE TREATMENT DISCONTINUATION WITH INVESTIGATIONAL PRODUCT(S)

The patients may withdraw from treatment with Investigational Product if they decide to do so, at any time and irrespective of the reason, or this may be the Investigator's decision. All efforts should be made to document the reason for discontinuation and this should be documented in the CRF.

11.2.1 List of criteria for definitive treatment discontinuation

Investigational Product should be discontinued in any of the following cases:

- Unacceptable AE.
- Disease progression.
- Poor compliance to the study protocol.
- Study termination.
- Patients lost to follow up will also be considered permanently discontinued, as of the time of their last IP administration.

11.2.2 Handling of patients after definitive treatment discontinuation

Patients will be followed up according to the study procedures as specified in this protocol up to the study cut-off date, or up to recovery or stabilization of a study drug related AE or SAE (regardless of casual relationship to study drug) which has been followed-up, whichever comes last.

If possible, and after the permanent discontinuation of treatment, the patients will be assessed using the procedure normally planned for the last dosing day with the Investigational Product including a PK sample, if appropriate.

All definitive treatment discontinuation should be recorded by the Investigator in the appropriate pages when considered as confirmed.

Patients who have been withdrawn from the study cannot be re-included in the study.

11.3 PROCEDURE FOR WITHDRAWAL OF PATIENTS FROM STUDY FOLLOW-UP SCHEDULE

The patients may withdraw from the study follow-up schedule, before study completion if they decide to do so, at any time and irrespective of the reason:

- All study withdrawals should be recorded by the Investigator in the appropriate CRF pages or screens of the e-CRF and in the patient's medical records when considered as confirmed (at least date of and reason for withdraw).
- If possible, the patients are assessed using the procedure normally planned for the end-of-study visit including a PK sample, if appropriate (or according to other procedures to be specified here such as follow-up phase).

The Investigator should make every effort to recontact the patient, to identify the reason why he/she failed to attend the visit, and to determine his/her health status, including at least his/her vital status. Attempts to contact such patients must be documented in the patient's records (eg, times and dates of attempted telephone contact, receipt for sending a registered letter).

11.4 CONSEQUENCE

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

In the Phase 1 part patients who withdraw from the study treatment may be replaced if considered to be appropriate by the Study Committee.

In the Phase 2 part, only screened patients who did not meet the study inclusion/exclusion criteria and were not treated will be replaced.

12 STUDY PROCEDURES

12.1 PHASE 1 VISIT SCHEDULE

During the course of the study, all patients entering the study must be evaluated according to the schedules outlined in the Study Flowcharts and described below. The results of the evaluation will be recorded in the e-CRF pages until the patients are not followed anymore. After the screening/baseline visit, all the patients eligible and included in the study will have a visit on site as detailed below. A complete visit will be performed at End of Treatment (30 days (+/-5 days) after last IP administration). The patients will be followed beyond 30 days until recovery or consolidation of any IP related AE. Additionally, PK and ADA samples are required (60 days) (+/-5 days) after last IP administration). In the Phase 1 part, a cycle is 14 days.

12.1.1 Pretreatment evaluation (screening/baseline)

The pretreatment examinations are to be performed within 15 days (unless specified otherwise) prior to the first IP administration. The informed consent must be signed by the patient before any procedure specific to the study is performed.

- History and Clinical Examination:
  - Medical/Surgical History: includes relevant history of previous/associated pathologies, other than the tumor.
  - Disease History: includes date of initial diagnosis, stage and extent of the disease, previous anti-tumor therapy (type and response to), disease status at inclusion (primary refractory, refractory to last therapy, or recurrent), results of additional procedures (such as karyotype, FISH, etc).
  - Prior anti-cancer therapies and Concomitant Medications.
  - Physical Examination: consists of examination of major body systems, including neurological, digestive exam, extramedullary myeloma localizations, respiratory, hepatomegaly, splenomegaly, lymphadenopathy.
  - Weight and Height.
  - Vital Signs: includes blood pressure, heart rate, temperature, and respiration rate.
  - Performance Status (Karnofsky).
- Laboratory Assessments:
  - CD38 Expression (for Cohorts 1-10): Archival samples may be used. If no archival sample, will be assessed at screening by flow cytometry and/or immunohistochemistry using malignant cells from peripheral blood, bone marrow and/or lymph node tissue depending on the disease type. When feasible, bone marrow and tissue samples will be obtained by Fine Needle Aspiration (FNA).
  - Serum β2-microglobulin (CLL, MM only).
  - Immunoglobulins: IgG, IgA, IgM (MM only).

- Pregnancy Test: women of child bearing potential must have a negative serum pregnancy test result within 7 days prior to first IP administration.
- Blood Chemistry: SGOT (AST), SGPT (ALT), bilirubin (total and direct), alkaline phosphatase (AP), lactate dehydrogenase (LDH), sodium, potassium, chloride, bicarbonate/carbon dioxide, calcium, magnesium, phosphate, uric acid, blood urea nitrogen (BUN), serum creatinine and estimated creatinine clearance, glucose, albumin, total protein, peptide C, Erythrocyte sedimentation rate (ESR).
- Hematology: hemoglobin, hematocrit, RBC, WBC with differential, MCV, platelet count, blast counts (B-cell ALL/AML).
- Coagulation: PT/INR, PTT.
- Urinalysis: blood, protein, glucose, pH, ketones, bilirubin, leucocytes, nitrates, specific gravity.

- Disease Assessment**:** (Up to 28 days prior to first IP administration):
  - MM: Bone marrow biopsy/aspiration as clinically indicated, radiologic imaging of plasmocytoma as clinically indicated, bone skeletal survey as clinically indicated, M-protein quantification (serum and/or 24-hr urine), serum free light chain levels, or urinary light chain levels as clinically indicated.
  - B-cell NHL: Bone marrow biopsy/aspiration as clinically indicated, lymph node biopsy as clinically indicated, radiologic tumor assessment (by X-ray, computed tomography [CT] scan, PET scan or magnetic resonance imaging [MRI]; ultrasound is not sufficient).
  - B-cell ALL: Bone marrow biopsy/aspiration as clinically indicated, blood count with differential including blast count.
  - AML: Bone marrow biopsy/aspiration as clinically indicated, blood count with differential including blast count.
  - CLL: Clinical examination, bone marrow biopsy/aspiration as clinically indicated, lymph node biopsy as clinically indicated, blood count with differential.

Patients who meet all the inclusion criteria, and none of the exclusion criteria, will be eligible for inclusion in the study. Each patient will receive an incremental identification number corresponding to his/her order of enrollment in the study.

12.1.2 Assessments for patients with an every 2 week administration (Cohorts 1-10)

12.1.2.1 Before the first investigational product administration and prior to IP administration at each cycle (within 1 day before)

The same parameters as performed at screening/baseline will be performed for each of the required evaluations. The evaluations below are to be performed prior to first IP administration.

- Clinical Examination: includes physical examination, weight, vital signs, and performance status.

- Chest X-ray, Spirometry, Diffusion Capacity (can be performed within one week prior to IP administration for the first 2 cycles and then as clinically indicated)
- Laboratory Assessments:
  - Pregnancy Test: a negative urine pregnancy test result required prior to IP administration at each cycle.
  - Blood Chemistry including blood glucose measurement.
  - Hematology.
  - PSA, Pituitary Hormone Levels (GH, FSH/LH, ACTH, TSH).
  - Coagulation.
  - Urinalysis.
  - hs-CRP.
  - Cytokines (TNF-α, IL-1-β, IL-6, IFN-γ) (Baseline sample to be drawn prior to first IP administration at Cycle 1).
  - PK/RO/ADA: (see Pharmacokinetics/Pharmacodynamics Accelerated/Basic Flowcharts) (RO at Cycles 1 and 2 only).
- 12-Lead ECG: Baseline to be performed just before starting infusion and as clinically indicated throughout the study. Will be reviewed by central cardiologist.
- Holter Monitoring: To be placed on the patient 1-2 hours before starting the infusion and remain on the patient until 24 hours after the infusion (Cycles 1 and 2); to detect atrio-ventricular conduction abnormalities, other potential ventricular arrhythmias, QTc. Will be reviewed by central cardiologist.

12.1.2.2 During the treatment period (Cycles 1 and 2)

(Day 1)

- SAR650984 Administration
- Vital Signs: middle of infusion (basic phase), end of infusion, and 1, 2, 4, and 6 hours post-infusion.
- ECG: to be performed just before starting infusion, middle of infusion (Basic Phase), and end of infusion.
- Laboratory Assessments:
  - hs-CRP: 6 hours post-infusion
  - Cytokines: 6 hours post-infusion
  - PK/RO: (see Pharmacokinetics/Pharmacodynamics Accelerated/Basic Flowcharts)
  - Blood Chemistry: end of infusion, 6 hours post-infusion

(Day 2)

- Vital Signs: 24 hours post-infusion
- Laboratory Assessments:
  - hs-CRP: 24 hours post-infusion.
  - Cytokines: 24 hours post-infusion.
  - PK/RO: (see Pharmacokinetics/Pharmacodynamics Accelerated Flowchart).
  - Blood Chemistry: 24 hours post-infusion.
- Holter Monitoring: Will be removed 24 hours after the infusion

(Day 3)

- Laboratory Assessments:
  - PK/RO/ADA: (see Pharmacokinetics/Pharmacodynamics Accelerated/Basic Flowcharts) (Cycle 1); PK/RO: (see Pharmacokinetics/Pharmacodynamics Accelerated Flowchart) (Cycle 2).

(Day 8)

- Clinical Examination: includes physical examination, vital signs, and performance status
- Laboratory Assessments:
  - Blood Chemistry
  - Hematology
  - Coagulation
  - Urinalysis
  - PK: (see Pharmacokinetics/Pharmacodynamics Accelerated/Basic Flowcharts)
- 12-Lead ECG

(Day 14)

- Clinical Examination: includes physical examination, weight, vital signs, and performance status.
- Laboratory Assessments:
  - Serum β2-microglobulin (CLL, MM only).
  - Immunoglobulins: IgG, IgA, IgM (MM only).
  - Pregnancy Test: urine (Cycle 2).
  - Blood Chemistry.
  - Hematology.
  - PSA, Pituitary Hormone Levels (GH, FSH/LH, ACTH, TSH): (Cycle 2).

- Coagulation.
- Urinalysis.
- hs-CRP (Cycle 2).
- PK/RO/ADA: (see Pharmacokinetics/Pharmacodynamics Accelerated/Basic Flowcharts) (Cycle 2).

- 12-Lead ECG: (Cycle 2).
- Disease Assessment: Response is assessed on the basis of clinical, laboratory, radiologic, and pathologic (ie, bone marrow) findings at the end of Cycle 2, to determine if patient is eligible to continue treatment.

12.1.2.3 During the treatment period (subsequent cycles)

Patients continuing after Cycle 2 will have evaluations performed as per Section 12.1.2.2 (prior to IP administration), Day 1, Day 2, and Day 8 (for weekly administration only) above.

The below assessments will be done every 4 weeks (end of even-numbered cycles)

- Laboratory Assessments:
  - Serum β2-microglobulin (CLL, MM only).
  - Immunoglobulins: IgG, IgA, IgM (MM only).
- Disease Assessment: Patients continuing after Cycle 2 should be evaluated for disease status at least every 4 weeks (even-numbered cycles), whenever disease progression is suspected (eg, symptomatic deterioration), to confirm a partial or complete response (4-6 weeks after initial documentation of response), and at the End of Treatment visit.

12.1.3 Assessments for patients with an every week administration (from Cohort 11)

12.1.3.1 Before the first investigational product administration and prior to IP administration at each cycle (within 1 day before)

The same parameters as performed at screening/baseline will be performed for each of the required evaluations. The evaluations below are to be performed prior to first IP administration on Day 1 and Day 8.

- Clinical Examination: includes physical examination, weight (Day 1 only), vital signs, and performance status.
- Chest X-ray, Spirometry, Diffusion Capacity (Day 1 only, can be performed within one week prior to IP administration for the first 2 cycles and then as clinically indicated)
- Laboratory Assessments:
  - Pregnancy Test: a negative urine pregnancy test result required prior to IP administration on Day 1 at each cycle.

- Blood Chemistry including blood glucose measurement.
- Hematology.
- PSA, Pituitary Hormone Levels (GH, FSH/LH, ACTH, TSH) (Day 1 only).
- Coagulation.
- Urinalysis.
- hs-CR.
- Cytokines (TNF-α, IL-1-β, IL-6, IFN-γ) (Baseline sample to be drawn prior to first IP administration at Cycle 1).

PK/RO/ADA: (see Pharmacokinetics/Pharmacodynamics Flowcharts Section 1.6, Cycle 1 and 2 only)

- 12-Lead ECG: Baseline to be performed just before starting infusion and as clinically indicated throughout the study. Will be reviewed by central cardiologist.
- Holter Monitoring: To be placed on the patient 1-2 hours before starting the infusion and remain on the patient until 24 hours after the infusion (Cycles 1 and 2); to detect atrio-ventricular conduction abnormalities, other potential ventricular arrhythmias, QTc. Will be reviewed by central cardiologist.

12.1.3.2 During the treatment period (Cycles 1, 2 and 3)

(Day 1 and Day 8)

- SAR650984 Administration
- Vital Signs: middle of infusion, end of infusion, and 1, 2, 4, and 6 hours post-infusion.
- ECG: to be performed just before starting infusion, middle of infusion, and end of infusion.
- Laboratory Assessments:
  - hs-CRP: 6 hours post-infusion
  - Cytokines: 6 hours post-infusion

PK: (see Pharmacokinetics/Pharmacodynamics Flowcharts Section 1.6, Cycle 1 and 3 only)

- Blood Chemistry: end of infusion, 6 hours post-infusion

(Day 2)

- Vital Signs: 24 hours post-infusion (Cycle 1 and 2 only)
- Laboratory Assessments:
  - hs-CRP: 24 hours post-infusion (Cycle 1 and 2 only)
  - Cytokines: 24 hours post-infusion (Cycle 1 and 2 only)

PK: (see Pharmacokinetics/Pharmacodynamics Flowchart Section 1.6, Cycle 1 and 3 only)

- Blood Chemistry: 24 hours post-infusion (Cycle 1 and 2 only)

- Holter Monitoring: Will be removed 24 hours after the infusion (Cycle 1 and 2 only)

(Day 3, Cycle 1 and 3 only)

- Laboratory Assessments:

PK/ADA: (see Pharmacokinetics/Pharmacodynamics Flowcharts Section 1.6)

(Day 4, Cycle 1 and 3 only)

- Laboratory Assessments:
  - PK: (see Pharmacokinetics/Pharmacodynamics Flowcharts Section 1.6)

(Day 14, Cycle 1 and 2 only)

- Clinical Examination: includes physical examination, weight, vital signs, and performance status.
- Laboratory Assessments:
  - Serum β2-microglobulin.
  - Immunoglobulins: IgG, IgA, IgM.
  - Pregnancy Test: urine (Cycle 2).
  - Blood Chemistry.
  - Hematology.
  - PSA, Pituitary Hormone Levels (GH, FSH/LH, ACTH, TSH): (Cycle 2).
  - Coagulation.
  - Urinalysis.
  - RO: (see Pharmacokinetics/Pharmacodynamics Flowcharts Section 1.6) (Cycle 2).
- 12-Lead ECG: (Cycle 2).
- Disease Assessment: Response is assessed on the basis of clinical, laboratory, radiologic, and pathologic (ie, bone marrow) findings at the end of Cycle 2, to determine if patient is eligible to continue treatment.

12.1.3.3 During the treatment period (subsequent cycles)

Patients continuing after Cycle 2 will have evaluations performed as per Section 12.1.3.2 (prior to IP administration) Day 1 and Day 8 above.

The below assessments will be done every 4 weeks (end of even-numbered cycles)

- Laboratory Assessments:
  - Serum β2-microglobulin.

- Immunoglobulins: IgG, IgA, IgM.

Disease Assessment: Patients continuing after Cycle 2 should be evaluated for disease status at least every 4 weeks (even-numbered cycles), whenever disease progression is suspected (eg, symptomatic deterioration), to confirm a partial or complete response (4-6 weeks after initial documentation of response), and at the End of Treatment visit.

12.1.4 Assessments for patients with an every 2 week administration (from Cohort 12)

12.1.4.1 Before the first investigational product administration and prior to IP administration at each cycle (within 1 day before)

The same parameters as performed at screening/baseline will be performed for each of the required evaluations. The evaluations below are to be performed prior to first IP administration.

- Clinical Examination: includes physical examination, weight, vital signs, and performance status.
- Chest X-ray, Spirometry, Diffusion Capacity (can be performed within one week prior to IP administration for the first 2 cycles and then as clinically indicated)
- Laboratory Assessments:
  - Pregnancy Test: a negative urine pregnancy test result required prior to IP administration at each cycle.
  - Blood Chemistry including blood glucose measurement.
  - Hematology.
  - PSA, Pituitary Hormone Levels (GH, FSH/LH, ACTH, TSH).
  - Coagulation.
  - Urinalysis.
  - hs-CRP.
  - Cytokines (TNF-α, IL-1-β, IL-6, IFN-γ) (Baseline sample to be drawn prior to first IP administration at Cycle 1).
  - PK/RO/ADA: (see Pharmacokinetics/Pharmacodynamics Flowcharts Section 1.7, Cycle 1 and 2 only).
- 12-Lead ECG: Baseline to be performed just before starting infusion and as clinically indicated throughout the study. Will be reviewed by central cardiologist.
- Holter Monitoring: To be placed on the patient 1-2 hours before starting the infusion and remain on the patient until 24 hours after the infusion (Cycles 1 and 2); to detect atrio-ventricular conduction abnormalities, other potential ventricular arrhythmias, QTc. Will be reviewed by central cardiologist.

12.1.4.2 During the treatment period (Cycles 1 and 2)

(Day 1)

- SAR650984 Administration
- Vital Signs: middle of infusion, end of infusion, and 1, 2, 4, and 6 hours post-infusion.
- ECG: to be performed just before starting infusion, middle of infusion, and end of infusion.
- Laboratory Assessments:
  - hs-CRP: 6 hours post-infusion.
  - Cytokines: 6 hours post-infusion.

PK: (see Pharmacokinetics/Pharmacodynamics Flowcharts Section 1.7)

  - Blood Chemistry: end of infusion, 6 hours post-infusion.

(Day 2)

- Vital Signs: 24 hours post-infusion.
- Laboratory Assessments:
  - hs-CRP: 24 hours post-infusion.
  - Cytokines: 24 hours post-infusion.

PK: (see Pharmacokinetics/Pharmacodynamics Flowcharts Section 1.7)

  - Blood Chemistry: 24 hours post-infusion.
- Holter Monitoring: Will be removed 24 hours after the infusion

(Day 3, Cycle 1 only)

- Laboratory Assessments:

PK/ADA: (see Pharmacokinetics/Pharmacodynamics Flowcharts Section 1.7)

(Day 4, Cycle 1 only)

- Laboratory Assessments:

PK: (see Pharmacokinetics/Pharmacodynamics Flowcharts Section 1.7)

(Day 8)

- Clinical Examination: includes physical examination, vital signs, and performance status
- Laboratory Assessments:
  - Blood Chemistry.
  - Hematology.
  - Coagulation.

- Urinalysis.

PK: (see Pharmacokinetics/Pharmacodynamics Flowcharts Section 1.7, Cycle 1 only)

- 12-Lead ECG.

(Day 14)

- Clinical Examination: includes physical examination, weight, vital signs, and performance status.
- Laboratory Assessments:
  - Serum β2-microglobulin.
  - Immunoglobulins: IgG, IgA, IgM.
  - Pregnancy Test: urine (Cycle 2).
  - Blood Chemistry.
  - Hematology.
  - PSA, Pituitary Hormone Levels (GH, FSH/LH, ACTH, TSH): (Cycle 2).
  - Coagulation.
  - Urinalysis.
  - RO: (see Pharmacokinetics/Pharmacodynamics Flowcharts Section 1.7) (Cycle 2).
- 12-Lead ECG: (Cycle 2).
- Disease Assessment: Response is assessed on the basis of clinical, laboratory, radiologic, and pathologic (ie, bone marrow) findings at the end of Cycle 2, to determine if patient is eligible to continue treatment.

12.1.4.3 During the treatment period (subsequent cycles)

Patients continuing after Cycle 2 will have evaluations performed as per Section 12.1.4.1 (prior to IP administration) and Day 1 above.

The below assessments will be done every 4 weeks (end of even-numbered cycles)

- Laboratory Assessments:
  - Serum β2-microglobulin.
  - Immunoglobulins: IgG, IgA, IgM.
- Disease Assessment: Patients continuing after Cycle 2 should be evaluated for disease status at least every 4 weeks (even-numbered cycles), whenever disease progression is suspected (eg, symptomatic deterioration), to confirm a partial or complete response (4-6 weeks after initial documentation of response), and at the End of Treatment visit.

12.1.5 During the treatment period (all cycles, all cohorts)

- AE/SAE Assessment.
- Concomitant Medication.

12.1.6 End of treatment visit (to be performed at least 30 days (+/-5 days) after the last investigational product administration)

- Clinical examination: includes physical examination, weight, vital signs, and performance status.
- Chest X-ray, Spirometry, Diffusion Capacity
- Laboratory Assessments:
  - Serum β2-microglobulin (CLL, MM only).
  - Immunoglobulins: IgG, IgA, IgM (MM only).
  - Pregnancy Test: serum.
  - Blood Chemistry.
  - Hematology.
  - PSA, Pituitary Hormone Levels (GH, FSH/LH, ACTH, TSH).
  - Coagulation.
  - Urinalysis.
  - hs-CRP.
  - PK/RO/ADA: (see Pharmacokinetics/Pharmacodynamics Accelerated/Basic Flowcharts).
- 12-lead ECG.
- Disease Assessment.
- AE/SAE Assessment.
- Concomitant Medication.

12.1.7 Follow-up period (>30 days after last IP administration)

- Laboratory Assessment:
  - PK/ADA: (60 days (+/-5 days) after last IP administration and then if sample is positive or inconclusive, every 30 days (+/-5 days) until sample is negative).
- AE/SAE Assessment: (if IP-related AE and/or unresolved toxicity).
- Concomitant Medication: (if IP-related AE and/or unresolved toxicity).

12.2 PHASE 2 VISIT SCHEDULE

During the course of the study, all patients entering the study must be evaluated according to the schedules outlined in the Study Flowchart (Section 1.13,Section 1.14 and Section 1.15) and described below. The results of the evaluation will be recorded in the eCRF pages until the patients are not followed anymore. In the Phase 2 part, a cycle is 28 days.

12.2.1 Pretreatment evaluation (screening/baseline)

The pretreatment examinations are to be performed within 21 days (unless specified otherwise) prior to the first IP administration. The informed consent must be signed by the patient before any procedure specific to the study is performed.

- History and Physical Examination:
  - Demography: Includes age, gender and race.
  - Medical/Surgical History: includes relevant history of previous/associated pathologies, other than multiple myeloma. Respiratory function history will be checked.
  - Disease History: includes date of initial diagnosis, stage and disease sybtype, previous anti-tumor therapy (drug names, reason for discontinuation, duration and response to), results of additional procedures (such as karyotype, FISH, etc).
  - Prior medications
  - Physical Examination: consists of examination of major body systems, including neurological, digestive exam, plasmacytoma assessment, respiratory, hepatomegaly, splenomegaly, lymphadenopathy
  - Weight and Height
  - Vital Signs: includes blood pressure, heart rate, temperature, and respiration rate
  - Performance Status (Karnofsky) in Phase 1 and Phase 2 Stage 1 and ECOG Performance status in Phase 2 Stage 2)
- AE/SAE assessment
- 12-Lead ECG
- Chest X-ray
- Laboratory Assessments:
  - Pregnancy Test: women of child bearing potential must have a negative serum pregnancy test result within 7 days prior to first IP administration.
  - Blood Chemistry: SGOT (AST), SGPT (ALT), bilirubin (total and direct), alkaline phosphatase (AP), lactate dehydrogenase (LDH), sodium, potassium, chloride, bicarbonate/carbon dioxide, ionized calcium and corrected serum calcium, magnesium, phosphate, uric acid, blood urea nitrogen (BUN), serum creatinine and estimated creatinine clearance (using Cockcroft and Gault formula [(140 - age) x mass (kg) / (72 x creatinine mg/dL)], multiply result by 0.85 if female), glucose, albumin and total

protein. In Stage 2 the estimated Glomerular Filtration Rate will be calculated according the Modification of diet in Renal Disease (MDRD) equation (see Appendix B).

- Hematology: hemoglobin, hematocrit, RBC, WBC with differential, MCV, platelet count.
- Blood type (if not already done), complete blood phenotyping (C,c; E,e; Kell. Kidd; Duffy; S,s) and antibody screening (Indirect Coombs test, Indirect Antiglobulin Test (IAT)) only to be obtained prior C1D1 administration (blood type card will be kept by the patient with the study card). Antibody screen information made before any blood transfusion and blood transfusions are to be recorded in the eCRF if performed during the study treatment. The blood bank needs to be informed that the patient is receiving a treatment with an anti-CD38 and a potential interference with the indirect Coombs test is possible.
- A blood type card will be provided to the patient indicating he (she) is receiving an anti-CD38 treatment and the site will notify its blood bank that the patient is receiving an anti-CD38 treatment (see Appendix K).
- Coagulation: PT/INR, PTT.
- Urinalysis: blood, protein, glucose, pH, ketones, bilirubin, leucocytes, nitrates, specific gravity.
- Serum β2-microglobulin

- Disease Assessment: (all lab assessments to be performed within 7 days in Stage 1 part and all radiologic assessments to be performed within 21 days prior to first IP administration. Local lab results for M-protein and sFLC to be used to determine eligibility criteria.)
  - M-protein quantification (serum and 24-hr urine to be completed prior to dosing), including sub-types IgG, IgA, IgM, IgD and IgE; an additional blood sample will be collected to test M protein with an assay without interference of the SAR650984 antibody.
  - Serum free light chain levels.
  - Bone marrow biopsy/aspiration.
  - Radiologic imaging (PET-CTscan or MRI scan) of plasmacytoma. For Stage 2 - patients with known lesions at baseline.
  - Skeletal survey (X-ray; including skull, all long bones, pelvis and chest) or low dose whole body CT scan.

For Stage 2: at screening, disease assessment procedures should be performed within 21 days prior to first IP administration. Local lab results for M-protein and sFLC will be used to determine eligibility criteria. All disease and laboratory assessments should be repeated prior of first dose (see flowchart in Section 1.14 and Section 1.15).

- PD/Exploratory Studies:
  - Bone marrow biopsy/aspiration for CD38 RD (Stage 1 patient only).

- Bone marrow aspirate for FISH.
- Bone marrow aspirate for genomics/CD38 Mrna.
- Bone marrow aspirate for immune phenotyping.
- Bone marrow biopsy/aspirate for CD38 RO (Stage 1 patients only).
- Bone marrow aspirate for MRD assessment.

12.2.2 Randomization/registration

Patients, who meet all the inclusion criteria, and none of the exclusion criteria, will be eligible for inclusion in the study. Each patient will be registered via an IVRS/IWRS and receive an incremental identification number corresponding to his/her order of enrollment in the study. In addition, all Stage 1a and Stage 2 eligible patients will be randomized by the IVRS/IWRS to a treatment arm (see Section 8.4). In Stage 1b eligible patients will be enrolled.

12.2.3 Cycle 1-3 evaluations

The same parameters as performed at screening/baseline will be performed for each of the required evaluations unless specified in the flowchart and in the following sections.

Day 1

The evaluations below are to be performed prior to first IP administration on Day 1 of Cycle 1-3 unless otherwise indicated.

- ePROs: QLQ-C30, MY20 (performed prior to any assessments) (Stage 1 only).
- EQ-5D (performed prior to any assessments, Cycle 1 only) (Stage 1 only).
- Physical Examination: consists of examination of major body systems, including neurological, digestive exam, plasmacytoma assessment, respiratory, hepatomegaly, splenomegaly, lymphadenopathy.
- Weight.
- Vital Signs.
- Performance Status (Karnofsky in Phase 1 and Phase 2 Stage 1 and ECOG Performance status in Phase 2 Stage 2).
- AE/SAE assessment.
- Concomitant medications.
- Laboratory Assessments:
  - Blood Chemistry (Required prior to pre-medication and IP administration on D1, D8, D15 and D22 of Cycle 1 and D1 and D15 of every subsequent cycle).
  - Hematology (Required prior to pre-medication and IP administration on D1, D8, D15 and D22 of Cycle 1 and D1 and D15 of every subsequent cycle).

- If not performed during screening and prior to C1D1: Blood type (if not already done), complete blood phenotyping (C,c; E,e; Kell. Kidd; Duffy; S,s is recommended, if not available follow site's standard)and antibody screening (Indirect Coombs test, Indirect Antiglobulin Test (IAT)) only to be obtained prior C1D1 administration (blood type card will be kept by the patient with the study card). Antibody screen information made before any blood transfusion and blood transfusions are to be recorded in the eCRF if performed during the study treatment.The blood bank needs to be informed that the patient is receiving a treatment with an anti-CD38 and a potential interference with the indirect Coombs test is possible.
- Indirect Antiglobulin Test (IAT) to be obtained prior C2D1 administration . Antibody screen information made before any blood transfusion and blood transfusions are to be recorded in the eCRF if performed during the study treatment.
- Cytokines (Cycle 1 only)
- Safety labs (if ≥Grade 2 infusion reaction) (Stage 1 only)
- Serum β2-microglobulin (Cycle 2 and 3 only)
- PK/ADA (Day 1) (refer to Section 1.8 and Section 1.16) Samples will be collected up to and including C10.
- Serum or urine Pregnancy test (except Cycle 1 if done within 7 days).

- Disease Assessment:
  - M-protein quantification (serum and 24-hr urine to be completed prior to dosing including IgG, IgA, IgM, IgD and IgE) (In Stage 2: Required prior to pre-medication and IP administration on D1 of Cycle 1 and D1 of every subsequent cycle). In Stage 2: an additional blood sample will be collected to test M protein with an assay without interference of the SAR650984 antibody).
  - Serum free light chain levels (Required prior to pre-medication and IP administration on D1, D8, D15 and D22 of Cycle 1 and D1 of every subsequent cycle).
  - Bone marrow biopsy/aspiration (only required to confirm a sCR, CR or PD).
  - Radiologic imaging: skeletal survey and/or PET-CT scan or MRI scan to confirm response or in case of suspicion of progression according to IMWG criteria and/or when clinically indicated, or in case of plasmocytoma at baseline to be performed every 2 cycles.
- PD/Exploratory Studies:
  - Bone marrow biopsy/aspirate for CD38 RO (Stage 1 patients only, Cycle 2 only).
  - Bone marrow aspirate sample for MRD assessment (only at CR confirmation).
  - Blood sample for soluble CD38 (Stage 1 only: Cycle 1 and 3 only).
  - Blood sample for immune phenotyping (Cycle 1 and 3 only).
  - Blood sample for immune genetic determinants (Cycle 1 only).

- Blood sample for adaptive immune response - T cell repertoire (Stage 2: Cycle 1 and 3 only).
- Blood sample for adaptive immune response - humoral and cellular response (Stage 2: Cycle 1 and 2 only).

Samples for all the parameters listed in the flowchart (Section 1.14 and Section 1.15) and in the corresponding footnotes will be sent to a central laboratory. At each time point, blood samples will be split for central and local laboratory evaluations.

Administration of SAR650984

The evaluations below are to be performed during and after IP administration:

- Vital Signs: middle of infusion and end of infusion
- Laboratory Assessments:
  - PK (Cycle 1 only refer to Section 1.8 and Section 1.16)

Day 8 (Cycle 1 only for patients on a QW schedule).

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

- Physical Examination: consists of examination of major body systems, including neurological, digestive exam, plasmacytoma assessment, respiratory, hepatomegaly, splenomegaly, lymphadenopathy.
- Weight.
- Vital Signs.
- Performance Status (Karnofsky in Phase 1 and Phase 2 Stage 1 and ECOG Performance status in Stage 2).
- AE/SAE Assessment.
- Concomitant Medication.
- Laboratory Assessments:
  - Blood Chemistry (Required prior to pre-medication and IP administration).
  - Hematology (Required prior to pre-medication and IP administration).
  - PK(Cycle 1 only refer to Section 1.8 and Section 1.16)

Administration of SAR650984 on Day 8 of Cycle 1 for patients on the QW schedule.

The evaluations below are to be performed during and after IP administration.

- Vital Signs: middle of infusion and end of infusion
- Laboratory Assessments:
  - Safety labs (if ≥ Grade 2 infusion reaction) (Stage 1 only).

Day 15

The evaluations below are to be performed prior to IP administration on Day 15 of Cycles 1-3 unless otherwise indicated.

- Physical Examination: consists of examination of major body systems, including neurological, digestive exam, plasmacytoma assessment, respiratory, hepatomegaly, splenomegaly, lymphadenopathy.
- Weight.
- Vital Signs.
- Performance Status (Karnofsky in Phase 1 and Phase 2 Stage 1 and ECOG Performance status in Stage 2).
- AE/SAE Assessment.
- Concomitant Medication.
- Laboratory Assessments:
  - Blood Chemistry (Required prior to pre-medication and IP administration)
  - Hematology (Required prior to pre-medication and IP administration)
  - PK/ADA (refer to Section 1.8 and Section 1.16)

Administration of SAR650984 on Day 15 of Cycle 1 and 2 for all patients.

Administration of SAR650984 on Day 15 of Cycle 3 for patients remaining on the Q2W schedule.

The evaluations below are to be performed during and after IP administration.

- Vital Signs: middle of infusion and end of infusion
- Laboratory Assessments:
  - PK (Cycle 1 only refer to Section 1.8).
  - Safety labs (if ≥ Grade 2 infusion reaction) (Stage 1 only).

Day 22 (Cycle 1 only for patients on a QW schedule).

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

- Physical Examination: consists of examination of major body systems, including neurological, digestive exam, plasmacytoma assessment, respiratory, hepatomegaly, splenomegaly, lymphadenopathy.
- Weight.
- Vital Signs.
- Performance Status (Karnofsky in Phase 1 and Phase 2 Stage 1 and ECOG Performance status in Stage 2).

- AE/SAE Assessment.
- Concomitant Medication.
- Laboratory Assessments:
  - Blood Chemistry (Required prior to pre-medication and IP administration).
  - Hematology (Required prior to pre-medication and IP administration).

Administration of SAR650984 on Day 22 of Cycle 1 for patients on the QW schedule.

The evaluations below are to be performed during and after IP administration.

- Vital Signs: middle of infusion and end of infusion
- Laboratory Assessments:
  - Safety labs (if ≥ Grade 2 infusion reaction) (Stage 1 only)
  - PK(Cycle 1 only refer to Section 1.8 and Section 1.16)

12.2.4 During treatment period (subsequent cycles)

Patients following the Q2W schedule: The evaluations below are to be performed prior to IP administration on Day 1 and Day 15 of subsequent cycles.

Patients following the Q4W schedule: The evaluations below are to be performed prior to IP administration on Day 1 of every cycle.

- ePROs: QLQ-C30, MY20 (Day 1 of every cycle, performed prior to any assessments) (Stage 1 only).
- ePRO: EQ-5D (Day 1 of every 3rd cycle starting Cycle 4, performed prior to any assessments) (Stage 1 only).
- Physical Examination: consists of examination of major body systems, including neurological, digestive exam, plasmacytoma assessment, respiratory, hepatomegaly, splenomegaly, lymphadenopathy.
- Weight.
- Vital Signs.
- Performance Status (Karnofsky) in Phase 1 and Phase 2 Stage 1 and ECOG Performance status in Stage 2).
- AE/SAE Assessment.
- Concomitant Medication.
- Laboratory Assessments:
  - Blood Chemistry (Required prior to pre-medication and IP administration on D1 and D15 of every subsequent cycle).

- Hematology (Required prior to pre-medication and IP administration on D1 and D15 of every subsequent cycle).
- Indirect Antiglobulin Test [IAT]) to be repeated at C2D1 if the test is not performed at this visit, it can be done at the next blood sampling. Antibody screen information made before any blood transfusion and blood transfusions are to be recorded in the eCRF if performed during the study treatment.
- Serum β2-microglobulin (Day 1 of every cycle) (Required prior to pre-medication and IP administration on D1of every subsequent cycle).
- PK /ADA (refer to Section 1.8 and Section 1.16) Samples will be collected up to and including C10.

- Disease Assessment (Day 1 of every cycle):
  - M-protein quantification (serum and 24-hr urine to be completed prior to dosing including IgG, IgA, IgM, IgD and IgE). An additional blood sample will be collected to perform the interference test.
  - Serum free light chain levels.
  - Bone marrow biopsy/aspiration (only required to confirm a sCR, CR or PD).
  - Radiologic imaging: Skeletal survey and/or PET-CTscan or MRI scan only required if clinically indicated or to confirm response or progression according to IMWG criteria. CT/MRI scan is required every 2 cycles (ie, Cycle 5, Cycle 7, etc) if a plasmacytoma was present at baseline.
- Serum or urine Pregnancy test

Samples for all the parameters listed in the flowchart (Section 1.14) and in the corresponding footnotes will be sent to a central laboratory. At each time point, blood samples will be split for central and local laboratory evaluations.

- PD/Exploratory Studies:
  - Bone marrow sample for MRD assessment (only at CR confirmation).
  - Blood sample for adaptive immune response - T cell repertoire (Stage 2: Cycle 5 only).
  - Blood sample for adaptive immune response - humoral and cellular response (Stage 2: Day 1 of Cycles 4, 7 and 10).

Administration of SAR650984 on Day 1 of subsequent Cycles for all patients.

Administration of SAR650984 on Day 15 of subsequent cycles for patients on the Q2W schedule.

The evaluations below are to be performed during and after IP administration.

- Vital Signs: middle of infusion and end of infusion
- Laboratory Assessments:
  - Safety labs (if ≥ Grade 2 infusion reaction) (Stage 1 only)

- PK (Day 1 of Cycle 4 only, refer to Section 1.8 and Section 1.16)

12.2.5 End of treatment visit (to be performed up to 30 days after the last study treatment administration)

- ePROs: QLQ-C30, MY20, PRO: EQ-5D (performed prior to any assessments) (Stage 1 only)
- Clinical examination: includes physical examination, weight, vital signs, and performance status.
- Laboratory Assessments:
  - Pregnancy Test: serum.
  - Blood Chemistry.
  - Hematology.
  - Serum β2-microglobulin.
  - PK/ADA (refer to Section 1.8 and Section 1.16). Only to be collected if the patient has not completed 10 cycles or if the last ADA was positive and will collect one additional sample in 3 months.
- Exploratory Studies:
  - Bone marrow biopsy/aspiration for genomics (only patients who have responded to the study treatment but subsequently develop progressive disease, in Stage 1 only).
  - Blood sample for soluble CD38 (only patients with progressive disease, in Stage 1 only).
  - Blood sample for immune phenotyping.
  - Blood sample for adaptive immune response - humoral and cellular response (in disease progression patients, Stage 2 only).
- Disease Assessment
  - M-protein quantification (serum and/or 24-hr urine to be completed prior to study treatment dosing, including IgG, IgA, IgM, IgD and IgE); an additional blood sample will be collected to test M protein with an assay without interference of the SAR650984 antibody.
  - Serum free light chain levels.
  - Radiologic imaging (PET-CT or MRI scan) of plasmacytoma (only required if plasmacytoma present at baseline or developed during treatment period).
  - Skeletal survey (X-ray) or low dose whole body CT scan (only required if bone lesion present at baseline or developed during treatment period).

Samples for all the parameters listed in the flowchart (Section 1.14) and in the corresponding footnotes will be sent to a central laboratory. At each time point, blood samples will be split for central and local laboratory evaluations.

- AE/SAE Assessment.
- Concomitant Medication.
- New anticancer treatment.
- Survival status.

12.2.6 Follow-up period at 60 days (±5 days) after last study treatment administration

- Disease Assessment (only for patients who have discontinued study treatment for reasons other than disease progression). Radiologic imaging and bone marrow biopsy/aspiration are only required if clinically indicated or to confirm response or progression according to IMWG criteria.
  - M-protein quantification (serum and 24-hr urine).
  - Serum free light chain levels.
  - Bone marrow biopsy/aspiration.
  - Radiologic imaging: PET-CT scan or MRI scan of plasmacytoma and skeletal survey (plain X-ray) or low dose whole body scan.
- Pregnancy Test: serum monthly.
- AE/SAE Assessment: all AEs related to study treatment and all SAEs regardless of study treatment ongoing 30 days after last study treatment administration (SAR650984 or dexamethasone, whichever comes last) and all new AEs related to study treatment (serious or not) occurring after 30 days will be collected and followed until recovery or stabilization.

Concomitant Medication (all AEs related to study treatment and all SAEs regardless of study treatment ongoing 30 days after last study treatment administration (SAR650984 or dexamethasone, whichever comes last) and all new AEs related to study treatment (serious or not) occurring after 30 days will be collected and followed until recovery or stabilization.)

- New anticancer therapy.
- Survival status.

12.2.7 Post 60 day follow-up period

For patients who have discontinued study treatment for reasons other than disease progression and have not yet started treatment with another anti-cancer therapy, follow-up visits will be performed every month until the patient has disease progression or the patient initiates a new anticancer therapy. At this point, patients will be followed every 3 months (±14 days) after the last study treatment administration.

For patients who discontinued study treatment for disease progression, assessments will be performed every 3 months (±14 days) after last study treatment administration unless otherwise specified.

- Laboratory Assessment:
  - ADA: only if patient is positive at the last sample. Patient should have a sample 3 months later. No further ADA will be sampled, even if this 3-month sample is positive.
- Disease Assessment (only for patients who have discontinued study treatment for reasons other than disease progression and have not yet started treatment with another anti-cancer therapy). Laboratory disease assessments are required every month (±7 days) after last study treatment administrations. Radiologic imaging and bone marrow biopsy/aspiration are required if clinically indicated or to confirm response or progression according to IMWG criteria. Disease assessments not required once patient starts treatment with another anti-cancer therapy.
  - M-protein quantification (serum and 24-hr urine).
  - Serum free light chain levels.
  - Bone marrow biopsy/aspiration.
  - Radiologic imaging: PET-CT scan or MRI scan of plasmacytoma and skeletal survey (plain X-ray) or low dose whole body CT scan only for patients who discontinued for other reason than PD.

The following information will be collected at each follow-up visit:

- Pregnancy Test: serum monthly for 5 months after the last administration of SAR650984.
- AE/SAE Assessment: All AEs related to study treatment and all SAEs regardless of study treatment ongoing 30 days after last study treatment administration (SAR650984 or dexamethasone, whichever comes last) and all new AEs related to study treatment (serious or not) occurring after 30 days will be collected and followed until recovery or stabilization.
- Concomitant Medication (if IP-related AE, new SAE and/or unresolved toxicity).
- New anticancer therapy.
- Survival status.

12.3 DATA COLLECTION AFTER FINAL ANALYSIS CUTOFF DATE

For patients still receiving SAR650984 at time of the final analysis cutoff date, treatment with SAR650984 may be continued according to investigator judgment on benefit/risk, until disease progression, unacceptable toxicity or patient refusal. After treatment discontinuation, patients will be followed for a minimum of 30 days following the last use of study drug.

Procedures and data collection for patients still receiving SAR650984 at the time of the final analysis cutoff date will be as follows:

- Laboratory Assessment:
  - ADA: if last ADA before cut-off date is positive, one additional sampling time for ADA evaluation should be collected 3 months later. No further ADA will be sampled, even if this 3-month sample is positive.
  - In case of viral reactivation during study treatment (greater than 1 $\log_{10}$ IU/mL increase in HBV DNA or reappearance of HBsAg or detection of HBV DNA in patients with resolved infection), ALT and AST will be closely monitored every month up to study treatment discontinuation. HBV DNA to be done as per specialist advice.
- Study treatment administration (SAR650984 and dexamethasone).
- Pregnancy Test: serum monthly for 5 months after the last administration of SAR650984.
- Pre-medication will be given as indicated but will not be collected in eCRF (Stage 2 only).
- Ongoing related AE(s) and ongoing SAE(s), up to stabilization or resolution.
- New SAE(s) regardless of relationship with study treatments, new related AE(s).
- End of treatment reason upon SAR650984 discontinuation.

Patients with ongoing related AE(s) and ongoing SAE(s) after treatment discontinuation will be followed until stabilization (stabilization defined as no change for 3 months) or resolution of the AE/SAE. All relevant laboratory results and medications given for SAE will be captured in the SAE complimentary form in the eCRF

13 STATISTICAL CONSIDERATIONS

13.1 DETERMINATION OF SAMPLE SIZE

Phase1 part:

The Phase 1 part of this study aims to establish the MTD of SAR650984 according to DLTs observed.

Cohorts of 3 to 6 patients will be screened and treated at each DL during the basic dose escalation phase. The number of DLs examined and the emerging SAR650984 related toxicities will determine the sample size.

Up to 18 patients will be enrolled in the standard risk and up to 18 patients in the high risk expansion cohorts may be enrolled and treated at the RP2D.

It is anticipated that up to approximately 85 patients in total will be enrolled to this part of the study.

Phase 2 part:

Stage1:

Although Stage 1b has been added in protocol amendment 10 and will start enrollment after completion of accrual in Stage 1a (ie, patients will not be randomized between the 4 doses/schedules tested), sample size for Stage 1 will be calculated considering Stage 1a and 1b as a whole with 4 arms.

Stage 1 of the Phase 2 portion of the study is based on a selection design (7). Such a design is used to maximize the probability of selecting the best of the four SAR650984 doses tested during Stage 1 using ORR as endpoint. No statistically significant difference between the four treatment arms is required to select a recommended Stage 2 dose.

A total of 96 patients (24 patients by arm) will provide at least 80% probability to select the best SAR650984 dose assuming an ORR of 10% in the 3 mg/kg arm and assuming the difference in ORR between the best dose and the 3 mg/kg arm is at least 15%.

Stage 2**:**

SAR650984 arm: 105 patients need to be randomized and treated in the SAR650984 arm (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).

SAR650984+dexamethasone arm: 55 patients need to be randomized and treated in the SAR650984+dexamethasone 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).

For the Phase 2 Stage 2, the sample size calculation was performed using nQuery Advisor 7.0 software.

13.2 PATIENT DESCRIPTION

13.2.1 Disposition of patients

The number of screened patients as well as the number and percentage of patients included in the analysis populations defined in Section 13.3 will be provided. Reasons for treatment discontinuation will be summarized using the all treated/safety population.

13.2.2 Protocol deviations

All critical or major deviations potentially impacting evaluation of the MTD (Phase 1 only) efficacy analyses, as well as drug-dispensing irregularities and other major or critical deviations will be summarized in tables giving numbers and percentages of patients with deviations.

13.3 ANALYSIS POPULATIONS

13.3.1 All treated/safety population

For both Phase 1 and Phase 2 parts of the study, the all treated/safety population will include all patients who have given their informed consent and who have received at least one dose (even incomplete) of SAR650984.

For Stage 2, patients who received dexamethasone in addition to isatuximab (excluding when given as part of premedication) will be included in the ISAdex arm.

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

13.3.2 Patients evaluable for DLT assessment

The DLT evaluable population is only applicable to the Phase 1 part of the study.

The evaluable for DLT population is the subset of patients from the all treated population with a DLT assessment at the end of Cycle 2. In practice, a “Dose Limiting toxicities” form should have been filled in at the end of Cycle 2. This includes patients followed up to the end of the evaluation period or patients having experienced a DLT validated by the study committee. If there are missing or incomplete data that influence the evaluation of DLT, the patient will not be evaluable for DLT, except if a DLT is documented during Cycle 1 or 2. Patients excluded from this population will be replaced.

13.3.3 Pharmacokinetic population

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

13.3.4 Pharmacodynamic population

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

13.3.5 PRO population

There will be no population flag for PRO. PRO endpoints will be analyzed using patients from the all treated population who have a baseline assessment and/or an on-treatment assessment, depending on the analysis being performed (Phase 2 – Stage 1 only).

13.4 STATISTICAL METHODS

The statistical methods defined in this section will be used for the analysis of the data from the Phase 1 and Phase 2 portion of the study, unless otherwise specified. Data from Phase 1 and each stage of the Phase 2 will be analyzed and reported separately (see Section 6.9.2). In particular, data from Stage 1a and Stage 1b will be presented in the same set of tables. Summary tables will be presented by dose levels/arm (when appropriate) and overall, unless otherwise noted.

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

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

13.4.1 Demographics and baseline characteristics

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

13.4.2 Extent of investigational product exposure

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

The dose information will be assessed by the following variables:

1. Duration of study treatment exposure: 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.

2. Cumulative dose: The cumulative dose is the sum of all doses from first dose to last SAR650984 administration.
3. Actual dose intensity (ADI): defined as the cumulative dose divided by the number of weeks on study.
4. Relative dose intensity (RDI): defined as the ratio of the actual dose intensity to the planned dose intensity. The RDI is an indicator of the feasibility of the chosen schedule of administration.
5. Dose reduction and reason for dose reduction.
6. Dose delays: A cycle is deemed to have been delayed if start date of the current cycle – 14 (for Phase 1 part) or 28 (for the Phase 2 part) – start date of previous cycle >2 days.
7. Dose interruption.

Similar analyses will be performed for dexamethasone exposure (ISAdex arm, Phase 2 Stage 2).

Dose information variables will be summarized descriptively (N, Mean, SD, Median, Q1:Q3, Min, and Max). Analyses will be performed based, on one hand, on the number of patients and, on the other hand, on the number of cycles.

13.4.3 Prior/concomitant medication/therapy

The following parameters regarding prior anticancer will be summarized for patients with MM:

- Prior anticancer treatments: number of prior lines, main anticancer treatments, time from completion of last line of treatment to first SAR650984 administration (months), best response to last line, duration of last line of therapy
- Prior transplant: number (%) of patients with transplant, type of transplant, number of transplant by patient
- Prior surgery: number (%) of patients with any prior surgery related to cancer, type of surgery and time from last surgery to first SAR650984 administration (months)
- Prior radiotherapy: number (%) of patients with any prior radiotherapy related to cancer, intent, location and time from last radiotherapy to first study treatment infusion (months).

Medications will be summarized by treatment group according to the WHO-DD dictionary, considering the first digit of the ATC class (anatomic category) and the first three digits of the ATC class (therapeutic category). All ATC codes corresponding to a medication will be summarized patients will be counted once in each ATC categories (anatomic or therapeutic) linked to the medication.

Medications of specific interest such as antibiotics and hematopoietic growth factors (G-CSF, GM-CSF and erythropoietin or red blood cells transfusion) will be summarized and listed by DL.

Further treatment of interest for the analysis and given to the patient after withdrawal from IP will be listed.

13.4.4 Analysis of efficacy endpoints

All efficacy analyses will be performed using the all treated/safety population.

13.4.4.1 Efficacy endpoints for Phase 1 part of the study

The following efficacy endpoints will be analyzed for Phase 1 study:

- Overall response rate (ORR).
- Duration of response defined as the time from initial response to the first documented tumor progression.

ORR and duration of response will be listed along with relevant patient/disease characteristics. In addition, ORR and duration of response will be summarized with descriptive statistics and 95% confidence interval (for ORR only) for patients with MM.

13.4.4.2 Analysis of primary efficacy endpoint for Phase 2 part of the study

The data cut for the primary analysis of ORR will be 4 months and 12-months for Stage 1 and Stage 2 respectively after the last enrolled patient receives first study treatment. ORR will be summarized with descriptive statistics. A 95% two-sided confidence interval will be computed using Clopper-Pearson method. For Stage 2, the null hypothesis that the true response rate (ORR) is <15% will be tested for each arm using a one-sided exact binomial test with a significance level of 0.025.

Secondary/Exploratory analyses of primary efficacy endpoint (eg, analysis of patients with high-risk cytogenetics) will be detailed in the statistical analysis plan.

13.4.4.3 Analysis of secondary efficacy endpoint for Phase 2 part of the study

- CBR: the CBR will be analyzed using the same method as the primary efficacy analysis of ORR.
- DOR: Kaplan-Meier estimates such as median and Kaplan-Meier curves will be provided for DOR for patients who achieve a response (CR and PR).
- PFS: the PFS will be analyzed using the Kaplan-Meier method. The Kaplan-Meier estimates of the 25th, 50th and 75th percentiles and the 95% confidence intervals of median will also be computed. The Kaplan-Meier curves will be plotted. The PFS will be analyzed based upon all treated population.
- OS: the OS will be analyzed using the same method as PFS.

13.4.5 Analysis of patient reported outcomes (Phase 2 Stage 1 only)

For each questionnaire the compliance profile over time will be summarized (number and percentage of forms received versus expected, and number and percentage of forms evaluable versus expected).

For each EORTC QLQ-C30 and QLQ-MY20 scales a descriptive summary at each visit and change from baseline will be provided for each group: the five functional scales (physical functioning, role functioning, emotional functioning, cognitive functioning, and social functioning), the three symptom scales (fatigue, nausea and vomiting, and pain), the GHS/ quality of life scale, and the six single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties) of the QLQ-C30 and the 2 functional subscales (body image, future perspective), and 2 symptoms scales (disease symptoms and side-effects of treatment) of the MY20. In addition, the proportion of patients who achieve clinically meaningful improvements on all scales will be reported, with the primary scales of importance being pain, fatigue, and physical functioning. A clinically meaningful improvement will be defined as a change from baseline <= -10 for the symptoms pain and fatigue and as a change from baseline >=10 for the physical functioning scale. Clinically meaningful improvements will be further detailed in the statistical analysis plan.

The responses of each EQ-5D items will be presented by visit and group. The tables will contain information on the frequency and proportion of the population reporting level 1 (no problems), level 2 (some problems) and level 3 (extreme problems) per item. Tables will also be presented cross-tabulating a visit with the baseline visit. Descriptive summary statistics (size, mean, standard deviation, median, range) will be provided for the single index utility score and the visual analogue scale at each visit. Change from baseline will be also described.

13.4.6 Analyses of safety data

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

13.4.6.1 Dose-limiting toxicities

For the Phase 1 part of the study, DLTs will be summarized by DL. Details will be provided (characteristics of DLTs) by patient.

13.4.6.2 Analyses of adverse events

Adverse events will be assessed according to NCI-CTCAE v4.03 from the time informed consent is signed until at least 30 days after the last IP administration. AEs will be classified by System Organ Class/preferred term according to the latest available version of MedDRA dictionary.

Definitions

Period of observation: The observation period will be divided into three segments: pre-treatment, on-treatment and post-treatment. The pre-treatment period is defined as the time from when the patients give informed consent and the start of IP. The on-treatment period is defined as the time

from first dose of IP up to 30 days after the last dose of IP. The post-treatment period is defined as the time starting 31 days after the last dose of IP to the study closure.

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

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

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

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

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

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

Sorting within tables should ensure same presentation for the set of all AE within the observation period (pre, on and post treatment). For that purpose, the table of all TEAEs presented by system organ class (SOC), high level group terms, high level terms and preferred terms (PT) sorted by internationally agreed order unless otherwise specified.

The following TEAE summaries will be generated:

- Overview of TEAEs, summarizing number (%) of patients with any
  - TEAE.
  - Any Grade 3-4 TEAE.
  - Serious TEAE.
  - TEAE leading to death.
  - TEAE leading to permanent treatment discontinuation.

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

- Number (%) of patients experiencing TEAEs by primary SOCs and PT will be summarized by CTCAE grade (all grades and Grade ≥ 3). Similar tables will be prepared for drug-related TEAEs, TEAEs leading to IMP/NIMP discontinuation, TEAEs leading to dose modification, serious TEAEs, AESI, IARs and AEs/SAEs occurring during the post treatment dosing period.

13.4.6.3 Deaths

The following deaths summaries will be generated;

- Number (%) of patients who died by study period (pre-treatment, on-treatment, post-treatment).
- TEAEs leading to death (death as an outcome on the AE e-CRF page as reported by the Investigator) and related TEAEs leading to death by primary system organ class, alphabetic order of high level group level terms, high level terms, and preferred terms showing number (%) of patients.

A listing of deaths will be provided.

13.4.6.4 Clinical laboratory evaluations

For patients with multiple occurrences of the same laboratory variable during the on treatment period, the maximum grade (worst) per patient and/or per cycle will be used. The denominator used for the summary by cycle is the total number of cycles administered. For a given laboratory variable, a patient contributes 1 to the numerator for each cycle in which an episode occurred. An episode occurs during a cycle, if the date of sampling is on or after the first day of the cycle, but prior to the first day of the next cycle. Hematological and clinical biochemistry toxicities will be assessed from laboratory test parameters. Each test result will be graded by NCI-CTCA v4.03. The number of patients with abnormal lab tests at baseline will be presented by grade. The frequency of patients and/or cycles in each grade of lab tests during treatment will be summarized (similar analysis will be performed based on data recorded at Cycle 1). When appropriate, the summary table will present the frequency of patients and/or cycles with any grade of abnormal laboratory tests and with Grade 3-4 of abnormal laboratory tests.

13.4.6.5 Vital signs

The summary statistics (including mean, median, Q1, Q3, standard error, minimum and maximum) of all vital signs variables (raw data and changes from baseline) will be calculated for each visit or study endpoint (baseline, each post baseline time point, last on treatment value and/or worst value). Mean changes from baseline with the corresponding standard error (or boxplots) will be plotted over time (at same time points).

13.4.6.6 Analyses of other safety variables

Not applicable.

13.4.7 Analyses of pharmacokinetic variables

Pharmacokinetic parameters of SAR650984 will be summarized by descriptive statistics (such as mean, geometric mean, median, SD, SEM, CV, minimum, and maximum) under the responsibility of Translational Medicine and Early Development, Sanofi.

Individual plasma concentrations and PK parameters of SAR650984 will be tabulated with standard descriptive statistics. Individual and mean profiles will be presented graphically.

The relationship between dose and exposure will be investigated, using analysis of variance. Analyses of pharmacodynamic/genomic population variables (as appropriate)

Time dependence will be investigated with C_{eoi} (Concentration at end of infusion) and C_{trough} (plasma concentration observed before treatment administration after repeated administration, if relevant) data from all cycles.

13.4.8 Analysis of anti-drug antibody

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

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

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

Definitions:

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

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

ADA prevalence and ADA incidence will be also described.

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

13.4.9 Analysis of pharmacodynamic variables

The CD38 receptor density and receptor occupancy (Phase 1 and Phase 2 – Stage 1 parts only) will be summarized for the Phase 1 and Phase 2 part.

A graph showing ORR/non-responder rate (in y-axis) by CD38 RD level (ranging from 0 to 500,000 by increment of 1,000 in x-axis) will be provided.

The relationship between CD38 RO and SAR650984 concentrations will be analyzed. A graph of CD38 RO versus SAR650984 concentration at 4 week will be provided. Another analysis will be performed when all patients will have been followed for at least 4 months to confirm dose selection.

13.5 INTERIM ANALYSIS

An interim analysis of the data from Stage 1 will be performed when all patients have completed at least two disease assessments. This analysis will be used for the selection of the dose of SAR650984 to be used in Stage 2. Response rate along with safety, PK, PD, and overall efficacy will be used to select the dose and schedule for Stage 2. Another analysis will be performed when all patients will have been followed for at least 4 months to confirm dose selection.

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

14 ETHICAL AND REGULATORY STANDARDS

14.1 ETHICAL PRINCIPLES

This Clinical Trial will be conducted in accordance with the principles laid down by the 18th World Medical Assembly (Helsinki, 1964) and all applicable amendments laid down by the World Medical Assemblies and the ICH guidelines for Good Clinical Practice (GCP).

14.2 LAWS AND REGULATIONS

This Clinical Trial will be conducted in compliance with all international laws and regulations, and national laws and regulations of the country(ies) in which the Clinical Trial is performed, as well as any applicable guidelines.

14.3 INFORMED CONSENT

The Investigator (according to applicable regulatory requirements), or a person designated by the Investigator, and under the Investigator's responsibility, should fully inform the Patient of all pertinent aspects of the Clinical Trial including the written information giving approval/favorable opinion by the Ethics Committee (IRB/IEC). All participants should be informed to the fullest extent possible about the study, in language and terms they are able to understand.

Prior to a patient’s participation in the Clinical Trial, the written Informed Consent Form should be signed, name filled in and personally dated by the patient or by the patient’s legally acceptable representative, and by the person who conducted the informed consent discussion. A copy of the signed and dated written Informed Consent Form will be provided to the patient.

Prior to collection of blood for pharmacogenetics, the optional pharmacogenetic informed consent form (written) should be signed, name filled in, and personally dated by the patient or by the subject’s legally acceptable representative, and by the person who conducted the informed consent discussion. A copy of the signed and dated written optional informed consent form will be provided to the subject.

The informed consent form and the optional pharmacogenetic informed consent form used by the Investigator for obtaining the patient's informed consent must be reviewed and approved[2] by the Sponsor prior to submission to the appropriate ethics committee (IRB/IEC) for approval/favorable opinion.

14.4 INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE (IRB/IEC)

As required by local regulation, the Investigator or sanofi-aventis must submit this Clinical Trial Protocol to the appropriate Ethics Committee (IRB/IEC), and is required to forward to the respective other party a copy of the written and dated approval/favorable opinion signed by the Chairman with Ethics Committee (IRB/IEC) composition.

The Clinical Trial (study number, Clinical Trial Protocol title and version number), the documents reviewed (Clinical Trial Protocol, Informed Consent Form, Investigator's Brochure, Investigator's CV, etc) and the date of the review should be clearly stated on the written (IRB/IEC) approval/favorable opinion.

Investigational Product will not be released at the study site and the Investigator will not start the study before the written and dated approval/favorable opinion is received by the Investigator and sanofi-aventis.

During the Clinical Trial, any amendment or modification to the Clinical Trial Protocol should be submitted to the Ethics Committee (IRB/IEC) before implementation, unless the change is necessary to eliminate an immediate hazard to the patients, in which case the IRB/IEC should be informed as soon as possible. It should also be informed of any event likely to affect the safety of patients or the continued conduct of the Clinical Trial, in particular any change in safety. All updates to the Investigator's Brochure will be sent to the Ethics Committee (IRB/IEC).

A progress report is sent to the Ethics Committee (IRB/IEC) at least annually and a summary of the Clinical Trial's outcome at the end of the Clinical Trial.

15 STUDY MONITORING

15.1 RESPONSIBILITIES OF THE INVESTIGATOR(S)

The Investigator(s) undertake(s) to perform the Clinical Trial in accordance with this Clinical Trial Protocol, ICH guidelines for Good Clinical Practice and the applicable regulatory requirements.

The Investigator is required to ensure compliance with all procedures required by the Clinical Trial Protocol and with all study procedures provided by the Sponsor (including security rules). The Investigator agrees to provide reliable data and all information requested by the Clinical Trial Protocol (with the help of the Case Report Form [CRF], Discrepancy Resolution Form [DRF] or other appropriate instrument) in an accurate and legible manner according to the instructions provided and to ensure direct access to source documents by Sponsor representatives.

If any circuit includes transfer of data particular attention should be paid to the confidentiality of the patient's data to be transferred.

The Investigator may appoint such other individuals as he/she may deem appropriate as Sub-Investigators to assist in the conduct of the Clinical Trial in accordance with the Clinical Trial Protocol. All Sub-Investigators shall be appointed and listed in a timely manner. The Sub-Investigators will be supervised by and work under the responsibility of the Investigator. The Investigator will provide them with a copy of the Clinical Trial Protocol and all necessary information.

15.2 RESPONSIBILITIES OF THE SPONSOR

The Sponsor of this Clinical Trial is responsible to Health Authorities for taking all reasonable steps to ensure the proper conduct of the Clinical Trial Protocol as regards ethics, Clinical Trial Protocol compliance, and integrity and validity of the data recorded on the Case Report Forms. Thus, the main duty of the Monitoring Team is to help the Investigator and the Sponsor maintain a high level of ethical, scientific, technical and regulatory quality in all aspects of the Clinical Trial.

At regular intervals during the Clinical Trial, the site will be contacted, through monitoring visits, letters or telephone calls, by a representative of the Monitoring Team to review study progress, Investigator and patient compliance with Clinical Trial Protocol requirements and any emergent problems. These monitoring visits, will include but not be limited to review of the following aspects : patient informed consent, patient recruitment and follow-up, Serious Adverse Event documentation and reporting, AESI documentation and reporting ,AE documentation, Investigational Product allocation, patient compliance with the Investigational Product regimen, Investigational Product accountability, concomitant therapy use and quality of data.

15.3 SOURCE DOCUMENT REQUIREMENTS

According to the ICH guidelines for Good Clinical Practice, the Monitoring Team must check the Case Report Form entries against the source documents, except for the pre-identified source data directly recorded in the Case Report Form. The Informed Consent Form will include a statement by which the patient allows the Sponsor's duly authorized personnel, the Ethics Committee (IRB/IEC), and the regulatory authorities to have direct access to original medical records which support the data on the Case Report Forms (eg, patient's medical file, appointment books, original laboratory records, etc.). These personnel, bound by professional secrecy, must maintain the confidentiality of all personal identity or personal medical information (according to confidentiality rules).

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

An electronic CRF will be used to collect the data for all enrolled patients. A separate manual will describe in detail the procedures for using the e-CRF. The Sponsor is responsible for ensuring that appropriate material is available at the investigative sites for completion of the e-CRFs or for providing this material, if needed. It is the responsibility of the Investigator to maintain adequate and accurate e-CRFs (according to the technology used) designed by the Sponsor to record (according to Sponsor instructions) all observations and other data pertinent to the clinical investigation. All e-CRFs should be completed in their entirety in a neat, legible manner to ensure accurate interpretation of data.

Should a correction be made, the corrected will be entered in the e-CRF overwriting the initial information. An audit trail will allow identifying the modification.

Data are available within the system to the sponsor as soon as they are entered in the e-CRF.

The computerized handling of the data by the Sponsor after receipt of the e-CRFs may generate additional requests (DRF) to which the Investigator is obliged to respond by confirming or modifying the data questioned. The requests with their responses will be managed through the e-CRF.

15.5 USE OF COMPUTERIZED SYSTEMS

Computerized systems used during the different steps of the study are:

- For data management activities: Oracle Clinical.
- For pharmacokinetic activities: PKDMS (Pharsight).
- For statistical activities: SAS.
- For pharmacovigilance activities: AWARE.
- For monitoring activities: IMPACT.
- For medical writing activities: GRESDA/DOMASYS (Documentum).
- For ePRO: site-based electronic tablets with internet capability.

16 ADMINISTRATIVES RULES

16.1 CURRICULUM VITAE

A current copy of the curriculum vitae describing the experience, qualification and training of each Investigator and Sub-Investigator will be provided to sanofi-aventis prior to the beginning of the Clinical Trial.

16.2 RECORD RETENTION IN STUDY SITES (S)

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

It is recommended that the Investigator retain the study documents at least fifteen (15) years after the completion or discontinuation of the Clinical Trial.

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

The Investigator must notify sanofi-aventis prior to destroying any study essential documents following the Clinical Trial completion or discontinuation.

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

16.3 CONFIDENTIALITY

All information disclosed or provided by sanofi-aventis (or any company/institution acting on their behalf), or produced during the Clinical Trial, including, but not limited to, the Clinical Trial Protocol, the CRFs, the Investigator's Brochure and the results obtained during the course of the Clinical Trial, is confidential, prior to the publication of results. The Investigator and any person under his/her authority agree to undertake to keep confidential and not to disclose the information to any third party without the prior written approval of sanofi-aventis.

However, the submission of this Clinical Trial Protocol and other necessary documentation to the Ethics Committee (IRB/IEC) is expressly permitted, the IRB/IEC members having the same obligation of confidentiality.

The Sub-Investigators shall be bound by the same obligation as the Investigator. The Investigator shall inform the Sub-Investigators of the confidential nature of the Clinical Trial.

The Investigator and the Sub-Investigators shall use the information solely for the purposes of the Clinical Trial, to the exclusion of any use for their own or for a third party's account.

16.4 PROPERTY RIGHTS

All information, documents and Investigational Product provided by sanofi-aventis or its designee are and remain the sole property of sanofi-aventis.

The Investigator shall not mention any information or the Product in any application for a patent or for any other intellectual property rights.

All the results, data, documents and inventions, which arise directly or indirectly from the Clinical Trial in any form, shall be the immediate and exclusive property of sanofi-aventis.

Sanofi-aventis may use or exploit all the results at its own discretion, without any limitation to its property right (territory, field, continuance). Sanofi-aventis shall be under no obligation to patent, develop, market or otherwise use the results of the Clinical Trial.

As the case may be, the Investigator and/or the Sub-Investigators shall provide all assistance required by sanofi-aventis, at sanofi-aventis' expense, for obtaining and defending any patent, including signature of legal documents.

16.5 DATA PROTECTION

The patient's personal data and Investigator's personal data which may be included in the sanofi-aventis database shall be treated in compliance with all applicable laws and regulations;

When archiving or processing personal data pertaining to the Investigator and/or to the patients, sanofi-aventis shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.

16.6 INSURANCE COMPENSATION

Sanofi-aventis certifies that it has taken out a liability insurance policy covering all clinical trials under its sponsorship. This insurance policy is in accordance with local laws and requirements. The insurance of sanofi-aventis does not relieve the Investigator and the collaborators from maintaining their own liability insurance policy. An insurance certificate will be provided to the Ethics committees/IRB or Health Authorities in countries requiring this document.

16.7 SANOFI-AVENTIS AUDITS AND INSPECTIONS BY REGULATORY AGENCIES

For the purpose of ensuring compliance with the Clinical Trial Protocol, Good Clinical Practice and applicable regulatory requirements, the Investigator should permit auditing by or on the behalf of sanofi-aventis and inspection by regulatory authorities.

The Investigator agrees to allow the auditors/inspectors to have direct access to his/her study records for review, being understood that this personnel is bound by professional secrecy, and as such will not disclose any personal identity or personal medical information.

The Investigator will make every effort to help with the performance of the audits and inspections, giving access to all necessary facilities, data, and documents.

As soon as the Investigator is notified of a planned inspection by the authorities, he will inform sanofi-aventis and authorize sanofi-aventis to participate in this inspection.

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

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

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

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

The sponsor reserves the right to discontinue this study under the conditions specified in the clinical trial agreement.

16.9 DECIDED BY SANOFI-AVENTIS IN THE FOLLOWING CASES:

- If the information on the product leads to doubt as to the benefit/risk ratio.
- If the Investigator has received from sanofi-aventis all Investigational Product, means and information necessary to perform the Clinical Trial and has not included any patient after a reasonable period of time mutually agreed upon.
- In the event of breach by the Investigator of a fundamental obligation under this agreement, including but not limited to breach of the Clinical Trial Protocol, breach of the applicable laws and regulations or breach of the ICH guidelines for Good Clinical Practice
- If the total number of patients are included earlier than expected.
- If the study no longer meets the development needs of the compound or business needs of the company.

In any case sanofi-aventis will notify the Investigator of its decision by written notice.

16.10 DECIDED BY THE INVESTIGATOR

The Investigator must notify (30 days' prior notice) sanofi-aventis of his/her decision and give the reason in writing.

In all cases (decided by sanofi-aventis or by the Investigator), the appropriate Ethics Committee(s) (IRB/IEC) and Health Authorities should be informed according to applicable regulatory requirements.

16.11 CLINICAL TRIAL RESULTS

Sanofi-aventis will be responsible for preparing a Clinical Study Report and to provide a summary of study results to Investigator;

When the data from all investigational sites have been fully analyzed by sanofi-aventis, the latter will communicate the results of the Clinical Trial to the Investigator(s).

16.12 PUBLICATIONS AND COMMUNICATIONS

As the Study is being conducted at multiple sites, sanofi-aventis agrees that, consistent with scientific standards, first presentation or publication of the results of the Study shall be made only as part of a publication of the results obtained by all sites performing the Protocol. However, if no multicenter publication has occurred within twelve (12) months of the completion of this Study at all sites, the Investigator shall have the right to publish or present independently the results of this Study patient to the review procedure set forth herein. The Investigator shall provide sanofi-aventis with a copy of any such presentation or publication derived from the Study for review and comment at least thirty (30) days in advance of any presentation or submission for publication. In addition, if requested by sanofi-aventis, any presentation or submission for publication shall be delayed for a limited time, not to exceed ninety (90) days, to allow for filing of a patent application or such other measures as sanofi-aventis deems appropriate to establish and preserve its proprietary rights.

The Investigator shall not use the name(s) of sanofi-aventis and/or of its employees in advertising or promotional material or publication without the prior written consent of sanofi-aventis. sanofi-aventis shall not use the name(s) of the Investigator and/or the Collaborators in advertising or promotional material or publication without having received his/her and/or their prior written consent(s).

Sanofi-aventis has the right at any time to publish the results of the Study.

17 CLINICAL TRIAL PROTOCOL AMENDMENTS

All appendices attached hereto and referred to herein are made part of this Clinical Trial Protocol.

The Investigator should not implement any deviation from, or changes of the Clinical Trial Protocol without agreement by sanofi-aventis and prior review and documented approval/favorable opinion from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to Clinical Trial Patients, or when the change(s) involves only logistical or administrative aspects of the trial. Any change agreed upon will be recorded in writing, the written amendment will be signed by the Investigator and by sanofi-aventis and the signed amendment will be filed with this Clinical Trial Protocol.

Any amendment to the Clinical Trial Protocol requires written approval/favorable opinion by the Ethics Committee (IRB/IEC) prior to its implementation, unless there are overriding safety reasons.

In some instances, an amendment may require a change to the Informed Consent Form. The Investigator must receive an IRB/IEC approval/favorable opinion concerning the revised Informed Consent Form prior to implementation of the change.

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19 APPENDICES

Appendix A National Cancer Institute Common Terminology Criteria for Adverse Events

Refer to NCI CTC AE v. 4.03(45) in the Study Reference Manual, or online at the following NCIwebsite: http://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcaev4.pdf

Toxicity grade should reflect the most severe degree occurring during the evaluated period, not an average.

When 2 criteria are available for similar toxicities, the one resulting in the more severe grade should be used.

The evaluator must attempt to discriminate between disease/treatment and related signs/symptoms.

An accurate baseline prior to therapy is essential.

Appendix B Karnofsky/ECOG Performance Status Evaluation and creatinine clearance calculation formula

Karnofsky performance status scale	Score
Normal; no complaints; no evidence of disease	100
Able to carry on normal activity; minor signs or symptoms of disease	90
Normal activity with effort; some signs or symptoms of disease	80
Cares for self; unable to carry on normal activity or to do active work	70
Requires occasional assistance but is able to care for most of his or her needs	60
Requires considerable assistance and frequent medical care	50
Disabled; requires special care and assistance	40
Severely disabled; hospitalization is indicated although death not imminent	30
Hospitalization necessary; very sick, active supportive treatment is necessary	20
Moribund; fatal processes progressing rapidly	10

National Cancer Institute. Cancer therapy evaluation program. Available at: http://ctep.cancer.gov/reporting/adeers.html.

ECOG performance status scale

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

AND

Formula creatinine clearance

Modification of Diet in Renal Disease (MDRD) equation

GFR (mL/min/1.73 m^2) =

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

Appendix C Definition of Line of Therapy and Refractory Myeloma

Taken from Rajkumar et al (1).

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

Refractory myeloma is defined as disease that is nonresponsive while on primary or salvage therapy, or progresses within 60 days of last therapy. Nonresponsive disease is defined as either failure to achieve minimal response or development of progressive disease while on therapy.

Appendix D Phase 1 Response Criteria

EBMT Response criteria for multiple myeloma (MM) (6)

The following response criteria for secretory multiple myeloma, developed by an international group of multiple myeloma and bone marrow transplant experts, is referred to as the EBMT criteria (6)

Complete response (CR)

CR requires all of the following:

- Absence of the original M-protein in serum and urine by immunofixation, maintained for a minimum of 6 weeks. The presence of oligoclonal bands consistent with oligoclonal immune reconstitution does not exclude CR.
- <5% plasma cells in a bone marrow aspirate and also on trephine bone biopsy if biopsy is performed. If absence of M-protein is sustained for 6 weeks it is not necessary to repeat the bone marrow.
- No increase in size or number of lytic bone lesions (development of a compression fracture does not exclude response).
- Disappearance of soft tissue plasmacytomas.

Subjects in whom some, but not all, the criteria for CR are fulfilled are classified as PR, providing the remaining criteria satisfy the requirements for PR. This includes subjects in whom routine electrophoresis is negative but in whom immunofixation has not been performed.

Partial response (PR)

PR requires all of the following:

- ≥50% reduction in the level of the serum M-protein, maintained for a minimum of 6 weeks.
- Reduction in 24 hour urinary light chain excretion either by ≥90% or to <200 mg, maintained for a minimum of 6 weeks.
- ≥50% reduction in the size of soft tissue plasmacytomas (by radiography or clinical examination).
- No increase in size or number of lytic bone lesions (development of a compression fracture does not exclude response).

Subjects in whom some, but not all the criteria for PR are fulfilled are classified as MR, provided the remaining criteria satisfy the requirements for MR.

Minimal response (MR)

MR requires all of the following:

- 25 to 49% reduction in the level of the serum M-protein maintained for a minimum of 6 weeks.
- 50 to 89% reduction in 24 hour urinary light chain excretion, which still exceeds 200 mg/24 hour, maintained for a minimum of 6 weeks.
- 25 to 49% reduction in the size of soft tissue plasmacytomas (by radiography or clinical examination).
- No increase in the size or number of lytic bone lesions (development of a compression fracture does not exclude response).

MR also includes subjects in whom some, but not all, the criteria for PR are fulfilled, provided the remaining criteria satisfy the requirements for MR.

No change (Stable disease)

- Not meeting the criteria of either MR or progressive disease.

Plateau

- Stable values (within 25% above or below value at the time response is assessed) maintained for at least 3 months.

Complete response relapse

Relapse from CR requires at least 1 of the following:

- Reappearance of serum or urinary M-protein on immunofixation or routine electrophoresis, confirmed by at least 1 further investigation and excluding oligoclonal immune reconstitution.
- ≥5% plasma cells in a bone marrow aspirate or on trephine bone biopsy.
- Development of new lytic bone lesions or soft tissue plasmacytomas or definite increase in the size of residual bone lesions (development of a compression fracture does not exclude continued response and may not indicate progression).
- Development of hypercalcemia (corrected serum calcium >11.5 mg/dL or 2.8 mmol/L) not attributable to any other cause.

Progressive disease

Progressive disease (for subjects not in CR) requires 1 or more of the following:

- >25% increase in the level of the serum M-protein, which must also be an absolute increase of at least 5 g/L and confirmed by at least 1 repeated investigation.
- >25% increase in the 24 hour urinary light chain excretion, which must also be an absolute increase of at least 200 mg/24 hour and confirmed by at least 1 repeated investigation.

- >25% increase in plasma cells in bone marrow aspirate or on trephine biopsy, which must also be an absolute increase of at least 10%.
- Definite increase in the size of existing bone lesions or soft tissue plasmacytomas.
- Development of new bone lesions or soft tissue plasmacytomas. Development of compression fracture does not exclude continued response and may not indicate progression.
- Development of hypercalcemia (corrected serum calcium >11.5 mg/dL or 2.8 mmol/L) not attributable to any other cause.

Response criteria for serum free light chain analysis in non-secretory multiple myeloma (MM) (1)

The following response criteria are for patients who have non-secretory or oligosecretory multiple myeloma, developed by International Myeloma Working Group (IMWG).

CR - In patients who lack measurable M proteins in the serum and urine being monitored using the FLC levels, the definition of CR requires a normalization of the FLC ratio in addition to the above criteria.

VGPR - In patients who lack measurable M proteins in the serum and urine being monitored using the FLC levels, the definition of VGPR requires >90 percent decrease in the difference between involved and uninvolved free light chain levels.

PR - In patients who lack measurable M proteins in the serum and urine being monitored using the FLC levels, the definition of PR requires ≥50 percent decrease in the difference between involved and uninvolved free light chain levels FLC levels. If the FLC levels were also unmeasurable at baseline, a 50 percent reduction in bone marrow plasma cells is acceptable as long as the original bone marrow contained at least 30 percent plasma cells.

SD - Does not meet criteria for CR, VGPR, PR, or PD.

PD - Difference in the kappa and lambda FLC (absolute increase must be >10 mg/dL).

Response criteria for acute myelogenous leukemia (AML) (14)

Anti-leukemia activity of SAR650984 will be evaluated as follows:

By inclusion criteria, all patients enrolled will have evidence of AML, on the basis of peripheral blood count and bone marrow aspiration or biopsy.

Response to treatment will be defined using the following criteria:

- Complete remission (CR): Neutrophil count >1 x 10^9/L, platelet count ≥100 x 10^9/L, normal bone marrow morphology with <5% blasts and absence of extra-medullary localizations. Patients must be independent of transfusions.

- Remission with incomplete platelet recovery (CRp): As per CR but platelet count <100 x 10^9/L.
- Partial remission (PR): Criteria for CR in the peripheral blood, but with 5% to 25% blasts in the bone marrow or ≥50% reduction in bone marrow blasts compared with pre-treatment values (ie, If the pretreatment bone marrow blast percentage is 50% to 100%, the percentage of blasts must decrease to a value between 5% to 25%; if the pretreatment blast percentage is 20% to less than 49%, they must decrease by at least half to a value of more than 5%).
- Progressive disease (PD): An increase in bone marrow blasts of more than 50% of the pre-treatment value and to a level >70% *and/or* a doubling of the percentage of peripheral blood blasts to a level >70%.
- Stable disease (SD): Failure to fulfill criteria for response or progression.

Response criteria for acute lymphoblastic leukemia (ALL) (53)

The primary efficacy endpoint in this study is sustained hematologic response lasting at least 4 weeks, assessed as:

1. Complete hematologic response (CHR), defined according to conventional criteria as blast count below 5% in bone marrow, no blasts in peripheral blood, neutrophil count at least 1.5 x 10^9/L, platelet count at least 100 x 10^9/L, and no evidence of extramedullary involvement.
2. Complete marrow response (marrow-CR) in patients achieving a blast count of less than 5% in bone marrow, no blasts in peripheral blood, no evidence of extramedullary involvement, a neutrophil count at least 1.0 x 10^9/L, but no platelet recovery (platelet count at least 20 x 10^9/L).
3. Partial response, defined as fewer than 15% blasts in peripheral blood and bone marrow. Sustained responses are required to be observed at 2 consecutive evaluations at least 4 weeks apart.

Response criteria for chronic lymphocytic leukemia (CLL) (4)

Complete remission (CR)

CR requires all of the following criteria as assessed at least 2 months after completion of therapy:

- Peripheral blood lymphocytes (evaluated by blood and differential count) below 4 x 10^9/L.
- Absence of significant lymphadenopathy (eg, lymph nodes >1.5 cm in diameter) by physical examination.

  CT scan of the abdomen, pelvis, and thorax is desirable if previously abnormal. Lymph nodes should not be larger than 1.5 cm in diameter.
- No hepatomegaly or splenomegaly by physical examination.

CT scan of the abdomen should be performed at response assessment if found to be abnormal before therapy or if physical examination is inconclusive at the time of evaluation.

- Absence of constitutional symptoms.
- Blood counts above the following values:
  - Neutrophils more than 1.5 x 10^9/L without need for exogenous growth factors.
  - Platelets more than 100 x 10^9/L without need for exogenous growth factors.
  - Hemoglobin more than 110 g/L (11.0 g/dL) without red blood cell transfusion or need for exogenous erythropoietin.
- A marrow aspirate and biopsy should be performed at least 2 months after the last treatment and if clinical and laboratory results listed in bullet 5 above has been achieved.

  To define a CR, the marrow sample must be at least normocellular for age, with less than 30% of nucleated cells being lymphocytes. Lymphoid nodules should be absent. If lymphoid nodules can be found, these nodules should be recorded as "nodular PR." Immunohisto-chemistry should be performed to define whether these nodules are composed primarily of T cells or lymphocytes other than CLL cells or of CLL cells. If the marrow is hypocellular, a repeat determination should be performed after 4 weeks, or until peripheral blood counts have recovered. However, this time interval should not exceed 6 months after the last treatment. A marrow biopsy should be compared with that of pretreatment marrow. The use of a marrow biopsy for evaluating a CR is at the discretion of the physician.

CR with incomplete marrow recovery (CRi)

Patients who fulfill all the criteria for a CR (including the marrow examinations) but who have a persistent anemia or thrombocytopenia or neutropenia unrelated to CLL but related to drug toxicity. For the definition of this category, CRi, the marrow evaluation should be performed and not show any clonal infiltrate.

Partial remission (PR)

- A decrease in the number of blood lymphocytes by 50% or more from the value before therapy.
- Reduction in lymphadenopathy (by CT scans in clinical as defined by the following:
  - A decrease in lymph node size by 50% or more either in the sum products of up to 6 lymph nodes, or in the largest diameter of the enlarged lymph node(s) detected prior to therapy.
  - No increase in any lymph node, and no new enlarged lymph node. In small lymph nodes (2 cm), an increase of less than 25% is not considered to be significant.
- A reduction in the noted pretreatment enlargement of the spleen or liver by 50% or more, as detected by CT scan

- The blood count should show one of the following results:
  - Neutrophils more than 1.5 x 10^9/L without need for exogenous growth factors.
  - Platelet counts greater than 100 x 10^9/L or 50% improvement over baseline without need for exogenous growth factors.
  - Hemoglobin greater than 110 g/L (11.0 g/dL) or 50% improvement over baseline without requiring red blood cell transfusions or exogenous erythropoietin.

Progressive disease

Progressive disease during or after therapy is characterized by at least one of the following:

- Appearance of any new lesion, such as enlarged lymph nodes (>1.5 cm), splenomegaly, hepatomegaly, or other organ infiltrates.
- An increase by 50% or more in greatest determined diameter of any previous site.
- An increase in the previously noted enlargement of the liver or spleen by 50% or more or the de novo appearance of hepatomegaly or splenomegaly.
- An increase in the number of blood lymphocytes by 50% or more with at least 5000 B lymphocytes per microliter.
- Transformation to a more aggressive histology (eg, Richter syndrome). Whenever possible, this diagnosis should be established by lymph node biopsy.
- Occurrence of cytopenia (neutropenia, anemia, or thrombocytopenia) attributable to CLL.
- During therapy. Cytopenias may occur as a side effect of many therapies and should be assessed according to Table 8. (During therapy, cytopenias cannot be used to define disease progression)

Table 8 - Grading scale for hematologic toxicity in CLL studies

Grade*	Decrease in platelets† or Hb‡ (nadir) from pretreatment value, %	Absolute neutrophil count/μL§ (nadir)
0	No change to 10%	≥ 2000
1	11%-24%	≥ 1500 and < 2000
2	25%-49%	≥ 1000 and < 1500
3	50%-74%	≥ 500 and < 1000
4	≥ 75%	< 500

*Grades: 1, mild; 2, moderate; 3, severe; 4, life-threatening; 5, fatal. Death occurring as a result of toxicity at any level of decrease from pretreatment will be recorded as grade 5.

†Platelet counts must be below normal levels for grades 1 to 4. If, at any level of decrease, the platelet count is $< 20 \times 10^9$/L (20 000/μL), this will be considered grade 4 toxicity, unless a severe or life-threatening decrease in the initial platelet count (eg, 20×10^9/L [20 000/μL]) was present pretreatment, in which case the patient is not evaluable for toxicity referable to platelet counts.

‡Hb levels must be below normal levels for grades 1 to 4. Baseline and subsequent Hb determinations must be performed before any given transfusions. The use of erythropoietin is irrelevant for the grading of toxicity but should be documented.

§If the absolute neutrophil count (ANC) reaches $< 1 \times 10^9$/L (1000/μL), it should be judged to be grade 3 toxicity. Other decreases in the white blood cell count, or in circulating neutrophils, are not to be considered because a decrease in the white blood cell count is a desired therapeutic endpoint. A gradual decrease in granulocytes is not a reliable index in CLL for stepwise grading of toxicity. If the ANC was $< 1 \times 10^9$/L (1000/μL) before therapy, the patient is not evaluable for toxicity referable to the ANC. The use of growth factors such as G-CSF is not relevant to the grading of toxicity, but should be documented.

- After treatment. The progression of any cytopenia (unrelated to autoimmune cytopenia), as documented by a decrease of Hb levels by more than 20 g/L (2 g/dL) or to less than 100 g/L (10 g/dL), or by a decrease of platelet counts by more than 50% or to less than 100 x 10^9/L, which occurs at least 3 months after treatment, defines disease progression, if the marrow biopsy demonstrates an infiltrate of clonal CLL cells.

Stable disease

Patients who have not achieved a CR or a PR, and who have not exhibited progressive disease, will be considered to have stable disease (which is equivalent to a nonresponse).

Treatment failure

Responses that should be considered clinically beneficial include CR and PR; all others (eg, stable disease, nonresponse, progressive disease, or death from any cause) should be rated as a treatment failure.

Response criteria for Non-Hodgkin's lymphoma (NHL) (3)

INTERNATIONAL WORKING GROUP RECOMMENDATIONS (3)

Table 9 - Response definitions for clinical trials

Response	Definition	Nodal masses	Spleen, liver	Bone marrow
CR	Disappearance of all evidence of disease	(a) FDG-avid or PET positive prior to therapy: mass of any size permitted if PET negative (b) Variably FDG-avid or PET negative: regression to normal size on CT	Not palpable, nodules disappeared	Infiltrate cleared on repeat biopsy; if indeterminate by morphology, immunohistochemistry should be negative
PR	Regression of measurable disease and no new sites	50% decrease in SPD of up to 6 largest dominant masses; no increase in size of other nodes (a) FDG-avid or PET positive prior to therapy: one or more PET positive at previously involved site (b) Variably FDG-avid or PET negative: regression on CT	50% decrease in SPD of nodules (for single nodule in greatest transverse diameter); no increase in size of liver or spleen	Irrelevant if positive prior to therapy; cell type should be specified
SD	Failure to attain CR/PR or PD	(a) FDG-avid or PET positive prior to therapy: PET positive at prior sites of disease and no new sites on CT or PET (b) Variably FDG-avid or PET negative: no change in size of previous lesions on CT		
Relapsed disease or PD	Any new lesion or increase by 50% of previously involved sites from nadir	Appearance of a new lesion(s) >1.5 cm in any axis, 50% increase in SPD of more than one node, or 50% increase in longest diameter of a previously identified node >1 cm in short axis. Lesions PET positive if FDG-avid lymphoma or PET positive prior to therapy	>50% increase from nadir in the SPD of any previous lesions	New or recurrent involvement

CR, complete remission; FDG, [18F]fluorodeoxyglucose; PET, positron emission tomography; CT, computed tomography; PR, partial remission; SPD, sum of the product of the diameters; SD, stable disease; PD, progressive disease.

Complete remission (CR)

The designation of CR requires the following:

1. Complete disappearance of all detectable clinical evidence of disease and disease-related symptoms if present before therapy.

2a. Typically FDG-avid lymphoma: in patients with no pretreatment PET scan or when the PET scan was positive before therapy, a post-treatment residual mass of any size is permitted as long as it is PET negative.

2b. Variably FDG-avid lymphomas/FDG avidity unknown: in patients without a pretreatment PET scan, or if a pretreatment PET scan was negative, all lymph nodes and nodal masses must have regressed on CT to normal size (1.5 cm in their greatest transverse diameter for nodes >1.5 cm before therapy). Previously involved nodes that were 1.1 to 1.5 cm in their long axis and more than 1.0 cm in their short axis before treatment must have decreased to 1.0 cm in their short axis after treatment.

3. The spleen and/or liver, if considered enlarged before therapy on the basis of a physical examination or CT scan, should not be palpable on physical examination and should be considered normal size by imaging studies, and nodules related to lymphoma should disappear. However, determination of splenic involvement is not always reliable because a spleen considered normal in size may still contain lymphoma, whereas an enlarged spleen may reflect variations in anatomy, blood volume, the use of hematopoietic growth factors, or causes other than lymphoma.

4. If the bone marrow was involved by lymphoma before treatment, the infiltrate must have cleared on repeat bone marrow biopsy. The biopsy sample on which this determination is made must be adequate (with a goal of >20 mm unilateral core). If the sample is indeterminate by morphology, it should be negative by immunohistochemistry. A sample that is negative by immunohistochemistry but that demonstrates a small population of clonal lymphocytes by flow cytometry will be considered a CR until data become available demonstrating a clear difference in patient outcome.

CRu (CR unconfirmed)

The use of the above definition for CR and that below for PR eliminates the category of CRu.

Partial remission (PR)

The designation of PR requires all of the following:

1. At least a 50% decrease in sum of the product of the diameters (SPD) of up to six of the largest dominant nodes or nodal masses. These nodes or masses should be selected according to all of the following: they should be clearly measurable in at least 2 perpendicular dimensions; if possible they should be from disparate regions of the body; and they should include mediastinal and retroperitoneal areas of disease whenever these sites are involved.

2. No increase should be observed in the size of other nodes, liver, or spleen.

3. Splenic and hepatic nodules must regress by 50% in their SPD or, for single nodules, in the greatest transverse diameter.
4. With the exception of splenic and hepatic nodules, involvement of other organs is usually assessable and no measurable disease should be present.
5. Bone marrow assessment is irrelevant for determination of a PR if the sample was positive before treatment. However, if positive, the cell type should be specified (eg, large-cell lymphoma or small neoplastic B cells). Patients who achieve a CR by the above criteria, but who have persistent morphologic bone marrow involvement will be considered partial responders.

When the bone marrow was involved before therapy and a clinical CR was achieved, but with no bone marrow assessment after treatment, patients should be considered partial responders.

1. No new sites of disease should be observed.
2. Typically FDG-avid lymphoma: for patients with no pretreatment PET scan or if the PET scan was positive before therapy, the post-treatment PET should be positive in at least one previously involved site.
3. Variably FDG-avid lymphomas/FDG-avidity unknown: for patients without a pretreatment PET scan, or if a pretreatment PET scan was negative, CT criteria should be used.

In patients with follicular lymphoma or mantle-cell lymphoma, a PET scan is only indicated with one or at most two residual masses that have regressed by more than 50% on CT; those with more than two residual lesions are unlikely to be PET negative and should be considered partial responders.

Stable disease

Stable disease (SD) is defined as the following:

1. A patient is considered to have SD when he or she fails to attain the criteria needed for a CR or PR, but does not fulfill those for progressive disease (see Relapsed Disease [after CR]/Progressive Disease [after PR, SD]).
2. Typically FGD-avid lymphomas: the PET should be positive at prior sites of disease with no new areas of involvement on the post-treatment CT or PET.
3. Variably FDG-avid lymphomas/FDG-avidity unknown: for patients without a pretreatment PET scan or if the pretreatment PET was negative, there must be no change in the size of the previous lesions on the post-treatment CT scan.

Relapsed disease (after CR)/progressive disease (after PR, SD)

Lymph nodes should be considered abnormal if the long axis is more than 1.5 cm regardless of the short axis. If a lymph node has a long axis of 1.1 to 1.5 cm, it should only be considered abnormal if its short axis is more than 1.0. Lymph nodes 1.0 x 1.0 cm will not be considered as abnormal for relapse or progressive disease.

1. Appearance of any new lesion more than 1.5 cm in any axis during or at the end of therapy, even if other lesions are decreasing in size. Increased FDG uptake in a previously unaffected site should only be considered relapsed or progressive disease after confirmation with other modalities. In patients with no prior history of pulmonary lymphoma, new lung nodules identified by CT are mostly benign. Thus, a therapeutic decision should not be made solely on the basis of the PET without histologic confirmation.
2. At least a 50% increase from nadir in the SPD of any previously involved nodes, or in a single involved node, or the size of other lesions (eg, splenic or hepatic nodules). To be considered progressive disease, a lymph node with a diameter of the short axis of less than 1.0 cm must increase by 50% and to a size of 1.5 x 1.5 cm or more than 1.5 cm in the long axis.
3. At least a 50% increase in the longest diameter of any single previously identified node more than 1 cm in its short axis.
4. Lesions should be PET positive if observed in a typical FDG-avid lymphoma or the lesion was PET positive before therapy unless the lesion is too small to be detected with current PET systems (<1.5 cm in its long axis by CT).

Measurable extranodal disease should be assessed in a manner similar to that for nodal disease. For these recommendations, the spleen is considered nodal disease. Disease that is only assessable (eg, pleural effusions, bone lesions) will be recorded as present or absent only, unless, while an abnormality is still noted by imaging studies or physical examination, it is found to be histologically negative.

In clinical trials where PET is unavailable to the vast majority of participants, or where PET is not deemed necessary or appropriate for use (eg, a trial in patients with MALT lymphoma), response should be assessed as above, but only using CT scans. However, residual masses should not be assigned CRu status, but should be considered partial responses.

Appendix E Phase 2 Response Criteria

IMWG Uniform Response criteria for multiple myeloma (MM) (1)

The following response criteria for secretory multiple myeloma, developed by an international group of multiple myeloma and bone marrow transplant experts, is referred to the IMWG Uniform Response Criteria.

Table 1. IMWG uniform response criteria by response subcategory for multiple myeloma[7]

CR*	Stringent complete response (sCR)†	VGPR*	PR	SD	PD†
Negative immunofixation of serum and urine, *and*	CR as defined, *plus*	Serum and urine M-component detectable by immunofixation but not on electrophoresis, *or*	≥ 50% reduction of serum M-protein and reduction in 24-hour urinary M-protein by ≥ 90% or to < 200 mg/24 hours	Not meeting criteria for CR, VGPR, PR, or PD	Increase of 25% from lowest response value in any of the following:
Disappearance of any soft tissue plasmacytomas, *and*	Normal FLC ratio *and*	≥ 90% reduction in serum M-component plus urine M-component < 100 mg/24 h	If the serum and urine M-protein are not measurable, a decrease ≥ 50% in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria		Serum M-component (absolute increase must be ≥ 0.5 g/dL), *and/or*
< 5% PCs in bone marrow	Absence of clonal PCs by immunohistochemistry or 2- to 4-color flow cytometry		If serum and urine M-protein are not measurable, and serum free light assay is also not measurable, ≥ 50% reduction in bone marrow PCs is required in place of M-protein, provided baseline percentage was ≥ 30%		Urine M-component (absolute increase must be ≥ 200 mg/24 h), *and/or*
			In addition to the above criteria, if present at baseline, ≥ 50% reduction in the size of soft tissue plasmacytomas is also required		Only in patients without measurable serum and urine M-protein levels: the difference between involved and uninvolved FLC levels (absolute increase must be > 10 mg/dL)
					Only in patients without measurable serum and urine M protein levels and without measurable disease by FLC levels, bone marrow PC percentage (absolute percentage must be ≥ 10%)
					Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas
					Development of hypercalcemia (corrected serum calcium > 11.5 mg/dL) that can be attributed solely to the PC proliferative disorder

Adapted from Durie et al[7] and Kyle et al[13] with permission. All response categories (CR, sCR, VGPR, PR, and PD) require 2 consecutive assessments made at any time before the institution of any new therapy; CR, sCR, VGPR, PR, and SD categories also require no known evidence of progressive or new bone lesions if radiographic studies were performed. VGPR and CR categories require serum and urine studies regardless of whether disease at baseline was measurable on serum, urine, both, or neither. Radiographic studies are not required to satisfy these response requirements. Bone marrow assessments need not be confirmed. For PD, serum M-component increases of more than or equal to 1 g/dL are sufficient to define relapse if starting M-component is ≥ 5 g/dL.

PCs indicate plasma cells.

*Clarifications to IMWG criteria for coding CR and VGPR in patients in whom the only measurable disease is by serum FLC levels: CR in such patients indicates a normal FLC ratio of 0.26 to 1.65 in addition to CR criteria listed above. VGPR in such patients requires a > 90% decrease in the difference between involved and uninvolved FLC levels.

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

MR in patients with relapsed refractory myeloma adopted from the EBMT criteria[8]
≥ 25% but ≤ 49% reduction of serum M protein *and* reduction in 24-hour urine M-protein by 50%-89%
In addition to the above criteria, if present at baseline, 25%-49% reduction in the size of soft tissue plasmacytomas is also required
No increase in size or number of lytic bone lesions (development of compression fracture does not exclude response)

Phase 2 Stage 2 response criteria

Disease response will be assessed using the updated International Myeloma Working Group Response **Criteria (IMWG) (2).** A confirmation measurement for disease response and progression assessments is required within 4 weeks in this protocol.

Updated International Myeloma Working Group response criteria

Response	IMWG criteria
CR	• Negative immunofixation on the serum and urine and • disappearance of any soft tissue plasmacytomas and • <5% plasma cells in bone marrow. • In patients with only FLC disease, a normal FLC ratio of 0.26-1.65 is required. **Two consecutive assessments are needed**
sCR	CR as defined below plus: • normal FLC ratio and • absence of clonal cells in bone marrow by immunohistochemistry or 2-4 color flow cytometry **Two consecutive assessments of laboratory parameters are needed**
Immunophenotypic CR	sCR as defined plus absence of phenotypically aberrant plasma cells (clonal) in bone marrow with minimum of 1 million total bone marrow cells analyzed by multiparametric flow cytometry (with > four colors)
Molecular CR	CR as defined plus negative allele-specific oligonucleotide polylmerase chain reaction (sensitivity 10^{-5})
VGPR	• Serum and urine M-protein detectable by immunofixation but not on electrophoresis or • >90% reduction in serum M-protein plus urine M-protein level <100 mg/24 h. • In patients with only FLC disease, >90% decrease in the difference between involved and uninvolved FLC levels is required. **Two consecutive assessments are needed**
PR	• 50% reduction of serum M-protein and reduction in 24 hours urinary M-protein by >90% or to <200 mg/24 h • If the serum and urine M-protein are unmeasurable,3 a >50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria • If serum and urine M-protein are not measurable, and serum free light assay is also not measureable, >50% reduction in plasma cells is required in place of M-protein, provided baseline bone marrow plasma cell percentage was >30% • In addition to the above listed criteria, if present at baseline, a >50% reduction in the size of soft tissue plasmacytomas is also required **Two consecutive assessments are needed. No known evidence of progressive disease or new bone lesions if radiographic studies were performed**
MR for relapse refractory myeloma only	≥25% but <49% reduction in serum M-protein and reduction in 24 h urine M-protein by 50%-89%, which still excedd 200 mg/24 H. If present at baseline, 25%-49% reduction in size of soft tissue plasmacytomas; no increase in size or number of lytic bone lesions (developpement of compression fracture does not exclude response)

Response	IMWG criteria
Stable Disease	• Not meeting criteria for CR, VGPR, PR or progressive disease • No known evidence of progressive disease or new bone lesions if radiographic studies were performed
Progressive disease	Increase of >25% from lowest response value in any one of the following: • Serum M-component (the absolute increase must be >0.5 g/dL) 4 and/or • Urine M-component (the absolute increase must be >200 mg/24 h) and/or • Only in patients without measurable serum and urine M protein, the difference between involved and uninvolved FLC levels. The absolute increase must be >10 mg/dL • Only in patients without measurable serum and urine M-protein and without measurable disease by FLC levels, bone marrow plasma cell percentage (absolute % must be ≥10%) Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas • Development of hypercalcemia (corrected serum calcium >11.5 mg/dL) that can be attributed solely to the plasma cell proliferative disorder **Two consecutive assessments before new therapy are needed.**

Abbreviations: CR, complete response; FLC, free light chain; M, monoclonal; PD, progressive disease; PR, partial response; sCR, stringent complete response; SD, stable disease; VGPR, very good partial response.

Appendix F Staging Criteria

Staging criteria for multiple myeloma (MM)

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

*** There are two categories for stage II: serum β2 – microglobulin < 3.5 mg/L but serum albumin < 3.5 mg/L; or serum β2 – microglobulin 3.5 mg/L to < 5.5 mg/L irrespective of the serum albumine**

Classifications for acute myelogenous leukemia (AML)

While the FAB system is still the most commonly used, some doctors now refer to the World Health Organization (WHO) system of classification when diagnosing cases of AML and planning the most appropriate treatment. WHO Classification divides AML into broader groups based on factors such as genetic abnormalities and the presence of other leukemia-related blood disorders like myelodysplastic syndrome. These groups are as follows:

- **AML with Recurrent Genetic Abnormalities**
  - AML with translocation of certain genes between chromosomes 8 and 21.
  - AML with translocation of certain genes between chromosomes 15 and 17.
  - AML with inversion or translocation of certain genes on chromosome 16.
  - AML with abnormalities of chromosome 11.
  - Acute Promyelocytic Leukemia.
- **AML with multilineage dysplasia** (leukemia in which more than one abnormal myeloid cell type is involved).
  - With prior myelodysplastic syndrome.
  - Without prior myelodysplastic syndrome.
- AML with Myelodysplastic Syndrome, Therapy-Related.
  - Alkylating agent-related - alkylating agents are a certain type of drug used in chemotherapy for various cancers. Examples would include drugs like altretamine.
  - Epipodophyllotoxin-related - epipodophyllotoxins are also used in chemotherapy.
  - Other Types.

- AML Not Otherwise Categorized.
  - AML minimally differentiated (MO).
  - AML without maturation (M1).
  - AML with maturation (M2).
  - Acute myelomonocytic leukemia (M4).
  - Acute monocytic leukemia (M5).
  - Acute erythroid leukemia (M6).
  - Acute megakaryocytic leukemia (M7).
  - Acute basophilic leukemia.
  - Acute panmyelosis with myelofibrosis.

Classifications for acute lymphocytic leukemia (ALL)

The recent WHO International panel on ALL recommends that the FAB classification be abandoned, since the morphological classification has no clinical or prognostic relevance. It instead advocates the use of the immunophenotypic classification mentioned below.

- Acute lymphoblastic leukemia/lymphoma Synonyms:Former Fab L1/L2.
  - Precursor B acute lymphoblastic leukemia/lymphoma. Cytogenetic subtypes.
  - Precursor T acute lymphoblastic leukemia/lymphoma.
- Burkitt's leukemia/lymphoma Synonyms:Former FAB L3.
- Biphenotypic acute leukemia.

Staging criteria for chronic lymphocytic leukemia (CLL)

Modified Rai staging criteria

Modified 3-Stage System	Rai Stage	Clinical Features
Low Risk	0	Blood Lymphocytes (L) blood (>5000/µL) and marrow (>30%) only
Intermediate Risk	I	L + enlarged lymph nodes (LN)
	II	L + spleen and/or liver (LN + or -)
High Risk	III	L + anemia (Hemoglobin <11 gm/dL)
	IV	L + thrombocytopenia (platelets <100,000/µL)

Staging criteria for B-cell Non-Hodgkin's-lymphoma (NHL)

Staging criteria for the subjects with B-cell Non-Hodgkins' lymphoma is provided in Table 10 below.

Table 10 - Ann Arbor staging of lymphoma

Stage I	Involvement of a single lymph node region (I) or localized involvement of a single extralymphatic organ or site (IE).
Stage II	Involvement of 2 or more lymph node regions on the same side of the diaphragm (II) or localized involvement of a single associated extralymphatic organ or site and its regional lymph nodes with or without other lymph node regions on the same side of the diaphragm (IIE).
Stage III	Involvement of lymph node regions on both sides of the diaphragm (III) that may also be accompanied by localized involvement of an extralymphatic organ or site (IIIE) or by involvement of the spleen (IIIS) or both (IIIS+E). The number of regions involved may be indicated by a subscript (eg, II_3)
Stage IV	Disseminated (multifocal) involvement of 1 or more extralymphatic sites with or without associated lymph node involvement or isolated extralymphatic organ involvement with distant (nonregional) nodal involvement. Stage IV refers to disease that is diffusely spread throughout an extranodal site, such as the liver. If pathologic proof of involvement of 1 or more extralymphatic sites has been documented, the symbol for the site of involvement, followed by a plus sign (+), is listed.

a. The designation "E" is used when extranodal lymphoid malignancies arise in tissues separate from, but near, the major lymphatic aggregates.

Identification of the presence or absence of symptoms should be noted with each stage designation, as defined in Table 11.

Table 11 - Subclassification of non-Hodgkin's lymphoma (A and B categories)

A = asymptomatic

B = symptomatic

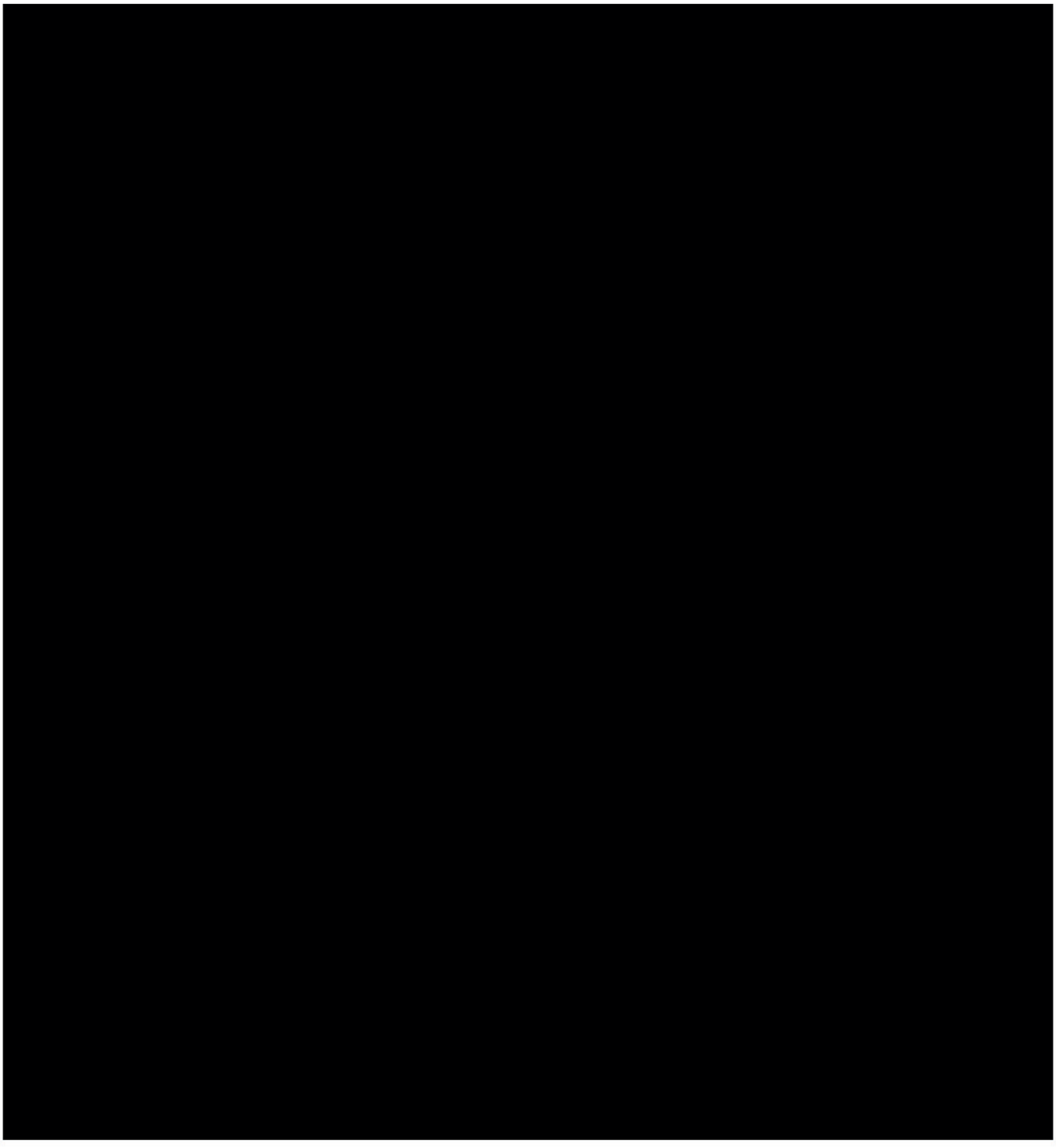
Commonly associated symptoms are:

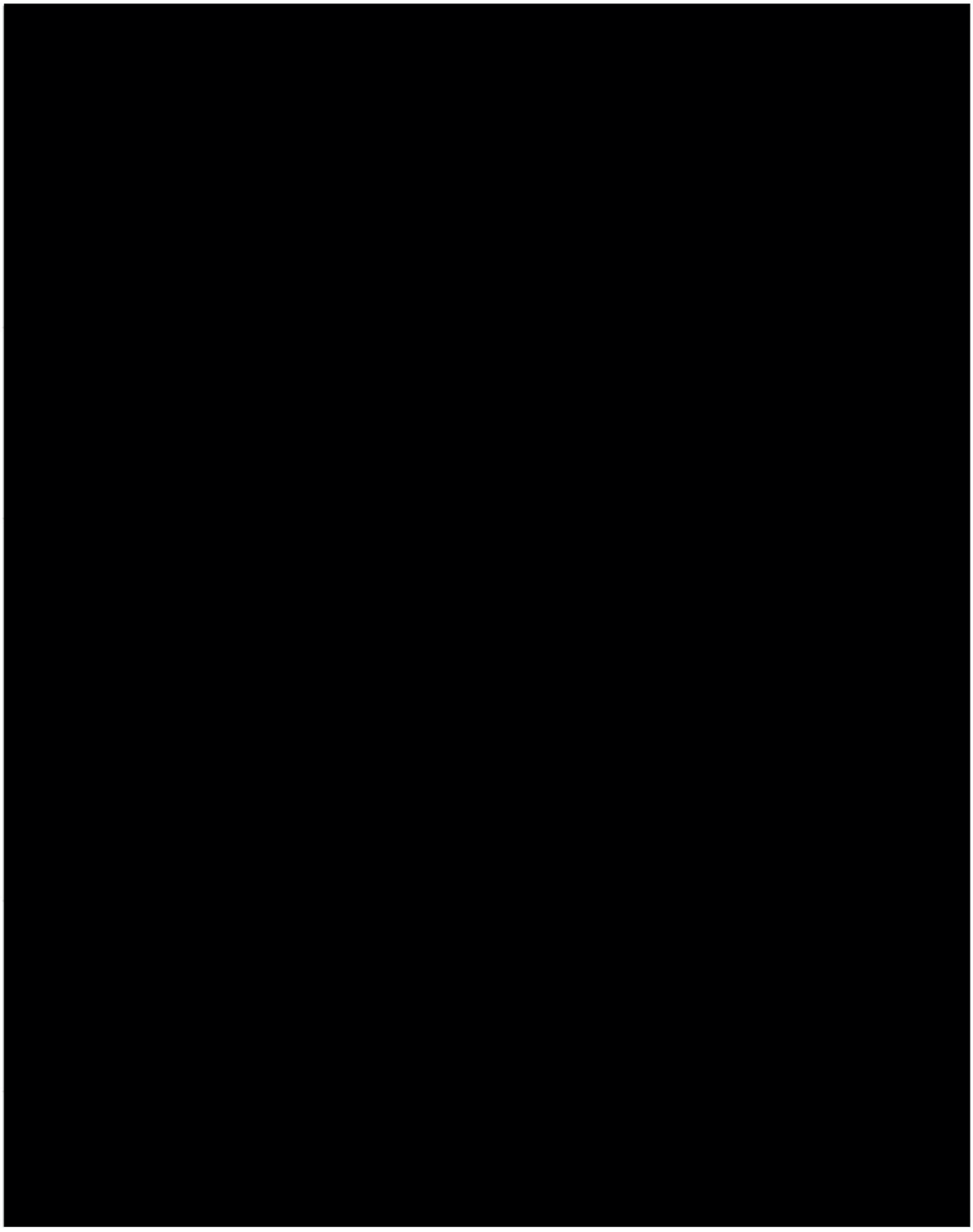
- Drenching night sweats
- Unexplained fever with temperatures > 38°C
- Unexplained loss of more than 10% body weight in the 6 months before diagnosis

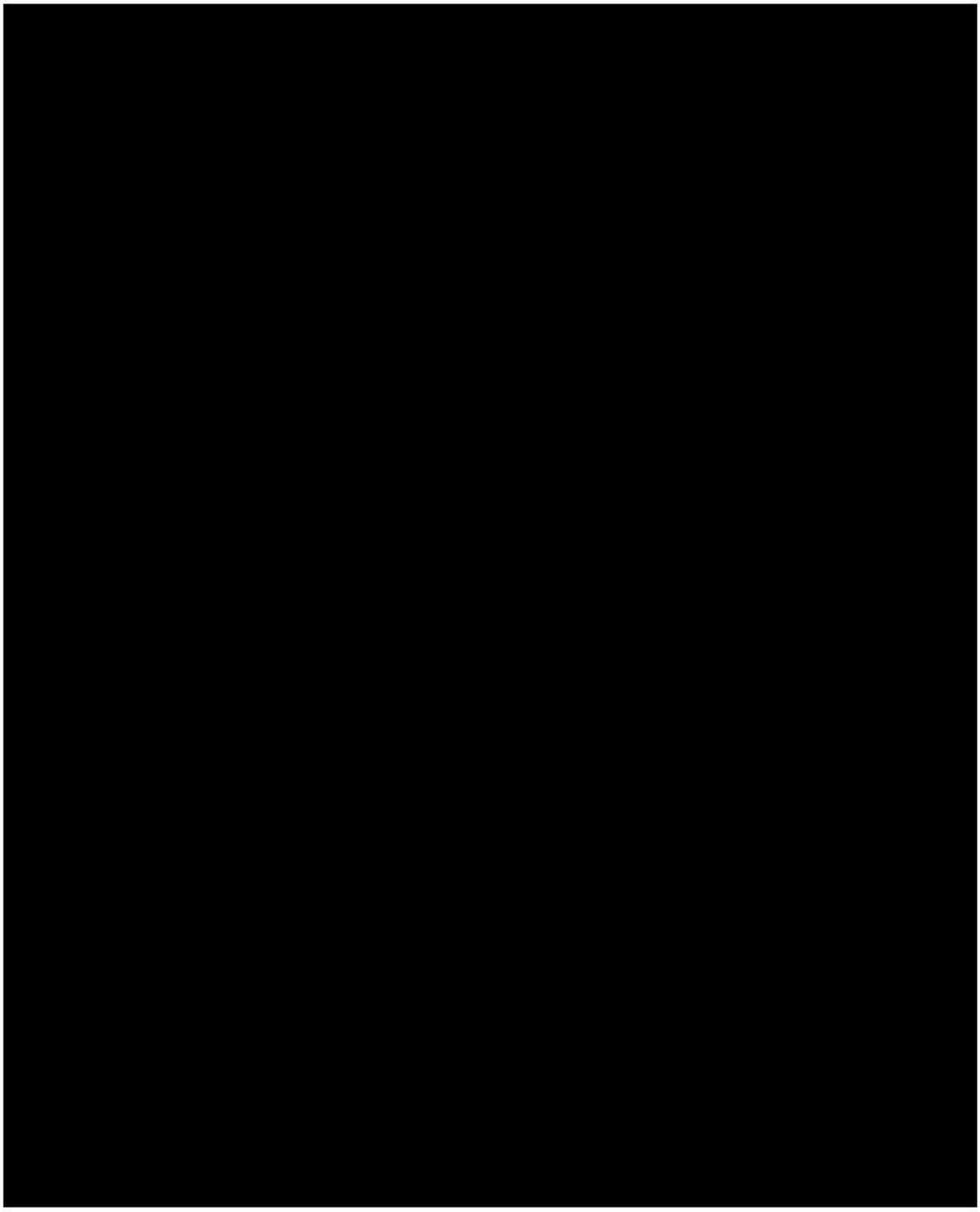
Notation for sites of involvement:

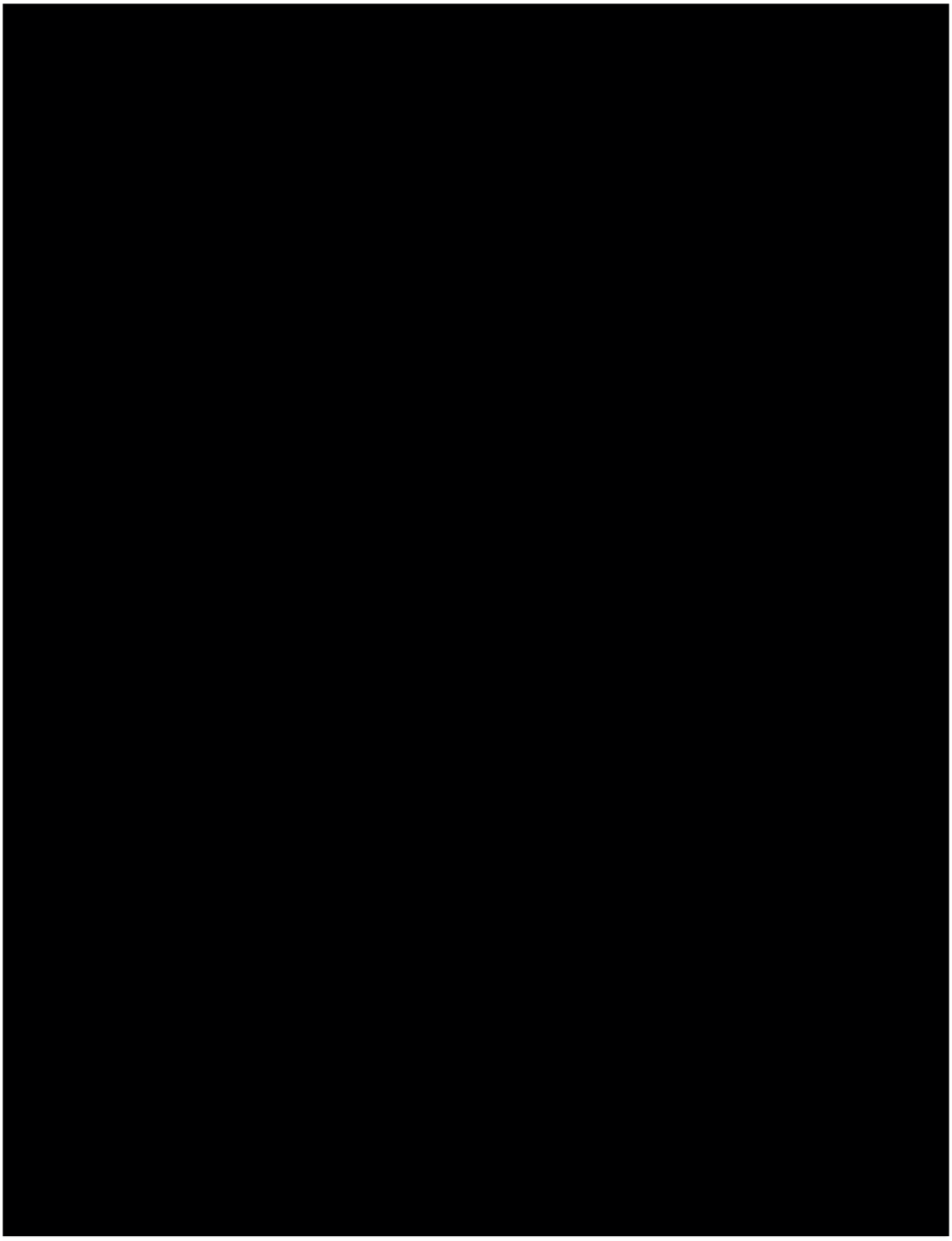
N	=	nodes
H	=	liver
L	=	lung
M	=	bone marrow
S	=	spleen
P	=	pleura
O	=	bone
D	=	skin

Appendix G PRO Questionnaires QLQ-C30 and MY20

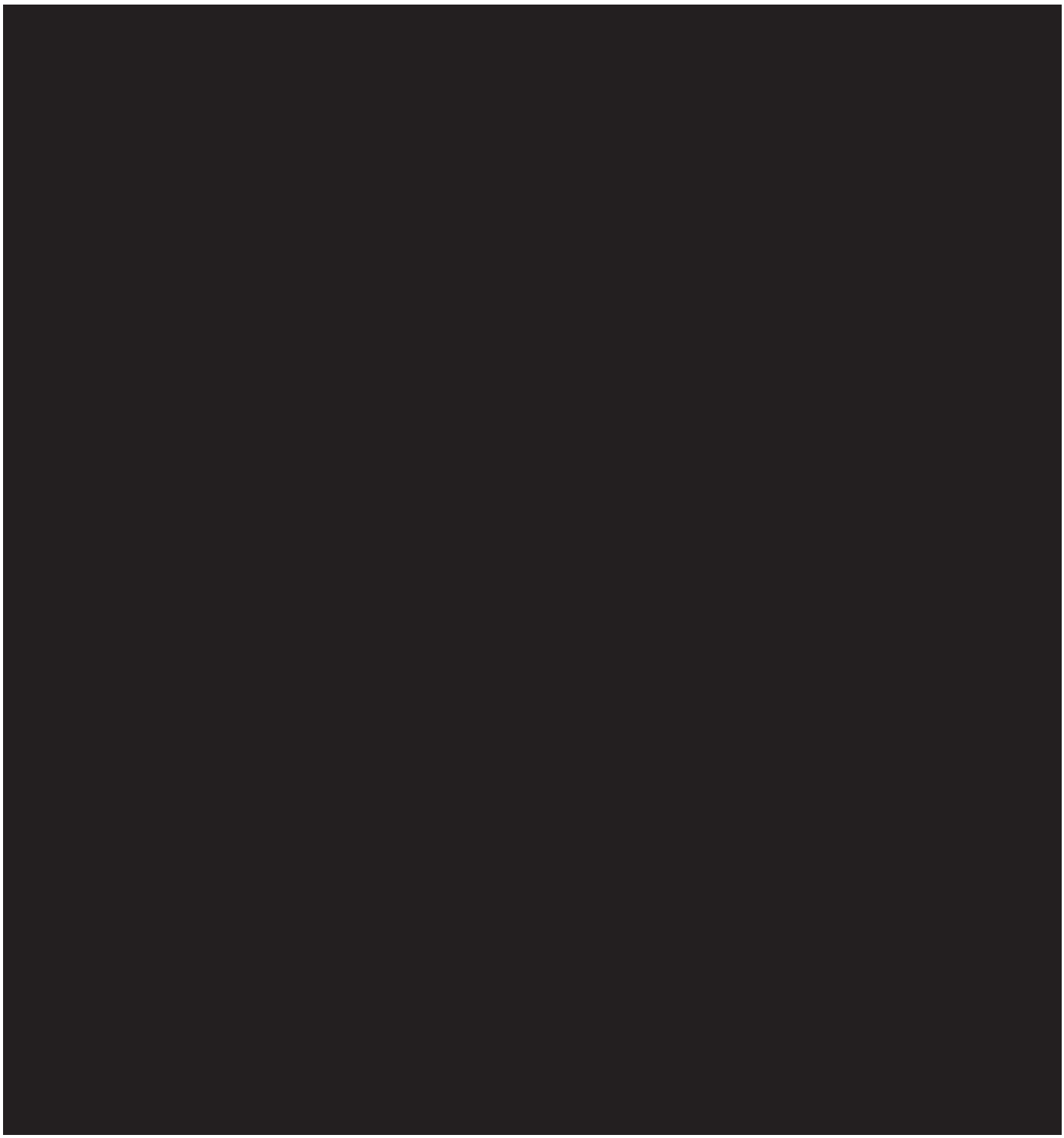








Appendix H PRO Questionnaire EQ-5D



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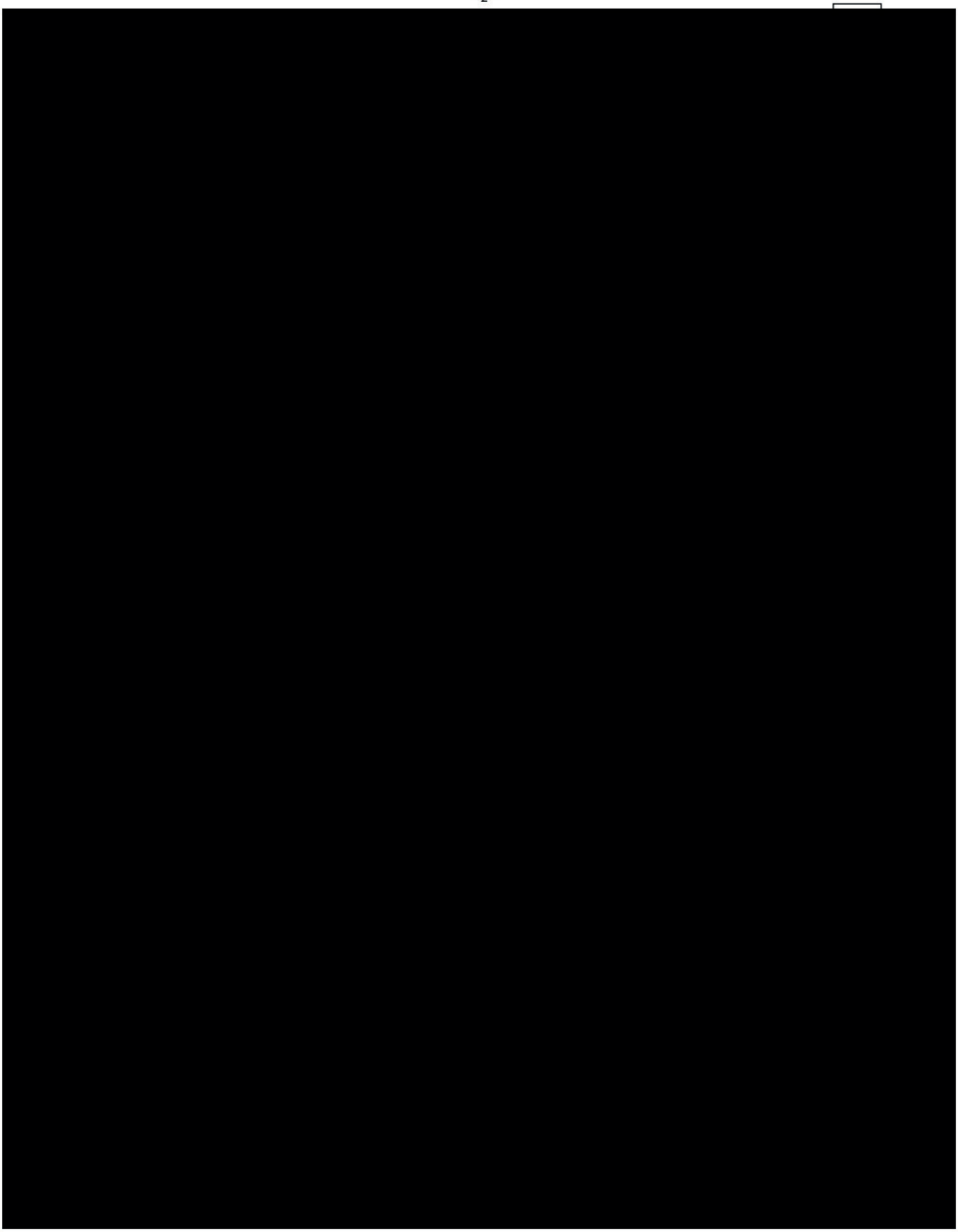

Appendix I Summary of PK/PD handling procedures and bioanalytical method

Table 12 - Summary of handling procedures

	PK	ADA	RO/RD
Blood sample volume:	3 mL	3 mL	5 mL of blood or 2 mL of bone marrow
Anticoagulant Tube Type:	Blood will be collected into EDTA tub	Blood will be collected into EDTA tube	Blood will be collected into EDTA tube
Handling procedures:	Blood is centrifuged at 2000 g for 20 minutes at +4°C within 30 min of sampling time.	Blood is centrifuged at 2000 g for 20 minutes at +4°C within 30 min of sampling time.	Refer to operator manual
Plasma aliquot split:	2 samples, 0.5 mL in aliquot 1 and the remaining in aliquot 2	2 samples, 0.5 mL in aliquot 1 and the remaining in aliquot 2	Refer to laboratory manual
Plasma storage conditions:	Polypropylene tubes with screw caps and frozen promptly (within 1 hour after collection of blood) at (-)80°C.	Polypropylene tubes with screw caps and frozen promptly (within 1 hour after collection of blood) at (-)20°C.	Refer to laboratory manual)
Plasma shipment conditions:	Dry ice	Dry ice	Ambient temperature

Table 13 - Bioanalytical method for SAR650984 in plasma

Analyte	SAR650984	ADA	RO/RD	RO/RD
Matrix:	Plasma	Plasma	Blood	Bone marrow
Analytical technique:	ELISA	PandA	Flow cytometry	Flow cytometry
Lower limit of quantification:	0.500 ng/mL	n.a.	n.a.	n.a.
Assay volume:	100 µL	20 µL	5 mL	2 mL
Site of bioanalysis:	Sanofi R&D DSAR, (Alfortville, France)	Sanofi R&D DSAR, (Alfortville, France)	Under the responsibility of Sanofi R&D DSAR, (Alfortville, France)	Under the responsibility of Sanofi R&D DSAR, (Alfortville, France)

Summary of procedures for collection, handling, storage and shipment of SAR650984 specimens for pharmacogenetic samples: please refer to laboratory manual.

* This list is not intended to be exhaustive

Appendix J CD38 blood test interference guideline AABB

Advancing Transfusion and Cellular Therapies Worldwide

Association Bulletin #16-02

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

Re: Mitigating the Anti-CD38 Interference with Serologic Testing

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

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

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

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

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

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

Other notes on anti-CD38 serologic interference:

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

Anti-CD38 interference can cause delays in issuing RBCs

If the transfusion service is unaware that a patient has received anti-CD38, the following scenario may occur when the patient's sample is tested:

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

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

Recommendations

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

BEFORE a patient begins taking anti-CD38:

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

AFTER a patient begins taking anti-CD38:

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

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

Crossmatch

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

Future/alternative approaches to mitigating the anti-CD38 interference

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

References

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4. Velliquette RW, Shakarian G, Jhang J, et al. Daratumumab-derived anti-CD38 can be easily Mistaken for clinically significant antibodies to Lutheran antigens or to Knops antigens (abstract). Transfusion 2015;55(3S):26A.

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Appendix K Summary of handling procedures for exploratory biomarker analysis in Phase 2 Stage 2

Table 14 - Summary of handling procedures

	FISH/Genomics/MRD/ Immune Phenotyping	Immune Phenotyping	Immune Genetics Determinants	Adaptive Immune Response[a] (including T-Cell Repertoire [TCR])
Sample volume:	6 mL of bone marrow aspirate (BMA)	4 mL of blood	4 mL of blood	6 mL of blood
Tube type:	BMA will be collected into K3 EDTA tube	Blood will be collected into K2 EDTA tube		
Handling procedures:	Collect bone marrow aspirate (BMA) according to local clinical procedures. Fill tube completely with BMA. Gently invert 8-10 times. Do not freeze BMA. Sample should remain AMBIENT.	Fill tube completely. Gently invert 8-10 times. Do not open tube. Do not centrifuge. Do not freeze sample. Sample should remain AMBIENT.		
Shipment conditions:	Ambient temperature.	Ambient temperature.		
Shipment to:	Do not ship to Medpace Reference Laboratories. Please ship directly via World Courier on the day of collection to Pr. Hervé AVET-LOISEAU (IUCT Toulouse) for Europe and ROW sites, or to Mayo Clinic (Scottsdale) for America sites. The central lab should receive samples within 24 hours after collection.	Do not ship to Medpace Reference Laboratories. Please ship directly via World Courier on the day of collection to Pr. Hervé AVET-LOISEAU (IUCT Toulouse) for Europe and ROW sites, or to Mayo Clinic (Scottsdale) for America sites. The central lab should receive samples within 24 hours after collection.		

a In addition to TCR analysis, blood samples will be collected for Adaptive Immune Response - Humoral and Cellular response assessment. Refer to Laboratory Manual for complete handling procedures and shipping instructions.

Appendix L Protocol amendment history

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

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

1. Amended clinical trial protocol 01 based on Amendement 1 (16-Dec-2009)

Reason for amendment

To address issues raised during FDA review of the final version of the protocol:

- Revise definition of DLT to include hematological toxicities
- Provide a procedure to notify investigators of DLTs and SAEs within 24 hours
- Ensure that the first 2 patients in a multiple-dose cohort do not receive study drug on the same day
- Remove patients with dose delays greater than 2 weeks for an AE from study
- Increase monitoring for glucose levels following the first 2 doses of study drug
- Clarify definition of patients considered unsuitable for standard first-line treatment but suitable for treatment with study drug
- Add assessment of vital signs 6 hours following first infusion of study drug

2. Amended Clinical Trial protocol 02 based on Amendement 2 (07-Apr-2010)

Reason for amendment

To make the following revisions and/or corrections:

- Update Clinical Study Director
- Correct Clinical Trial Summary, Assessment Schedule, Disease Response Evaluation as follows: Serum β2-microglobulin to be performed as indicated in Study Flowcharts; Add AML. Include blast counts for B-cell ALL/AML patients.
- Revise Pharmacokinetics/Pharmacodynamics Flowcharts as follows: Clarify that RO in blood to be performed on ALL, AML, and CLL patients only and that RO in bone marrow to be performed on MM patients only. Move RO in bone marrow from C1D8 to C2D14; Add PK, RO in blood, and ADA at C2D14 (Basic Phase).
- Correct Pharmacokinetics/Pharmacodynamics Flowcharts as follows: Correct S = Serum to P = Plasma for PK and ADA; Correct ADA = Anti-Drug Antibody.
- Revise Study Flowcharts as follows: Revise per revisions made to Pharmacokinetics/Pharmacodynamics Flowcharts; Clarify that archival sample may be used at screening for CD38 expression; Remove CD38 expression to be performed after screening/baseline; Add that spirometry and diffusion capacity will also be performed at

End of Treatment visit; Add additional parameters to be performed for urinalysis; Revise holter monitoring to have holter placed on the patient 2 hours before starting the infusion.

- Correct Study Flowcharts as follows: Correct per modificatons made to Pharmacokinetics/Pharmacodynamics Flowcharts; Correct respirometer to spirometry.
- Revise/Correct Section 12 Study Procedures to reflect changes made to Study Flowcharts.
- Clarify regarding secondary endpoint(s) for PK samples.
- Revised Appendix C to reflect Central Labs.
- Minor edits for consistency in formatting.

3. Amended Clinical Trial protocol 03 based on Amendement 3 (11-Oct-2010)

Reason for amendment

To make the following revisions and/or corrections:

- Revise study design to include intra-patient dose escalation.
- Revise main selection criteria to exclude patients with platelets <50 x 10^9/L for all indications.
- Clarify IP dilution and rate of infusion for patients.
- Revise Study Flowcharts as follows: Clarify CXR, Diffusion Capacity and Spirometry can be completed within one week prior to IP administration; Clarify timing of Day 1 RO bone marrow for multiple myeloma patients; Clarify that Day 1 RO bone marrow can be combined with disease assessment bone marrow if completed within 7 days of IP administration; Clarify that bone marrow for RO in multiple myeloma patients is optional for Cohorts 1-3.
- Minor edits for consistency in formatting.

4. Amended Clinical Trial protocol 04 based on Amendement 4 (05-Jan-2011)

Reason for amendment

To make the following revisions and/or corrections:

- Revise study design to remove intra-patient dose escalation.
- Clarify main selection criteria for multiple myeloma to include patients with free light chain disease.
- Revise main selection criteria to exclude patients with platelets <50 x 10^9/L for all indications.
- Clarify IP dilution and rate of infusion for patients.
- Revise Study Flowcharts as follows: Clarify CXR, Diffusion Capacity and Spirometry can be completed within one week prior to IP administration; Clarify multiple myeloma disease assessment parameters; Clarify timing of Day 1 RO bone marrow for multiple

myeloma patients; Clarify that Day 1 RO bone marrow can be combined with disease assessment bone marrow if completed within 7 days of IP administration; Clarify that bone marrow for RO in multiple myeloma patients is optional for Cohorts 1-3.

- Minor edits for consistency in formatting.
- Cover Page: Removed the Protocol amendment 1, 2, 3 titles to be compliant with current template standards.

5. Amended Clinical Trial protocol 05 based on Amendement 5 (10-Sep-2012)

Reason for amendment

- **Change to the DLT definition**

In section(s): Clinical Trial Summary and 9.1.1

Rationale: to modify DLT definition to remove Grade 2 or higher allergic reaction/hypersensitivity attributed to SAR650984

- **Change to the study flowchart for basic dose escalation**

In section(s): 1.6

Rationale: to modify acceptable timing of subsequent cycles following Cycle 2, to add +/-1 day window for Day 8 and Day 14 evaluations, and to modify timing of screening bone marrow biopsy/aspiration receptor occupancy assessment

- **Change to guidelines for management of hypersensitivity reactions**

In section(s): 6.7

Rationale: clarify management of hypersensitivity reactions in the setting of routine pre-medication with dexamethasone and diphenhydramine

- **Change to dose of drug per administration**

In section(s): 8.1.2

Rationale: clarify that actual body weight as measured at each cycle should be used for dose calculation

- **Institute routine pre-medication with dexamethasone and diphenhydramine**

In section(s): 8.1.5

Rationale: institute routine pre-medication for observed mild hypersensitivity reaction prophylaxis

- **Clarify disease assessment parameters**

In section(s): 1.6 and 12.2

Rationale: clarify that selection of disease assessment parameter is based on clinical indication and judgment of investigator

- **Clarify timing of safety evaluations to be performed including laboratory assessments and EKG**

In section(s): 12.3 and 12.4

Rationale: clarify timing of safety evaluations to be consistent with study flowcharts

- **Clarify response criteria for non-secretory multiple myeloma**

In section(s): Appendix D

Rationale: clarify response criteria for serum free light chain analysis for patients who have non-secretory multiple myeloma, as developed by the International Myeloma Working Group (IMWG)

In addition, other minor changes are listed in the description of changes (next section).

6. Amended Clinical Trial protocol 06 based on Amendement 6 (05-Apr-2013)

Reason for amendment

- **Addition of dose escalation and expansion cohorts**

In section(s): tabulated clinical trial summary, sections 1.2, 1.4, 1.5, 1.6, 1.9, 1.10, 4.8.2, 6.1, 6.2.2, 6.3, 6.6, 6.8, 8.1.2, 8.1.3, 9.1, 9.2, 9.3.2, 12.1, 12.4, 12.5 and 13.1 of the protocol

Rationale:

- Analysis of PK data up to Cohort 9 (5 mg/kg, every 2 weeks) and modeling of the 10 mg/kg every 2 weeks PK data indicates a higher steady state concentration is required to sustain the desired concentration anticipated for tumor elimination (based on preclinical data). Therefore, 2 dose escalation cohorts have been included to additional dose levels and schedules. Cohort 11 will evaluate 10 mg/kg every week and Cohort 12 will evaluate 20 mg/kg every 2 weeks.
- One expansion cohort and one optional expansion cohort have been added to fully evaluate the MTD or effective dose in multiple myeloma patients, the target population for future studies. The 2 expansion cohorts are defined as patients with (1) standard risk multiple myeloma and (2) an optional high risk multiple myeloma.
- The protocol has been updated through to reflect the study is now evaluating an every week and every 2 week schedule.

- **Change to the inclusion/Exclusion criteria**

In section(s): tabulated clinical trial summary, sections 7.2 & 7.3 of the protocol

Rationale:

- **I01.** was updated to define the multiple myeloma population that will be eligible for Cohorts 11, 12 and the standard risk and high risk expansion cohorts.
- **E09.** was clarified to exclude patients who have had an allogenic transplant within 1 year or have active graft versus host disease.

- **Addition of new rate of infusion information**

In section(s): tabulated clinical trial summary, section 8.1.2 of the protocol

Rationale:

- Information on the rate of infusion for the 20 mg/kg dose level was added.

- **Change to the assessment schedule**

In section(s): tabulated clinical trial summary, sections 1.4, 1.5, 1.6, 1.9, 1.10, 9.2, 9.3.2, 12.3, 12.4, 12.5 of the protocol

Rationale:

- A new assessment schedule for the weekly administration was introduced.
- A new assessment schedule for the every 2 week administration starting from chort 12 was introduced.
- The assessment schedule for the every 2 week administration (Cohorts 1-10) was updated to allow the C2D1 PK sample to be taken predose and to clarify the chest X-ray, spirometry and diffusion capacity assessments can be performed within one week prior to IP administration in each cycle.

In addition, other administrative corrections and clarifications were made. All changes are listed in the description of changes (next section).

7. Amended Clinical Trial protocol 07 based on Amendement 7 (13-Aug-2013)

Reason for amendment

- **Change to the Exclusion criteria**

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

Rationale:

- **E016.** were clarified/added in order to better define required contraception.

- **Change Clinical Study Director**

In section(s): Names and Addresses

Rationale:

- Change in study personnel for this study

8. Amended Clinical Trial protocol 08 based on Amendement 8 (19-Mar-2014)

Reason for amendment

- **Additional of the Phase 2 part to the protocol**

Sections that were amended or added: title page, tabulated clinical trial summary, 1.3, 1.8, 1.13, 4.7, 4.8, 5.1, 5.2, 6.2, 6.4, 6.6, 6.7, 7.1, 7.4, 7.5, 8.1, 8.3, 9.1, 9.2, 9.3, 9.4, 9.5, 9.6, 10.6, 11.4, 12.2, 12.3, 13.1, 13.2, 13.3, 13.4, 13.5, 15.5, 18, Appendix C, Appendix E, Appendix G, Appendix H, Appendix I

Rationale: the Phase 2 part of the study was added to evaluate the efficacy of SAR650984 in patients with relapsed and/or refractory multiple myeloma. The Phase 2 part is to commence after the standard risk expansion cohort has completed enrollment. The addition of the Phase 2 part will allow for a seamless enrollment of patients to the study once the standard risk expansion cohort has completed enrollment.

- Change to dose modification guidance

In section(s): 6.4

Rationale: To enable patients in the Phase 1 part of the study to be considered for intra-patient dose modifications if they have received treatment for at least 12 weeks on current dose level and they have no SAR-related AE > Grade 1.

- **Change to the frequency of Chest X-ray, Spirometry, Diffusion Capacity**

In section(s): 1.9, 1.10, 1.11, 12.1.2.1, 12.1.3.1, 12.1.4.1

Rationale: To reduce the frequency of chest X-ray, spriometry and diffusion capacity for patients, these assessments are only required during the first 2 cycles and then as clinically indicated.
In addition, other minor changes are listed in the description of changes (next section).

9. Amended Clinical Trial protocol 09 based on Amendement 9 (08-Apr-2014)

Reason for amendment

- **Change to the Exclusion criteria**

In section(s): tabulated clinical trial summary, Sections 7.3 & 7.5 of the protocol

Rationale: Phase 1 E08 and Phase 2 E17 exclusion criteria were modified to include known intolerance to histidine or known hypersensitivity to any components of the study therapy to ensure the exclusion criteria corresponds to the excipients listed in the investigator brochure.

- **Include a time window for collection of PK samples**

In Section(s): 1.8 of the protocol

Rationale: to provide a time window for collection of PK samples.

In addition, other minor changes are listed in the description of changes (next section).

10. Amended Clinical Trial protocol 10 based on Amendement 10 (22-Aug-2014)

Reason for amendment

- **Addition of Cohort 13 to the Phase 1 part of the study**

In section(s): tabulated clinical trial summary, Sections 4.8.2 and 6.1.1.2

Rationale: addition of Cohort 13 was added to enable evaluation of the 20 mg/kg every week (QW) dose level.

- **Addition of Stage 1b to the Phase 2 part of the study**

In section(s): tabulated clinical trial summary, PK/PD Flowchart 1.8, Study Flowchart 1.14, Sections 4.8.2, 4.8.4, 6.2, 6.7.5, 12.2, 13.1, 13.4, 13.5

Rationale: addition of Stage 1b was added to the Phase 2 part of the protocol following additional PK analysis of the dose escalation and expansion cohorts. The updated analysis of PK parameters of patients in the 10 mg/kg every 2 weeks (Q2W) dose escalation and standard risk expansion cohorts demonstrated a high level of variability in exposure and nonlinear clearance. These data suggest that SAR650984 exhibits nonlinear pharmacokinetics with target-mediated clearance dominating the elimination phase at low concentrations (10-20 μg/mL), which leads to low exposure and high inter-patient variability at 10 mg/kg Q2W. In order to overcome the mediated clearance disposition and reach the desired higher concentration, a higher dose and more intense 'loading' schedule may be required. Based on PK modeling and simulation a dose of 20 mg/kg QW for Cycle 1 then Q2W thereafter was selected for further evaluation in Arm 4 (Stage 1b). Enrollment into arm 4 will commence once safety has been established in Cohort 13 of the Phase 1 part of the study.

- **Addition of MRD and tumor cell CD38 mRNA to exploratory endpoints**

In section(s): tabulated clinical trial summary, Study Flowcharts 1.13, 1.14, Sections 5.3, 9.6 and 12.2

Rationale: the minimal residual disease (MRD) assessment was not included when the Phase 2 part was originally added to TED10893, however since Amendment 9 was issued the methodology to evaluate this important exploratory endpoint has been defined. It is being included to fully evaluate the depth of response in patients who achieve a complete response (CR) and determine if any minimal residual disease exists in these patients. For this assessment, a sample of the bone marrow aspirate collected for routine disease assessment will be used. In addition, an existing exploratory endpoint has been further clarified to specifically state tumor cell CD38 mRNA will be evaluated and correlated with clinical response. This protocol clarification does not result in any additional blood or bone marrow samples for the CD38 mRNA analysis.

- **Addition of optional pharmacogenetic sample**

In section(s): Study Flowcharts 1.13, 1.14, Sections 9.6 and 12.2

Rationale: an optional pharmacogenetic sample has been included in the Stage 2 part of the study. This sample will be collected on day 1 Cycle 1 only from patients who have signed the optional pharmacogenetic informed consent.

- **Change to dose modification guidance**

In section(s): Section 6.4

Rationale: to enable all patients in the Phase 2 part of the study to be considered for treatment at a higher dose level if they have disease progression while on study treatment. To be considered, patients must have been able to tolerate their original dose or schedule for at least 1 cycle and all modifications will be discussed on a case-by-case basis between Sanofi and the treating investigator.

- **Clarification of the Adverse Event of Special Interest and overdose definition**

In section(s): Sections 10.6, 10.8, and Appendix J

Rationale: the definition of AESI has been clarified and updated based on the ongoing safety review. In addition, 2 tables have been included in the Appendix to provide guidance on the symptoms and diagnosis typical of an infusion associated reaction. Clarification was also provided to the definition of an overdose to harmonize with the new AESI definition.

- **Clarification of the high risk cohort definition**

In section(s): tabulated clinical trial summary and Section 7.1

Rationale: to clarify the prior therapy inclusion requirements for the high risk cohort. These requirements are stated as general requirements for all patients enrolled into expansion cohorts (which include the high risk cohort); however, this clarifies specifically for the high risk.

- **Addition of refractory definition**

In section(s): Section 7.4 and Appendix C

Rationale: to provide a clear definition of refractory disease according to the IMWG guidance.

- **Clarification of AEs and SAEs during the follow-up period**

In section(s): tabulated clinical trial summary, Study Flowcharts 1.10, 1.11, 1.12, Sections 10.5.1 and 11.2.2

Rationale: clarification and harmonization within the protocol that all IP-related AEs and all SAEs (regardless of their causal relationship to study treatment) ongoing at the time of study treatment discontinuation need to be followed during the follow-up period until resolution or stabilization.

- **Clarification of assessments required during the follow-up period**

In section(s): footnotes of Study Flowchart 1.13, 1.14, Section 6.7.1 and 12.2

Rationale: clarification and harmonization within the protocol of those assessments that are required at 60 days and post-60 days after last IP administration.

- **Clarification on the guidelines for managing potential hypersensitivity reactions and potential tumor lysis syndrome**

In section(s): Sections 6.5 and 6.6

Rationale: to harmonize with updated AESI language the guidance on managing potential hypersensitivity. The guidance on managing potential tumor lists syndrome (TLS) has been further clarified to define laboratory TLS and clinical TLS.

- **Update to Immunoglobulins to be assessed**

In section(s): Study Flowcharts 1.13, 1.14, and Section 12.2

Rationale: IgD and IgE were added to the panel of immunoglobulins to be assessed during the Phase 2 part of the study.

- **Clarification to the PK parameters to be assessed**

In section(s): tabulated clinical trial summary and Section 9.3

Rationale: clarification of the PK software being used and parameters that are being assessed.

In addition, other minor changes are listed in the description of changes (next section).

11. Amended Clinical Trial protocol 11 based on Amendement 11 (22-Apr-2016)

Reason for amendment

- **To introduce the concentrated formulation of SAR650984/isatuximab that will be used in Phase 2 stage2**

  In sections: tabulated clinical trial summary, 4.7.1, 4.7.2, 8.1.1, 8.1.2 and 8.3.

  Changes: characteristics of the new formulation of SAR650984 are added.

  Rationale: The SAR650984 process and formulation (abbreviated C1P1F1 for cell 1, process 1, formulation 1) used in TED10893 Phase 1 and Phase 2 Stage 1 was adequate to supply these studies but larger scale production is required for TED10893 Phase 2 Stage 2 and phase 3 studies. Thus, a new drug product C1P2F2 (cell line 1, process 2, formulation 2) from the same cell line, a different process, a different manufacture site has being developed and is currently being evaluated in a Phase 1 safety study (TED14154) conducted in patients with multiple myeloma (MM). A preliminary safety analysis of the TED14154 study will be performed when all patients from dose escalation phase and dose expansion phase of the study will have completed at least one cycle of treatment.

  The Phase 2 Stage 2 part of the TED10893 study will be initiated only if the results from the preliminary analysis of safety and PK data are supporting the use of the C1P2F2.

Then all the patients enrolled in the Phase 2 Stage 2 part will be treated with C1P2F2, while ongoing patients in Phase 2 Stage 1 part will continue to receive C1P1F1. The study Investigators will be informed of the results from preliminary safety analysis of the TED14154 trial before treating any patients with C1P2F2 formulation in TED10893.

In addition, the data monitoring committee (DMC) will review preliminary safety data of the first 12 patients treated in the Phase 2 Stage 2 with a cut-off date 1 month after first dose of the last patient.

- **To provide the dose and schedule of administration of SAR650984 for the Phase 2 Stage 2 part of the study**

  In sections: 4.8.2, 4.8.4, and 6.2.

  Changes: clinical and pharmacokinetic data supporting the dose and schedule of SAR650984 administration are described.

  Rationale: As planned in the protocol, an interim analysis of efficacy, safety and pharmacokinetic (PK) data from the Phase 2 Stage 1 part of the TED10893 study was performed in September 2015 to define the dose and schedule to be used in Phase 2 Stage 2. Based on this analysis including also PK/PD modelling and simulation detailed in updated section 4.8.4, the following dose and the schedule of administration were selected for the Phase 2 Stage 2: 20 mg/kg every week for 4 infusions followed by 20 mg/kg every 2 weeks.

  In section: 6.4

  Changes: The definitions of dose delay, dose modifications and dose omission are clarified

  Rationale: dose delay, dose modifications and dose omission definitions are added for Phase 2 Stage 2 part in order to allow harmonization across project studies and to fix the rules for the data analysis.

- **To introduce the evaluation of SAR650984 alone (ISA) or in combination with dexamethasone (ISAdex) in Phase 2 Stage 2 and to clarify the route of administration of dexamethasone.**

  In sections: Tabulated summary, flow chart1.14, 4.8.4, 5, 6.2, 6.7, 8.2, 8.5, and 12.2

  Changes: In Phase 2 Stage 2, an isatuximab in combination with dexamethasone arm is added. In ISAdex arm, dexamethasone being part of isatuximab premedication and of the combination regimen, will be given IV or PO at the discretion of the investigator, on days 1, 8, 15 and 22 of each cycle. Doses will be adapted according patient age. Dose modifications are planned in case of adverse events related to dexamethasone. In ISA arm, steroids premedication will be given IV or PO at the discretion of the investigator and will still follow the rules as indicated in the protocol.

Rationale: dexamethasone has been used as monotherapy at a high dose, and more frequently at a lower dose in combination with other therapeutic agents for multiple myeloma treatment, including cytotoxic agents (cyclophosphamide, melphalan), proteasome inhibitor (Velcade®/bortezomib, carfilzomib, ixazomib), IMiD (thalidomide, lenalidomide, pomalidomide), HDAC inhibitor (panobinostat) and monoclonal antibody (elotuzumab). It has been demonstrated that the addition of dexamethasone onto a variety of regimens significantly increase the clinical activity, with adding limited toxicities. For example, in a heavily pre-treated RRMM population, pomalidomide alone achieved an over response rate of 7.4%, and adding dexamethasone increased overall response rate to 29.2%. As another example, for patients with relapsed multiple myeloma who failed to responding to Velcade® monotherapy (defined as progression after 2 cycles of treatment or stable disease after 4 cycles of treatment), adding dexamethasone onto Velcade® achieved 18% of response rate (minimal response or better). Therefore, a second arm is added in Stage 2 to evaluate the activity of isatuximab in combination with dexamethasone. Patients in Stage 2 will be randomized to either isatuximab or to isatuximab + dexamethasone arm using a 2:1 randomization ratio.

- **To update the inclusion/exclusion criteria for the Phase 2 Stage 2 part of the study**

  In section(s): tabulated clinical trial summary and section 7.4, 7.5.

  Changes: Clarification of inclusion criteria for Phase 2 Stage 2. Criteria for progressive disease and refractory disease are also detailed.

  Rationale: Inclusion criteria are modified to include clarification on patients status at study entry.

  In section(s): tabulated clinical trial summary and in section 7.5.

  Changes: a few exclusion criteria are adjusted for Phase 2 Stage 2.

  Rationale: For sake of clarity and to update few criteria according to the most recent reference

- **To add a section on Contraceptive measures and to add additional serum pregnancy tests during the study period**

  In section: flow chart 1.14, and in section 12.2

  Changes: serum pregnancy tests are added at the beginning of each cycle

  Rationale: to comply with European Guidance

  In section: 8.11

  Changes: Contraceptive measures is added

Rationale: to comply with European Guidance, a new section on “contraceptive measures” has been added.

- **To update the assessment of the Investigational Product**

  In sections: 6.5 and 6.6

  Changes: Table 3 and table 5 are added with updated general guidelines to be implemented for Infusion Associated Reactions and Tumor Lysis Syndrome, respectively.

  Rationale: to harmonize these general guidelines across the ongoing studies

  In section: 9.3

  Changes: Pharmacokinetic evaluation in Phase 2 Stage 2 part of the study is updated.

  Rationale: Sparse sampling has been implemented in Phase 2 to perform population PK analysis with pool data from Phase 1 and 2.

  In sections: Tabulated summary, 1.14 (Study Flowchart), footnotes 33-44, 9.6 and 12.2

  Changes: Phase 2 exploratory biomarker studies is changed for Phase 2 Stage 2 of the study

  Rationale: Based on recent publications, poor prognosis has been associated with several chromosomal abnormalities detected by FISH method. Additional tests will be performed to detect these abnormalities in Stage 2.

  According to clinical data (ASH 2015), increased adaptive immune responses contribute to Daratumumab’s efficacy in MM patients. Analysis of adaptive responses including the quantification of the T-cell receptor genetic variability (TCR) will be performed in blood at C1D1, C3D1 and C5D1 and correlated with clinical response in Stage 2.

- **To update the disease assessment procedures and IMWG criteria**

  In sections: 1.14 (Study Flowchart) and footnotes 26, 34, 37, 40 and 12.2

  Changes: the disease assessment procedures are detailed for Phase 2 Stage 2

  Rationale: to ensure an accurate and homogeneous evaluation of the efficacy of isatuximab in the selected population

- **To change the statistical part for Phase 2 Stage 2 part of the study**

  In sections: tabulated clinical trial summary and 1.3, 7.1, 13.1

  Changes: The sample size calculation has been revised.

Rationale: Assumptions for sample size calculations are adjusted to account for changes in inclusion criteria for Stage 2 and Stage 1 interim analysis results. Sample size calculation for the isatuximab + dexamethasone arm is also added.

- **To change appendices B and E and to add Appendix K**

  Changes: The modification of Diet in Renal Disease (MDRD) equation for creatinine clearance calculation is added for Phase 2 Stage 2 part for consistency across the studies. The IMWG criteria table is updated.

  The appendix K is added to provide the Investigators with the background information and guidance regarding anti-CD38 interference with serologic testing.

  Rationale: Appendices **B and E** are updated to keep consistency across the study protocol for Phase 2 Stage 2 part including the changes described above.

  CD38 monoclonal antibodies can result in interference with blood bank serologic tests and thereby cause delays in issuing Red Blood Cell (RBC) units to patients receiving these agents. The AABB Clinical Transfusion Medicine Committee has developed a bulletin (# 16-02) to provide background information and guidance to members regarding anti-CD38 interference with serologic testing. This bulletin is attached in the **Appendix K**. In addition, the patients treated in the study will receive a blood type card indicating the treatment with a CD38 agent and the study site will notify its blood bank that the patient is receiving an anti-CD38 treatment.

- **Finally, other additional minor changes and edits will be included in this amendment for the sake of clarity**

12. Amended Clinical Trial protocol 12 based on Amendement 12 (12-Jul-2017)

Reason for amendment

- **To add a potential interim analysis for Phase 2 Stage 2**
- In section(s): clinical trial summary and section 13.5 of the protocol

Rationale: 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.

- **To change the exclusion criteria #12 for the Phase 2 Stage 2**

In section(s): tabulated Clinical Trial Summary, section 7.5 of the protocol

Rationale: preliminary PK analyses shown that creatinine clearance is not a significant covariate on linear Clearance and volume of distribution from central compartment. To allow more heterogeneous population included in the study to better reflect multiple myeloma patient population, creatinine clearance exclusion criteria lowered from eGFR <30 mL/min/1.73 m^2 to <15 mL/min/1.73 m^2

- **To add Phase 2 exploratory study objectives: adaptive immune response**
- In section(s): Clinical Trial Summary and sections 1.15, 5.3, 9.6, 12.2.3, 12.2.4 and 12.2.5 of the protocol
- Rationale: the additional blood samples to be collected at baseline and post treatment for humoral and cellular response to further understand of the potential mechanism of action.
- **To remove exploratory blood sample: soluble CD38 and optional pharmacogenetic in Phase 2 Stage 2**
- In section(s): Clinical Trial Summary and sections 1.14 and 12.2.3 of the protocol

Rationale: These two analyses are to be removed from the protocol due to restricted total blood collection volume after inclusion of the new humoral and cellular immune response tests, which are deemed more important. PGx samples were for banking purpose only.

- **To remove the bone marrow sample for CD38 receptor density (RD) and receptor occupancy (RO) in Phase 2 Stage 2:**

In section(s): Clinical trial summary (endpoints and other evaluations), sections 1.8, 9.5, 1.15 and 12.2.1 of the protocol.

Rationale: The CD38 RD data have been collected in the TED10893 Phase 1, Phase 2 Stage 1. Although there was a trend of higher response rate in patients with higher CD38 RD, the correlation was not significant.

- **To remove central laboratory tests for blood chemistry, hematology, coagulation and urinalysis in Phase 2 Stage 2**
- In section(s): section 1.14 of the protocol

Rationale: To reduce the blood volume to be drawn for each assessment, and the operation procedure, safety laboratory assessment include for hematology, biochemistry and coagulation will be done locally at investigator's site only for Phase 2 Stage 2.

- **Removal of specific safety labs including cytokines, serum tryptase and markers of complement activation when a Grade 2 or higher Infusion Associated Reaction occurs in Phase 2 Stage 2**
- In section(s): Clinical Trial Summary and section 1.14 of the protocol
- Rational: preliminary analysis in Phase 1 and Phase 2 Stage 1 did not show a clear evidence of cytokine linked with IAR.
- **To remove the ePRO in Phase 2 Stage 2 secondary endpoints**
- In section(s): Clinical Trial summary, sections 1.14, 5.2, 9.2.3.2, 12.2.3, 12.2.4, 12.2.5 and 13.4.5 of the protocol
- Rationale: Without a comparator arm, it is not expected to have a meaningful data concluded from patient reported outcome; therefore ePRO is to be removed in Phase 2

Stage 2 to avoid extra effort required for this assessment from sponsor, investigator and patient.

- **To change Dexamethasone from NIMP to IMP**
- In section(s): Clinical Trial summary, section 8.0 of the protocol
- Rationale: requested by Austrian regulatory.
- **To add complete blood type, complete blood phenotyping and antibody screening tests at baseline and antibody test after study treatment in Phase 2 Stage 2**

In section(s): sections 1.15, 12.2.1 and 12.2.3 of the protocol

Rationale: it has been reported, treatment with anti-CD38 mAb can have potential interference with various blood bank serologic tests. Therefore, tests will be done before and after treatment with isatuximab to assess the potential interference.

- **To add the possibility to switch the drug product for patients enrolled in Phase 2 Stage 1 that are continued isatuximab treatment**

In section(s): tabulated Clinical Trial Summary (Investigational product(s)), sections 4.7.2 and 8.1.1.2 of the protocol

Rationale: The drug product used in Phase 2 Stage 1 was C1P1F1. The new drug product C1P2F2 has been studied in the TED14154 and the clinical safety and activity are similar to what was observed with C1P1F1. C1P2F2 is now used in ongoing and all new studies. Patients enrolled in TED10893 Phase 2 Stage 1 and are still receiving study treatment may be switched from C1P1F1 to C1P2F2 due to the drug availability.

- **To clarify the data collection for patients that are still on treatment after the final analysis cut-off date**

In section(s): tabulated Clinical Trial Summary, section 12.3 of the protocol

Rationale: Data to be collected for patients continuing study treatment after the cut-off date for final analysis required clarifications.

- **To update PK and ADA sampling schedule**

In section(s): tabulated Clinical Trial Summary, section 1.8, 1.15, 12.2.3, 12.2.4, 12.2.5, 12.2.6 and 12.2.7 of the protocol

Rationale: Based the PK and ADA profile, PK and ADA Sampling beyond Cycle 10 will not provide additional information.

- **Update the definition of Infusion Associated Reactions as Adverse Event of Special Interest**
- In section(s): sections 6.5 and 10.6 of the protocol

- Rational: With the information that has been learned from Phase 1 and Phase 2 Stage 1, Grade 1 and Grade 2 Infusion Associated Reactions are no longer needed for an expedited report, to reduce the work load of Investigator's site and sponsor.
- **To clarify the supply of Dexamethasone**
- In section: 8.1.6.1
- Rationale: Clarification on the supply of Dexamethasone when commercial supplies are not available Dexamethasone will be re-labeled by Sponsor before supplies are provided to the study sites.
- **To add Flowchart 1.15**
- In section(s): Flowchart 1.15
- Rationale: Flowchart 1.15 will be devoted to Phase 2 Stage 2 for a better clarity and easier to follow.
- **Updating Pharmacokinetic parameters in Phase 2 secondary endpoints**
- In sections: Clinical trial summary
- Rationale: To fit the wording to a modelling approach, that will be on isatuximab concentrations obtained during Phase 2 Stage 2, instead of a Non-Compartmental Analysis, to provide individual PK parameters.
- **Clarify the end time of 24 hour urine**
- In sections: 1.14, 1.15, 12.2.1, 12.2.3, 12.2.4 and 12.2.5
- Rationale: To provide clarity to the sites when the completion of the 24 hour urine for disease assessment must be completed.
- **Clarify dose delays/modifications**
- In section(s): 6.4
- Rational: It was not clear about dose delays/modifications window and allowances.
- **To clarify when premedication can be reconsidered**
- In section: 8.2.2
- Rational: To provide clarity to the Investigators when to reconsider the need for pre-medications.
- **Clarify the definition of study treatment exposure in statistical analysis**
- In section: 13.4.2
- Rational: To provide clarity of the assessment in the duration of study treatment exposure.
- **To clarify analysis of anti-drug antibody**
- In section(s): 13.4.8
- Rational: To provide specific detail in the ADA analysis

- **To delete Appendix J: Definitions of Infusion Associated Reactions (IAR)**
- In section(s): Appendix
- Rationale most up-to-date information has been provided in the last version (2017 edition 8) and will be updated with each version of IB. To avoid the need of revision in the study protocol, the definition of IAR will be cross-referenced to the most recent edition of IB.
- **To add Appendix K**
- In section(s): Appendix K
- Rationale: provide instruction for the sample handling/process of exploratory biomarkers.
- **Editorial corrections**
- In sections(s):
- Rationale: For better clarity and correct some editorial errors.

13. Amended protocol [13] (11 June 2019)

- This amended protocol (amendment 13) is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because it significantly impacts the safety or physical/mental integrity of participants.

Overall Rationale for the Amendment

- Based on updated pharmacokinetic characterization of isatuximab, the plasma half-life has been re-estimated to 28 days. As duration of contraceptive measures is required to last for 5 half-lives, a revised duration of contraceptive measures and pregnancy testing of 5 months after the last isatuximab dose is required.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Tabulated clinical trial summary, Section 7.3 Phase 1 Exclusion criteria and Section 7.5 Phase 2 (Stage 1 AND Stage 2) Exclusion criteria	E16 (Phase 1) and E24 (Phase 2) amended to indicate that female patients of child-bearing potential and male patients with female partners of child-bearing potential will be required to use contraception for 5 months after discontinuation of study treatment, and that female patients of child-bearing potential in Phase 2 will require monthly pregnancy tests for 5 months after discontinuation of study treatment.	Change from 12 weeks due to re-estimation of isatuximab plasma half-life
Tabulated clinical trial summary and Section 6.8.1 Duration of study participation for each patient	Added that female patients of childbearing potential will have the serum pregnancy test every month for 5 months after the last administration of isatuximab.	Due to re-estimation of isatuximab plasma half-life
Section 4.8.2 Design rationale	Re-estimation of isatuximab half-life of 28 days is included.	Due to re-estimation of isatuximab plasma half-life

Section # and Name	Description of Change	Brief Rationale
Section 8.11 Contraceptive measures	Amended to indicate that that female patients of child-bearing potential and male patients with female partners of child-bearing potential will be required to use contraception for 5 months after discontinuation of study treatment.	Change from 12 weeks due to re-estimation of isatuximab plasma half-life
Study flowchart for Phase 2, Stage 2, including footnote 15; Section 12.2.6 Follow-up period at 60 days (±5 days) after last study treatment administration; Section 12.2.7 Post 60 day follow-up period; and Section 12.3 Data collection after final analysis cutoff date	Amended to indicate that females of child-bearing potential will be required to be tested for pregnancy every month for 5 months after discontinuation of study treatment.	Due to re-estimation of isatuximab plasma half-life