Sponsor: Sanofi **Drug substance(s):** SAR650984 (Anti-CD38 mAb)	**Study Identifiers:** IND: 103217; NCT01749969; U1111-1119-3107 **Study code:** TCD11863

Title of the study:

A Phase 1b study of SAR650984 (Anti-CD38 mAb) in combination with lenalidomide and dexamethasone for the treatment of relapsed or refractory multiple myeloma

Study center(s):

5 study centers in the United States

Study period:

Date first patient enrolled: 06 February 2013

Date last study participant completed: 20 June 2023

Study Status: Completed

Phase of development: Phase 1

Objectives:

Primary:

- To determine the maximum tolerated dose (MTD) of isatuximab in combination with lenalidomide and dexamethasone (LD) in patients with relapsed or refractory multiple myeloma (MM) for each schedule of administration.
- For the Expansion Phase, to further evaluate preliminary evidence of anti-tumor activity (overall response rate [ORR]) of isatuximab in combination with LD using International Myeloma Working Group (IMWG) criteria.

Secondary:

- To evaluate the safety, including immunogenicity of isatuximab in combination with LD in relapsed or refractory MM. The severity, frequency and incidence of all adverse events (AEs), laboratory abnormalities, and vital signs abnormalities were assessed.
- To evaluate the pharmacokinetics (PK) of isatuximab when administered in combination with LD and the PK of lenalidomide in combination with isatuximab and dexamethasone.
- To assess the relationship between clinical (AE and/or tumor response) effects and pharmacologic parameters (PK/pharmacodynamic (PDy), and/or biologic (correlative laboratory) results.
- To assess the anti-MM activity using IMWG defined response criteria (ORR) of isatuximab plus LD.
- To describe the duration of progression-free survival (PFS) in patients treated with this combination.

Methodology:

This was a Phase 1b, open-label dose-escalation (DE) study to evaluate the MTD of 2 schedules of administration of isatuximab in combination with LD in patients with relapsed or refractory MM who had received at least two prior therapeutic treatments or regimens. Once the MTD was established or the highest planned dose was reached, an expansion cohort was enrolled to further establish safety and to evaluate the antitumor activity of isatuximab in combination with LD.

Dose escalation phase:

The following dose levels were sequentially evaluated with isatuximab administered Q2W:

- Cohort 1: 3 mg/kg (Q2W)
- Cohort 2: 5 mg/kg (Q2W)
- Cohort 3: 10 mg/kg (Q2W)

The following dose levels were sequentially evaluated for isatuximab administered every week during Cycle 1 and then Q2W in subsequent cycles:

- Cohort 4: 10 mg/kg (QW/Q2W)
- Cohort 5: 20mg/kg (QW/Q2W)

All cohorts included at least 3 patients. In the event that a confirmed DLT is reported during an individual cohort, up to 6 evaluable patients were assessed at this dose level. If <2 out of 6 patients experience a treatment related DLT at this dose level, the DE will proceed with at least 3 patients per dose level. If ≥2 out of 6 patients experience a treatment related DLT, the maximum administered dose is reached and DE was stopped. The MTD was defined as the highest dose level at which <2 out of 6 evaluable patients experience a treatment-related DLT.

There were regular meetings with the Study Committee (Sponsor and Investigator representatives) to examine potential DLTs and laboratory abnormalities on a regular basis.

Expansion phase

Once the MTD was established or the highest planned dose was reached, an Expansion Phase enrolled patients for additional safety and efficacy data. For the Q2W schedule, 18 to 21 additional patients were enrolled for a total of 24 patients treated at this dose level. For the QW/Q2W schedule, approximately 6 to 12 patients were to be treated in the dose escalation phase (approximately 6 to 9 patients in each expansion cohort) with the goal to have a total of 12 patients treated.

Study committee

Potential DLTs and laboratory abnormalities were examined at meetings with the Study Committee on a regular basis to decide about DE or expansion. Although the DE decision process is guided by the safety evaluation during C1 of treatment, AEs observed cumulatively in subsequent administrations were also considered upon agreement by the Study Committee. The Study Committee could also have decided on the evaluation and expansion of an intermediate dose level not higher than the maximum administered dose/MTD as well as the number of patients (6 to 9) enrolled at a dose level based on the safety data available from the dose levels already explored.

Duration of therapy

Patients were allowed to continue combination therapy until disease progression, intolerable toxicity, or Investigator, Sponsor, or patient decision to discontinue therapy. All patients were followed through end of treatment. The QW/Q2W schedule patients continued therapy until disease progression, intolerable toxicity, or Investigator, Sponsor, or patient decision to discontinue therapy.

Patients were followed until progression and if a patient discontinued for reasons other than progression, the patient was followed monthly until progression, initiation of subsequent therapy, or until the study cutoff date, whichever came first.

Number of patients:	Planned: 60 Enrolled: 57 Treated: 57
Number of patients evaluated:	
	Efficacy/pharmacodynamic: 52 Safety: 57 Pharmacokinetics: 53

Diagnosis and criteria for inclusion:

Male or female, 18 years or older, with diagnosis of MM and documentation of at least 2 prior therapies (induction therapy, autologous stem cell transplant, consolidation, and maintenance therapy is considered one prior therapy) one of which had to include an immunomodulatory drug (IMiD); confirmed evidence of disease progression following immediately prior MM therapy or refractory to the immediately prior therapy

Study treatments

Investigational medicinal product(s)

Isatuximab (SAR650984)

Formulation: 100 mg of isatuximab in a glass vial diluted to 5 mg/mL (100 mg/20 mL) with water for injection, sucrose, histidine (as base and hydrochloride salt), and polysorbate 80, pH 6.2 to 6.8.

Route(s) of administration; Intravenous (IV)

Dose regimen: 3, 5 and 10 mg/kg every 2 weeks (Q2W) and 10 and 20 mg/kg once weekly (QW) for Cycle 1 followed by Q2W

Lenalidomide

Formulation: Tablet

Route of administration: Orally

Dose regimen: 25 mg QD on Days 1, 8, 15, 22 of each 28 day cycle; dose reductions sequentially to 15, 10 or 5 mg were permitted due to toxicity. The starting dose was adjusted based on CrCl as follows: If CrCl was >60 mL/min, then the patient started at 25 mg daily. If CrCl was between 30 and 60 mL/min, then the patient started at 10 mg daily.

Dexamethasone

Formulation: IV and tablet

Routes of administration: IV and orally

Dose regimen: For the Q2W schedule, dexamethasone 40 mg IV or orally before isatuximab infusion (Day 1 and 15) and orally on Days 8 and 22; for the QW/Q2W schedule, dexamethasone 40 mg IV or orally before isatuximab infusion on Days 1, 8, 15, and 22 of Cycle 1 and as per the Q2W schedule thereafter. Sequential dose reductions to 20 or 10 mg were permitted due to toxicity. Dose was reduced to 20 mg if lenalidomide was discontinued.

Criteria for evaluation:

Safety endpoints: The safety variables included DLTs, AEs, clinical laboratory parameters, and clinical examinations including vital signs, electrocardiograms (ECG), and Karnofsky Performance Status (PS). The National Cancer Institute Common Terminology Criteria for Adverse Event (NCI-CTCAE), version 4.03 was used to grade the severity of AEs and laboratory results.

Efficacy/pharmacodynamic endpoints: Efficacy parameters included ORR (including confirmed best overall response [BOR] of stringent complete response [sCR], complete response [CR], very good partial response [VGPR] and partial response [PR]); duration of response (DOR), defined as the time from first response that was subsequently confirmed to the first documented tumor progression or death; PFS, defined as the time interval from the date of first study treatment administration to the date of progressive disease (PD), date of death due to any cause, or symptomatic deterioration, whichever came first.

Pharmacokinetic/Pharmacodynamics sampling times and bioanalytical methods:

Cohorts 1 to 3

Blood samples for analyses PK of isatuximab and pharmacodynamics (PDy) were collected Cycle 1 Day 1 predose, 2h, and end of infusion (EOI) and postdose at 3h, 5h, 24h (Day 2), 48h (Day 3), 72h (Day 4), and 168h (Day 8); Cycle 1 Day 15 predose and EOI; Cycle 2 Day 1 predose and EOI; Cycle 2 Day 15 predose; subsequent cycles on Day 1 predose and EOI; and 30 and 60 days after last administration.

Blood samples for PK analyses of lenalidomide a were collected Cycle 1 on Day 1 and Day 15 predose and 1h, 2h, 4h, 7h, and 24h (Day 2) postdose.

Cohorts 4 and 5

Blood samples or analyses PK of isatuximab and PDy were collected Cycle 1 Day 1 predose and EOI, and 24h (Day 2), 48h (Day 3), 72h (Day 4), Day 8 predose, Day 15 predose, and Day 22 predose; Cycle 2 Day 1 and Day 15 predose; Cycle 3 Day 1 predose, EOI, and 4h post EOI at 8h, 24h (Day 2), 48h (Day 3), and 72h (Day 4); subsequent cycles on Day 1 predose.

Blood samples for PK analyses of lenalidomide were collected Cycle 1 Day 1 and Cycle 3 Day 1 predose and 1h, 2h, 4h, 7h, and 24h (Day 2) postdose.

Serum/plasma markers included: cytokines for Q2W schedule only; CD38 RD and RO for Q2W schedule and RD only for QW/Q2W schedule; killer cell Ig-like receptors (KIR) genotyping; human leukocyte antigen (HLA) class genotyping; FCRgRIIIa polymorphisms; NK cell phenotype; NK cell function; macrophage phenotype; macrophage function; and tumor cell cytogenetics.

Isatuximab and lenalidomide plasma concentrations were analyzed using noncompartmental methods with the PKDMS software (Pharsight) or SAS program. Pharmacokinetic variables included maximum plasma concentration observed (C_{max}); plasma concentration observed just before treatment administration during repeated dosing (C_{trough}); time to reach C_{max}, (t_{max}); last observed concentration above the lower limit of quantification (C_{last}), area under the plasma concentration versus time curve calculated using the trapezoidal method from time 0 to the real time t_{last} (AUC_{last}); area under the plasma concentration versus time curve calculated using the trapezoidal method over the dosing interval (7 or 14 days for isatuximab and 24 h for lenalidomide) (AUC_{tau}); apparent total body clearance (CL/F); and apparent volume of distribution at steady state (V_{ss}/F).

Immunogenicity

Blood samples for anti-drug (ADA) analysis (ie, analysis of anti-isatuximab antibody) were collected Cycle 1 predose and Day 1 and Day 15 postdose (Cohorts 1-3 also had a sample collected Cycle 1 Day 3); Cycle 2 Day 1 and Day 15; at subsequent cycles on Day 1 predose; and 30 and 60 days after the last dose.

Statistical methods:

Analysis populations included the following:

- The All-treated (AT)/Safety population included all patients who gave their informed consent and received at least 1 dose (even if incomplete) of isatuximab. This was the primary population for the analyses of efficacy and safety parameters. All analyses using this population were based on the intended dose to be given at Cycle 1 Day 1.
- DLT-evaluable population: The DLT-evaluable population included patients from the DE phase of the trial who received the planned doses of isatuximab and at least 75% of lenalidomide doses during Cycle 1 and who completed the DLT observation period of 28 days after the first IMP administration, unless due to a DLT. Dose-limiting toxicity was validated by the Study Committee. Patients not evaluable for DLT were replaced.
- Pharmacokinetic-evaluable population: The PK-evaluable population included all treated patients for whom any PK parameter was available.
- Efficacy-evaluable population: The efficacy-evaluable population included all treated patients except those who received only 1 cycle of treatment and discontinued treatment due to an AE or other reason (excluding PD). Sensitivity efficacy analyses were performed on the efficacy evaluable population.
- Immunogenicity-evaluable population: Patients with at least one evaluable ADA result (i.e. non-missing result) during the ADA on-study observation period were considered evaluable for ADA.

Demographics and baseline characteristics were summarized for the AT population using descriptive statistics.

Safety

Patients with DLTs were presented using the DLT evaluable population. For treatment-emergent AEs, the incidence tables were presented for each dose level and overall, including the number (n) and percentage (%) of patients who experienced an AE, by severity, seriousness and relationship to study treatment. Pretreatment and post-treatment AEs were presented by SOC, PT and severity (Grade ≥3). Adverse events of special interest (AESIs) consisted of infusion-associated reactions (IARs) and IAR symptoms, DLTs, second primary malignancies, symptomatic overdoses, or pregnancies. The number (%) of patients with IARs was summarized by dose level and by initial infusion rate at cycle 1 and grade (all grades and Grade ≥3).

The numbers of patients with abnormal laboratory tests at baseline and during treatment were presented by dose level and grade. The frequency of patients with each grade of laboratory test during the on-treatment period was summarized. For patients with multiple occurrences of the same laboratory variable during the on treatment period, the maximum (worst) grade per patient was used.

For Vital signs, the number of patients with a potentially clinically significant abnormality (PCSA) during the on-treatment period was summarized by dose levels. ECG test results were presented in a listing. Karnofsky PS was mapped to ECOG PS, and shift tables of baseline ECOG PS versus best/worst ECOG PS on treatment values were provided.

Efficacy

Efficacy endpoints were analyzed for the AT population. Sensitivity analyses were provided on the efficacy evaluable population including ORR and DOR.

BOR, ORR, clinical benefit rate (CBR), duration of response (DOR), time to response (TTR) and follow-up duration (FUD) were summarized with descriptive statistics. ORR was also summarized for patients with high-risk cytogenetic status.

PFS was analyzed using the Kaplan-Meier method. The Kaplan-Meier estimates of the 25th, 50th and 75th percentiles and the 95% confidence interval of the median were computed and Kaplan-Meier curves were also plotted.

Pharmacodynamic Analyses

CD38 RD and RO were summarized with descriptive statistics. In addition, CD38 RD and RO were summarized by clinical response (responders/non-responders).

Pharmacokinetic Analyses

All individual concentrations and all pharmacokinetic parameters of isatuximab and lenalidomide were tabulated using descriptive statistics: arithmetic and geometric mean, median, standard deviation (SD), standard error of the mean, coefficient of variation, minimum and maximum for each dose level.

Maximum drug concentration (C_{max}) ratios were calculated between fifth and first administration of isatuximab for the QW/Q2W schedule. Minimum drug concentration (C_{trough}) ratios were calculated between 4th and 1st administration of isatuximab for QW/Q2W schedule.

Immunogenicity

The number (%) of patients who were ADA-positive at baseline, ADA-negative at baseline, had on-study ADA including treatment-induced ADA (persistent ADA, transient ADA, and indeterminate ADA) and treatment boosted ADA and ADA prevalence and incidence were summarized.

Summary Results:

Population characteristics:

A total of 57 patients with a median age of 61 years (42 to 76 years) were enrolled. Most patients (82.5%) had a Karnofsky PS ≥80%. At study entry, ISS was stage I in 42.1% of patients, stage II in 38.6% of patients and stage III in 19.3% of patients. The median number of prior lines was 5 (1 to 12 lines) with 15 (26.3%) patients having received 8 or more prior lines of treatment. Fifty-five (96.5%) patients were previously exposed to IMiDs, including 54 (94.7%) patients with prior lenalidomide treatment. The time from diagnosis was ≥5 years in 58.3% of the patients in the 10mg/kg QW/Q2W.

The 57 patients initiated 1014 cycles, defined as 4 week periods, and received 2010 isatuximab infusions. Overall, the median number of cycles was 9 (1 to 108 cycles) with 18 (31.6%) patients having received at least 21 cycles. Median RDI of isatuximab was above 90% for all dose levels.

Safety results:

- One DLT (pneumonia) was reported at dose level 20 mg/kg QW/Q2W out of the 21 DLT evaluable patients treated in the DE phase. The MTD was not reached therefore, 3 isatuximab doses and schedules were explored in expansion part (10 mg Q2W, 10 mg QW/Q2W, 20 mg QW/Q2W). No evidence of a difference in safety profile between dose levels was observed as summarized below, although the results should be taken with caution due to the small sample sizes in each dose level.
- At least one TEAE occurred in all the patients, regardless of relationship with study treatment. The most frequently reported non-hematological TEAEs (in >25% of patients) were infusion related reaction (32 patients, 56.1%), diarrhea (32 patients, 56.1%), fatigue (29 patients, 50.9%), upper respiratory tract infection (23 patients, 40.4%), nausea (20 patients, 35.1%), insomnia (20 patients, 35.1%), pyrexia (19 patients. 33.3%) dyspnea (16 patients, 28.1%), and cough (16 patients, 28.1% each). The incidence of TEAEs did not appear to be dose-dependent.
- The most frequently reported non-hematological Grade ≥3 TEAEs (in >5% of patients) regardless of relationship with study treatment were infusion related reaction (5 patients, 8.8%), pneumonia (10 patients, 17.5%), fatigue (4 patients, 7.0%), and hypokalemia, lung infection, anaphylactic reaction, disease progression, and febrile neutropenia (3 patients, 5.3% each). No apparent dose relationship was observed in the incidence of Grade ≥3 TEAEs.
- Five patients died within 30 days of their last dose, 2 because of AEs not considered to be related to study treatment (procedural hemorrhage, and bacterial sepsis), and 3 because of progressive disease. Four patients (7%) died more than 30 days after their last dose due to progressive disease.

- Serious TEAEs were reported in 32 (56.1%) patients. The most frequently reported SAEs were pneumonia (10 patients, 17.5%; 1 patient discontinued study treatment, and the other 5 patients had dose delays and/or reductions), followed byanaphylactic reaction, disease progression, febrile neutropenia and infusion related reaction (3 patients, 5.3% each). No dose relationship was observed in the incidence of serious TEAEs. Serious lower respiratory tract and pneumonia occurred in 9 patients (pneumonia in 8, and bronchitis in 1). One of these 9 patients (with Grade 3 pneumonia) discontinued treatment, 4 patients had no change in treatment, and the other patients had dose delays and/or reductions; all the patients recovered.
- Infusion reactions
  - IARs occurred in 32 (56.1%) patients (Grade 3 in 5 patients or 8.8%) in the overall safety population. There were no Grade 4 IARs.
  - The overall incidence of IARs was higher at the 20 mg/kg QW/Q2W dose level (11 patients, 78.6%) compared with the 10 mg/kg Q2W or QW/Q2W dose levels (13 patients, 54.2% and 7 patients, 58.3%, respectively). Grade 3 IARs occurred also more frequently in the 20 mg/kg QW/Q2W group (3 patients, 21.4%) compared with the incidence in the 10 mg/kg Q2W or QW/Q2W groups (1 patient, 4.2% and 0, respectively). Among patients at dose levels above 10 mg/kg, the incidence of IARs was lower (14/29, 48.3%) among the patients who were administered isatuximab at an initial infusion rate of 175 mg/h than among patients with an initial infusion rate of 250 mg/h (15/18, 83.3%); 2 patients experienced Grade 3 IAR among the 38 patients (5.3%) with the initial infusion rate of 175 mg/h, and 3 patients experienced Grade 3 among 18 patients (16.7%) with the initial infusion rate of 250 mg/h, suggesting that the faster initial infusion rate was associated with more frequent and more severe IARs.
  - The most frequent IAR manifestations were dyspnea, nausea, chest discomfort, vomiting, hypertension, flushing, and nasal congestion. The IAR manifestations included Grade 3 anaphylactic reaction in 3 patients: 2 patients had received isatuximab with an initial infusion rate of 250 mg/h. All of the anaphylactic reactions occurred on Day 1 of Cycle 1, resolved the same day, and led to study treatment discontinuation.
- Ten (17.5%) patients discontinued study treatment because of TEAEs; 7 of these TEAEs were related to study treatment, most frequently consisting of IARs (5 patients, 8.8%).
- Respiratory TEAEs occurred in 42 (73.7%) patients, with greater incidence in the 20 mg/kg QW/Q2W group (13 patients, 92.9%) than in the 10 mg/kg Q2W and 10 mg/kg QW/Q2W groups (17 patients, 70.8% and 6 patients, 50.0%, respectively). The incidence of Grade ≥3 TEAEs followed a similar trend. Among the respiratory TEAEs, dyspnea was the only TEAEs with severity of Grade ≥3 occurring in more than 1 patient (each in 3.5% of the patients). When analyzed without IAR symptoms and taking into account the small sample size at some dose levels, there was no evidence of substantially different incidences across dose levels or based on initial infusion rate.
- Although Grade 3 and 4 neutropenia occurred as a laboratory abnormality in 33 of 55 (60.0%) of patients, it was associated with neutropenic complications in 4 patients. Grade 3 or 4 lymphopenia and thrombocytopenia also occurred in 32 of 55 (58.2%) and 21 of 55 (38.2%) patients, respectively, but these abnormal values did not appear to be associated with clinical complications. There were no clinically important changes in hepatic and renal laboratory parameters during treatment.
- Four out of 55 patients (7.3%) had treatment-induced ADA, but no persistent ADA. Therefore, both the prevalence and incidence of ADA were 7.3%.
- No clear association can be drawn between IAR occurrence and change in cytokine levels for the 5 patients who presented Grade 3 IARs..

In conclusion, the MTD was not reached and no evidence of a difference in safety profile was observed between dose levels. Because of the limited sample size and differences in infusion rate across each dose levels, any conclusions should be interpreted with caution.

Efficacy/pharmacodynamic results:

- In the analysis for the all-treated population, the ORR was 50.9% (29 patients), including 2 (3.5%) patients with sCR and 17 (29.8%) patients with VGPR. Thirty-seven (64.9%) patients achieved clinical benefit.

- In the efficacy evaluable population which excludes 5 patients who discontinued study treatment due to AE before completion of Cycle 1, the ORR was 55.8% (29 patients). The rates of response and clinical benefit were generally similar across the 3 groups that enrolled more than 10 patients.
- The median duration of response was 10.94 months (range: 1.4 to 31.4) across all groups.
- The response rate was 46% in 50 patients refractory to IMiD, 47.6% in 42 patients refractory to lenalidomide, and 42.9% in 49 patients receiving ≥3 lines of patients, and 26.7% in 15 high risk cytogenetic patients.
- At the time of analysis, 37 (64.9%) patients had a PFS event and median PFS was 8.5 months (95% CI: 4.73 to 16.59).
- Seventeen (29.8%) patients received further anticancer treatment, with similar percentages of patients receiving post-study treatment across groups.
- Thirty-two of 52 (61.5%) patients evaluated for best percent change in paraprotein showed a >50% reduction and 22 patients showed a >90% reduction.
- The mean value of CD38 RD was 146 581 with a range of 58 555 to 442 110 RD/cell. The mean CD38 RD was similar in responders versus non responder patients (mean value of 164 951 versus 132 451, respectively).In the analysis of F158V dimorphism of FcgRIIIA, the overall response rate was higher in patients with V/V genotype (71.4%; n=7) compared to F/F and F/V phenotypes (53.3%; n=15 and 53.6%; n=28, respectively).
- Patients (n=21) with KIR3DL1+ and HLA-B Bw4-80Ile+ displayed slightly higher overall response rate of 57.1% while patients (n=36) KIR3DL1- or HLA-B Bw4-80Ile- displayed 47.2%.
- Patients (n=19) with activating receptor KIR3DS1+ displayed showed similar overall response rate than patients (n=38) KIR3DS1- (52.6% versus 50%, respectively).

Patients with at least one of the high-risk cytogenetic abnormalities (t[4;14], del[17p], t[14;16], t[11;14], gain[1q], del[13q], and/or hypodiploidy]) showed lower ORR (26.7%; 4 out of 15) compared to all-treated population (50.9%).

Pharmacokinetic results:

・Assessment of PK (N=52) demonstrated that isatuximab exposure in combination with lenalidomide and dexamethasone was supra-dose proportional over the 3 to 10 mg/kg dose range and showed a moderate total variability. An accumulation was observed between Cycle 1 and Cycle 3 and steady state was not reached during the observed period (6 cycles).

・When given with isatuximab, lenalidomide exposure (25 mg dose) showed no accumulation after repeated dosing and was within the range of exposure previously published for lenalidomide as single agent in patients with MM, suggesting no effect of isatuximab coadministration on lenalidomide PK.

Immunogenicity:

・Four out of 55 (7.3%) patients had treatment-induced ADA, but no persistent ADA. Therefore, both the prevalence and incidence of ADA were 7.3%.

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