Sponsor: Sanofi **Drug substance(s):** isatuximab	**Study Identifiers:** U1111-1116-5472, EudraCT: 2013-001418-13, NCT01084252 **Study code:** TED10893

Title of the study:

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 (TED10893)

Study center(s):

The phase 1 part of this study was conducted at 3 clinical centers in France, 2 clinical centers in Spain, and 8 clinical centers in the United States.

Study period:

Date first patient enrolled: 10 June 2010

Study Status: Completed

Phase of development: Phase 1

Objectives:

Primary:

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

Secondary:

The secondary objectives for the Phase 1 part of the study were to:

- To characterize the global safety profile including cumulative toxicities.
- To evaluate the pharmacokinetic (PK) profile of isatuximab in the proposed dosing schedules.
- To assess the pharmacodynamics (PDy), immune response, and preliminary disease response.

Methodology:

The Phase 1 part of the study was an open-label, international, and multicenter dose-escalation study designed to determine the MTD of single-agent isatuximab in patients with selected CD38+ hematological malignancies who had progressed on or after standard therapy or for whom no standard therapy exists. Once the MTD was established or the highest planned dose was reached, expansion cohorts were enrolled to further establish the tolerability, PK and disease response of isatuximab.

Two dose escalation schemes (accelerated dose and basic dose) were used. Dose escalation decisions were made by a Study Committee and based upon toxicities observed during the first 2 cycles or 28 days of treatment (a cycle was 14 days). However, cumulative toxicities observed on subsequent administrations were also considered for the dose escalation process and the dose selection decision. Safety assessments followed the National Cancer Institute Common Terminology Criteria for Adverse Event Version 4.0 (NCI-CTCAE v. 4.03) guidelines.

Accelerated dose-escalation scheme

In the accelerated dose-escalation scheme, 1 evaluable patient was to be enrolled per dose level (DL). Log dose-escalation was used until 0.1 mg/kg to determine the DLs to be explored:

- Cohort 1: 0.0001 mg/kg every 2 weeks (Q2W).
- Cohort 2: 0.001 mg/kg every 2 weeks (Q2W).
- Cohort 3: 0.01 mg/kg every 2 weeks (Q2W).
- Cohort 4: 0.03 mg/kg every 2 weeks (Q2W).
- Cohort 5: 0.1 mg/kg every 2 weeks (Q2W).

The data obtained from the 2 first cycles (ie, 4-week period) was used for acute safety monitoring and to make decisions regarding cohort expansion and/or dose escalation to the next cohort. Pharmacokinetic and CD38 receptor occupancy (RO) data were collected and also may have been used for dose-escalation decisions.

In the event of a Grade 1 or higher treatment-emergent, IP-related, nonhematological toxicity including fever, the cohort was to be expanded to 3 patients and a semi-log escalation was to be used between DLs for all future doses. All successive cohorts would then include 3 patients per DL. Additionally, in the event of Grade 2 or higher treatment-emergent (regardless of relationship to IP) nausea, vomiting, diarrhea, fatigue, asthenia, anorexia, alkaline phosphatase elevation, or local (injection site) reaction, the cohort was to be expanded to 3 patients with a switch to semi-log dose escalation. In the event that a DLT was reported at a DL during the accelerated dose escalation scheme, up to 6 patients were assessed at this DL. If <2 out of 6 patients experienced a DLT at this DL, the dose escalation proceeded to the next level with 3 patients per DL. If ≥2 of a maximum of 6 patients experienced a study treatment-related DLT, the MAD was considered to have been reached and dose escalation was to stop.

Basic dose-escalation scheme

In the basic dose-escalation scheme, successive cohorts included at least 3 evaluable patients, if no potential DLT was reported, or up to 6 evaluable patients if a potential DLT was experienced by 1 of the first 3 patients in the cohort. In each cohort, at least 7 days had to pass after dosing the first patient before the second patients was dosed. The cohorts included:

- Cohort 6: 0.3 mg/kg every 2 weeks (Q2W).
- Cohort 7: 1 mg/kg every 2 weeks (Q2W).
- Cohort 8: 3 mg/kg every 2 weeks (Q2W).
- Cohort 9: 5 mg/kg every 2 weeks (Q2W).
- Cohort 10: 10 mg/kg every 2 weeks (Q2W).
- Cohort 11 10 mg/kg every week (QW).
- Cohort 12: 20 mg/kg every 2 weeks (Q2W).

The data obtained from the dosing and post-dose observation periods were used for acute safety monitoring. Pharmacokinetic and CD38 RO data were collected and may have been used to make the dose escalation decision to the next cohort.

MAD/MTD

Dose escalation was to be stopped when the MAD (or the maximum planned dose) was reached. The definition of MAD was the dose at which ≥33% of evaluable patients experienced DLT occurring during the first 2 cycles (28 days) from a cohort of 3 to 6 patients. The definition of MTD was the highest DL at which no more than 1 patient of a maximum of 6 patients experienced a DLT (usually, the MTD is defined as 1 DL below the MAD).

Expansion cohorts

Once the MTD or recommended Phase 2 dose (RP2D) was established based on Cohorts 1-12 (up to 20 mg/kg Q2W), the decision to proceed to the expansion cohorts was based on the overall safety, PK, and efficacy observed during dose escalation. Two multiple myeloma (MM) specific expansion cohorts were planned: Standard and high risk cohort (expansion cohort 1 [EC1]) and a High Risk (HR) cohort (or expansion cohort 2 [EC2]).

Up to 18 additional patients per cohort (for a total accrual of 36 patients) were to be enrolled to further evaluate the safety, tolerability, PK and disease response at the selected isatuximab dose and schedule. Patients enrolled in the expansion cohorts were to be treated at 10 mg/kg Q2W that followed the every 2-week schedule corresponding to Cohort 10 visit schedules. **Cohort 13 (20 mg/kg QW)** After completion of a preliminary analysis of data from EC1, the Study Committee decided to explore an additional DL in the Phase 1 part of the study: 20 mg/kg QW (ie, Cohort 13). Patients initially received 4 doses of isatuximab at 1-week intervals followed by a 1-week post-fourth-dose observation period.
Number of study participants: Number of patients: Planned: 85 Enrolled: 89 Treated: 89 Number of patients evaluated: Pharmacodynamics: 56 Safety: 89 Pharmacokinetics: 87 (noncompartmental analysis [NCA]); 75 (population PK analysis) Efficacy: 84 (MM patients only)
Diagnosis and criteria for inclusion: All patients had to be ≥18 years old; have a Karnofsky performance status (PS) ≥60; and have adequate hematologic, renal, and liver function. In addition to the criteria noted above for all patients enrolled in the study, patients must have had no serious active disease or co-morbid condition, or concomitant or prior malignancy except adequately treated basal cell or squamous cell carcinoma of the skin, carcinoma in situ of the cervix, or other cancer for which the patient was disease-free for ≥5 years. No prior anticancer therapy (chemotherapy, targeted agents, radiotherapy, or immunotherapy) was permitted within 21 days except for alkylating agents 28 days were required. Hydroxyurea could be used up to 24 hours prior to the first study treatment and leukophoresis could be used up to 1 week prior to the first drug infusion. Patients who underwent autologous stem cell transplantation (ASCT) were allowed; however, allogeneic bone marrow transplant or an allogeneic peripheral blood stem cell transplant within 1 year prior to study entry or evidence of graft versus host disease (GVHD) requiring >10 mg prednisone were not permitted. Inclusion criteria for specific cohorts were as follows: Dose escalation Cohorts 1 to 10, and the Cohort 10 expansion: Patients with confirmed selected CD38+ hematological malignancies who progressed on or after standard therapy or for whom there was no effective standard therapy (refractory/relapsed patients). Dose escalation Cohorts 11, 12 and 13: 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 chain (FLC) of >10 mg/dL with abnormal FLC ratio who progressed on or after standard therapy that included an IMiD (immunomodulatory imide drug) and a proteasome inhibitor.

Expansion cohort (EC1): Same inclusion criteria as Cohorts 11, 12, and 13, but included patients who had progressed on or after at least 2 prior lines of standard therapy that included an IMiD and a proteasome inhibitor

High risk cohort (EC2): Same inclusion criteria as EC1, but included patients who also must have met one of the following criteria relapsed within 6 months of autologous transplantation; or had 17p deletion, t (4,14), t (14,16), t (14,20) or >3 copies of 1q21; or had a high-risk gene expression profiling (GEP) signature (if available).

Study products

Investigational medicinal product(s):

Isatuximab (SAR650984) process and formulation (cell1, process 1, formulation 1 [C1P1F1]) drug product

Formulation: Isatuximab 5 mg/mL (100 mg/20 mL) in a 10 mM histidine, 10% (w/v) sucrose, and 0.005% (w/v) polysorbate 80, pH 6.5 buffer.

Route(s) of administration: Intravenous (IV) infusion

Dose regimen:

Accelerated dose-escalation cohorts:

0.0001 mg/kg Q2W, 0.001 mg/kg Q2W, 0.01 mg/kg Q2W, 0.03 mg/kg Q2W, and 0.1 mg/kg Q2W

Basic dose-escalation cohorts and expansion cohorts:

0.3 mg/kg Q2W, 1 mg/kg Q2W, 3 mg/kg Q2W, 5 mg/kg Q2W, 10 mg/kg Q2W, 10 mg/kg QW, 20 mg/kg Q2W

Duration of treatment: Patients were treated until unacceptable toxicity, disease progression, death, withdrawal of consent, Investigator's decision to withdraw the patient, and/or availability of the study treatment.

Duration of observation: Patients were followed for a screening period of up to 2 weeks; study treatment administration over 2 weeks (cycle) followed by a 2-week observation period; any additional cycles/observation periods as long as clinical benefit was noted; and a post-treatment follow-up period of at least 30 days, or more than 30 days in case of unresolved treatment-emergent adverse event (TEAE) or initiation of another anticancer treatment.

Criteria for evaluation:

Safety: The safety variables included DLTs, adverse events (AEs), clinical laboratory parameters, physical examinations included vital signs, electrocardiograms (ECG), Karnofsky PS, immunogenicity, and cytokines (tumor necrosis factor alpha [TNF-α], interleukin-6 [IL-6], interleukin-1β [IL-1β], and interferon-γ [IFN-γ]. The NCI-CTCAE v. 4.03 was used to grade the severity of AEs and laboratory results.

Dose-limiting toxicities: DLTs occurring during the first 28 days (Cycle 1 and Cycle 2) were defined as any Grade 3 or higher non-hematological toxicity (including fever but excluding nausea, vomiting, diarrhea, fatigue, asthenia, anorexia, elevated alkaline phosphatase, and local [injection site] reaction with the exception of allergic reaction/hypersensitivity), and Grade 4 neutropenia and/or Grade 4 thrombocytopenia lasting longer than 5 days.

Immunogenicity: Samples for anti-drug antibodies (ADA) measurement were obtained before infusion of isatuximab at Cycles 1 and 2; Cycle 1, Day 3; Cycle 2, Day 14; before the end of infusion for subsequent cycles; and 30 days and 60 days after the last infusion of isatuximab. In addition, in the case of a positive ADA sample, every 30 days until the sample was negative.

Efficacy: Efficacy assessments were performed every other cycle using the European Society for Blood and Marrow Transplantation (EBMT) criteria and focused on patients with MM. Secondary efficacy variables included best overall response (BOR) defined as the best sequential response using the Investigator's assessment of response from the start of treatment through the entire study excluding any time point following the start of other anti-cancer treatment for MM. The ordering of evaluations from best to worse was complete response (CR), partial response (PR), stable disease, progressive disease (PD), and not evaluable. Additional efficacy endpoints included clinical benefit rate (CBR), duration of response (DOR), time to response (TTR), follow-up duration (FUD), and best percent change in paraprotein.

Pharmacokinetics: The following PK parameters were calculated from plasma concentrations of isatuximab using non-compartmental analysis (NCA): concentration observed at end of an IV infusion (C_{eoi}),maximum plasma concentration observed (C_{max}), first time to reach maximum plasma concentration observed (t_{max}), area under the plasma concentration versus time curve calculated using the trapezoidal method from 0 to 168 or 336 hours postdose (AUC_{tau}), area under the plasma concentration versus time curve calculated using the trapezoidal method from time 0 to t_{last} (AUC_{last}), last plasma concentration observed (C_{last}), and plasma concentration observed before treatment administration during repeated dosing (C_{trough}).

Population PK analysis: Isatuximab plasma concentrations after single and repeated dose administrations were analyzed using a nonlinear mixed-effects modeling approach with MONOLIX software version 4.3.2 (Lixoft). A basic population PK model was developed and the following PK individual parameters were calculated, for doses ≥1 mg/kg:

- Cumulative AUC over a 1, 2, or 4 week interval (AUC1W, AUC2W, AUC4W)
- C_{trough} (pre-dose concentration) at 1, 2, or 4 weeks (C_{trough} 1W, C_{trough}2W, C_{trough}4W)

Clearance (CL) for linear non-specific elimination pathway

Pharmacokinetics sampling times and bioanalytical methods:

Cohorts 1-5

Blood samples for analyses of PK of isatuximab were collected Cycle 1, Day 1 predose, at the mid infusion, just before end of infusion (EOI), 3 h and 7 h after EOI then 24 h (Day 2), 48 h (Day 3), and 168 h (Day 8) after the start of infusion; Cycle 2, Day 1 predose, at the mid infusion, just before EOI, 3 h and 7 h after EOI, then 24 h (Day 2), 48 h (Day 3),168 h (Day 8) and 312 h (Day 14) after the start of infusion of Cycle 2; and subsequent cycles just before EOI; and 30 and 60 days after last study treatment administration.

Cohorts 6-10

Blood samples for analyses of PK of isatuximab were collected Cycle 1, Day 1 predose, at the mid infusion, just before EOI, 3 h and 7 h after EOI then 24 h (Day 2), 48 h (Day 3), and 168 h (Day 8) after the start of infusion of Cycle 1; Cycle 2, Day 1 predose, and 312 h (Day 14) after the start of infusion; at EOI of subsequent cycles, and 30 and 60 days after last study treatment administration.

Cohort 11 + 13

Blood samples for analyses of PK of isatuximab were collected predose, at the mid infusion, just before EOI, 4 h after EOI, then 24 h (Day 2), 48 h (Day 3), 72 h (Day 4) and 168 h (just before Day 8 infusion) after the start of infusion of Cycle 1, Day 1 and Cycle 3, Day 1; at predose of Day 1 and Day 8 administration of Cycle 2 and subsequent cycles; and 30 and 60 days after last study treatment administration.

Cohort 12 + ECs

Blood samples for analyses PK of isatuximab were collected Cycle 1, Day 1 predose, at the mid infusion, just before EOI, 4 h after EOI then 24 h (Day 2), 48 h (Day 3), 72 h (Day 4) and 168 h (Day 8) after the start of infusion; predose of Cycle 2 and subsequent cycles; and 30 and 60 days after last study treatment administration.

Isatuximab concentrations in plasma were measured using a validated enzyme-linked immunosorbent assay (ELISA) method with a limit of quantitation of 0.500 ng/mL.

Pharmacodynamics: CD38 receptor occupancy (RO) and receptor density (RD) were assessed from bone marrow aspirates before infusion of isatuximab at Cycle 1, Day 1; and Cycle 2, Day 14.

Cytokines: Samples for cytokines (TNF-α, IL-1-β, IL-6, and IFN-γ) were drawn prior to first study treatment administration at Cycle 1, and as follows:

- Accelerated dose-escalation Cohorts 1-5: 6 and 24 h post first-infusion in each cycle.
- Basic dose-escalation Cohorts 6-10: 6 and 24 h post-infusion in each cycle.
- Basic dose-escalation for Cohorts 11 and 13: 6 h post-infusion on Day 1 and Day 8 of each cycle, and Day 2 (24 h post-infusion) of Cycle 1 and 2.
- Basic dose-escalation for Cohorts 12 and ECs: 6 and 24 h post first-infusion (Cycle 1 and 2) and then at 6 h post-infusion in each cycle.

Statistical methods:

Five analysis populations were defined for the statistical analyses:

- The All Treated (AT)/safety population included all patients who gave their informed consent and who received at least 1 dose (even incomplete) of isatuximab.
- The DLT evaluable population was the subset of patients from the AT population who were treated during the DE phase of the study and who had a DLT assessment at the end of Cycle 2. This population included patients followed up to the end of the observation period or patients having experienced a DLT validated by the Study Committee, whichever was first.
- The AT MM population included all MM patients from the AT/safety population.
- The PK population included all patients for whom any PK parameter was available.
- The PDy population included receptor density (RD) evaluable patients from the AT/safety population who had evaluable RD at baseline and RO evaluable population who had evaluable RO during treatment.

Safety

Patients with DLTs were presented using the DLT evaluable population. For treatment-emergent AEs (TEAEs), the incidence tables were presented for each DL and overall. Number (%) of patients experiencing TEAEs by primary system organ class and preferred term (PT) (according to Medical Dictionary for Regulatory Activities [MedDRA] version 19.1.) were summarized by CTCAE grade (all grades and Grade ≥3) for the all-treated population. Similar tables were presented for drug-related TEAEs, serious TEAEs, and AEs/SAEs occurring during the pre/post treatment dosing period. Infusion associated reactions were analyzed using both the Investigator reporting and TEAEs occurring within 24 hours after each isatuximab administration. Other significant AEs consisted of respiratory AEs, neutropenic complication, second primary malignancies, symptomatic overdoses, and pregnancies.

The numbers of patients with abnormal laboratory tests at baseline and during treatment were presented by DL and grade. The frequency of patients with each grade of laboratory test at baseline and 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 and ECG, the number of patients with a potentially clinically significant abnormality (PCSA) during the on-treatment period was summarized by DLs. Urate (uric acid laboratory parameter) was analyzed using PCSA at baseline and on-treatment. Karnofsky PS was mapped to Eastern Cooperative Oncology Group (ECOG) performance status (PS), and shift tables of baseline ECOG PS (Karnofsky PS) versus best/worst ECOG PS (Karnofsky PS) on treatment values were provided.

Immunogenicity

A polyethylene glycol precipitation and acid dissociation assay (PandA) was developed and validated to detect ADAs in human serum.

The number (%) of patients who had pre-existing anti-drug antibody (ADA) at baseline, who were 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.

Efficacy

Efficacy endpoints were analyzed for the all-treated MM population. The BOR, ORR, CBR, DOR, TTR, and FUD were summarized with descriptive statistics by DL and over-all using best confirmed response and best unconfirmed response. BOR, ORR and CBR were also summarized by measurable paraprotein at baseline and CD38 receptor occupancy. ORR was also summarized by CD38 receptor density threshold.

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).

Pharmacokinetics

All individual concentrations and all PK parameters of isatuximab were tabulated using descriptive statistics: arithmetic and geometric mean, median, standard deviation (SD), standard error of the mean, coefficient of variation, minimum, maximum, for each DL. Maximum drug concentration (C_{max}) ratios were calculated between fifth and first administration of isatuximab for the QW schedule. Minimum drug concentration (C_{trough}) ratios were calculated between 4th and 1st administration of isatuximab for the QW schedule.

Summary Results:

Population characteristics:

A total of 89 patients received at least 1 administration (even if incomplete) of study treatment. Of the 89 patients, 84 (94.4%) patients had MM; 2 (2.2%) patients had chronic lymphocytic leukemia (CLL); and 3 (3.4%) patients had non-Hodgkin's lymphoma (NHL). The median age in the AT population was 64.0 years (range 40 to 85 years) and 52.8% of the population was <65 years of age. The ECOG performance score was rated as 0, 1, or 2 in 13.5%, 69.7%, and 16.9% of patients, respectively.

In the MM population, the median time from initial MM diagnosis to first study treatment dose was 5.84 years (range 1.2 to 22.8 years). Of the 84 MM patients, the International Staging System (ISS) criteria at initial diagnosis were classified as Stage I, Stage II and Stage III in 13.1%, 27.4%, and 33.3%, respectively; and were missing in 26.2% of the patients. As per inclusion criteria, all 84 MM patients had received prior anticancer therapy. The median number of lines was 5.0 (range 1 to 13 lines) with 10.7% of patients receiving 8 or more prior lines of treatment. Of the 92.9% of patients who received alkylating agents, the majority (77.4%) received melphalan followed by cyclophosphamide (72.6%) and doxorubicin (23.8%). All patients received an IMiD agent (lenalidomide, thalidomide, pomalidomide) with the majority (94.0%) of patients receiving lenalidomide followed by thalidomide (63.1%). Similarly, all patients received a PI (bortezomib, carfilzomib, ixazomib) with the majority (98.8%) of patients receiving bortezomib followed by carfilzomib (42.9%). A total of 94.0% of patients received both lenalidomide and bortezomib, and 21.4% of patients received carfilzomib and pomalidomide. As of the final database lock, all 89 patients had discontinued study treatment. The main reasons for treatment discontinuation were disease progression (86.5%), “other” reasons (9.0%), and adverse events (4.5%).

Safety results:

During the basic escalation phase of the study, DLTs consistent with IARs (only initially included in the definition of DLTs) occurred at Cycle 1 in 1 patient each at the 0.3 mg/kg Q2W and at the 3 mg/kg Q2W DL. The definition of DLTs was then changed to not include IARs because these reactions are not dose dependent. No other DLTs were observed and the MTD was not reached at the highest planned dose (20 mg/kg QW) of study treatment.

A total of 89 patients received 867 cycles and 954 infusions of isatuximab. The median overall exposure to study treatment was 5.0 cycles, with a median duration of 10.1 weeks, and median relative dose intensity (RDI) of 98.54%. Cycle delays occurred in 48.8% of the patients, and isatuximab interruptions in 2.7% of the infusions, the majority (88.5%) during the first infusion.

A total of 98.9% of patients experienced at least 1 TEAE, and 55.1% of patients experienced at least 1 Grade ≥3 TEAE. TEAEs led to permanent study discontinuation in 4 (4.5%) patients. These TEAEs consisted of bone pain, apnea, infusion related reaction, acute coronary syndrome, hypertensive crisis, and acute kidney injury. The most common TEAEs overall (all grades) consisted of infusion related reaction (49.4%), fatigue (37.1%), nausea (32.6%), anemia (28.1%), cough and upper respiratory tract infection (22.5% each), and back pain and diarrhea (20.2% each). No apparent dose dependency was observed with respect to the incidence and severity of TEAEs.

Three (3.4%) patients experienced TEAEs leading to death: 1 patient died within 30 days from the last study treatment administration, because of acute kidney injury. The other 2 patients died >30 days from the last study treatment administration, respectively because of progressive disease and acute kidney injury, and of bacterial meningitis. Neither of these AEs was considered related to study treatment.

Serious TEAEs were reported in 40.4% of patients, the most frequent Grade ≥3 serious TEAEs being pneumonia (6.7%), sepsis and anemia (3.4% each), pneumocystis jirovecii pneumonia, hypercalcemia, bone pain, and acute kidney injury (2.2% each). With the exception of pneumonia, none of these AEs were considered related to study treatment.

Infusion-associated reactions (excluding symptoms) (all grades) were reported in 47.2% of the patients including 2 (2.2%) patients with Grade 4 IARs (no Grade 3 IARs were reported). Both patients with Grade 4 IARs discontinued study treatment due to IARs. The first episode of an IAR occurred upon the first infusion in 92.9% (39 of 42) of the patients who experienced IARs. IARs had a Grade 1-2 severity in 95.2% (40 of 42) of the patients who experienced IARs. The most frequently reported IARs and associated TEAEs involved the Injury, poisoning and procedural complications SOC (all grades, 47.2%), followed by Respiratory, thoracic, and mediastinal disorders SOC (all grades, 27.0%). The most frequently reported associated TEAEs consisted of dyspnea, nausea, and chills (11.2% each), headache (7.9%), chest discomfort (6.7%), pyrexia (5.6%), and vomiting (4.5%). All the patients recovered from the IARs, which were resolved within 2 days in 70.9% of the episodes.

Lower respiratory TEAEs (all grades) were reported in 44.9% of patients. Most frequently, these TEAEs consisted of coughing and associated symptoms (27.0%), followed by breathing abnormalities (19.1%), and bronchospasm and obstruction (9.0%). For 20 patients, lower respiratory TEAEs were manifestations of IARs. These adverse events did not developed in the context of IARs in 27 patients. Grade 1 to 2 cough was the only respiratory TEAE that appeared to occur more frequently not as a TEAE associated with an IAR episode. Grade ≥3 lower respiratory TEAEs were reported in 7.9% of the patients and included bronchospasm (2 patients) and apnea, dyspnea, hypoxia, hemoptysis, and acute respiratory failure (1 patient each). The incidence, severity, and seriousness of TEAEs mapped under the Respiratory, thoracic and mediastinal disorders SOC do not appear to show dose dependency.

Overall, lower respiratory tract and lung infections (HLT) occurred in 15.7% of the patients (Grade ≥3 in 7.9%), and upper respiratory tract infections (HLT) occurred in 29.2% of the patients (no Grade ≥3). Of the 34 patients with a reported respiratory medical history, 5 (14.7%) patients experienced lower respiratory tract and lung infection TEAEs (Grade ≥3 in 8.8%). Of the 54 patients with no reported respiratory medical history, 9 (16.7%) experienced lower respiratory tract and lung infection TEAEs (Grade ≥3 in 7.4%). The corresponding incidence of upper respiratory tract infection was 35.3% in patients with a reported respiratory medical history, and 25.9% in patients with no reported respiratory medical history; no Grade ≥3 upper respiratory tract infections were reported in either group. It appears from this analysis that respiratory conditions reported in medical history do not contribute to higher incidence and severity of respiratory infections while on study.

The most frequently reported on-treatment Grade 3 or 4 hematological abnormalities (measured as laboratory values) consisted of decreased lymphocyte count (Grade 3 or 4: 33.3%), anemia (Grade 3: 18.4%; no Grade 4), decreased platelet count (Grade 3 or 4: 15.9%), decreased neutrophil count (Grade 3 and 4: 12.6%), and decreased white blood cell count (Grade 3 or 4: 8.0%). Overall, the incidence, severity, and seriousness of hematological abnormalities do not appear to show dose dependency. Of the 41 patients who experienced laboratory neutropenia during treatment, 6 (14.6%) patients had Grade 3 neutropenia and 5 (12.2%) patients had Grade 4 neutropenia. Grade 3 febrile neutropenia occurred in a single patient in the 10 mg Q2W-HR DL. No neutropenic infections were reported as TEAEs. Overall, the incidence, severity, and seriousness of neutropenia and its complications do not appear to show dose dependency.

Liver abnormalities reported during treatment (measured as laboratory values) that were reported in more than 1 patient consisted of Grade 3 increased aspartate aminotransferase (ALT) and Grade 3 increased alanine aminotransferase (AST) (3.4% each; no Grade 4 abnormalities were reported. Renal function abnormalities during treatment consisted of Grade 3 hypercreatininemia which was reported with an incidence of 4.5%; no Grade 4 abnormalities were reported. The incidence of urate levels >408 µmol/L

was 51.1% without an apparent dose dependency. Metabolic abnormalities during treatment that occurred in more than 2 patients consisted of hyperglycemia (Grade 3 or 4, 20.4%) without an apparent dose dependency. Grade 3 or 4 electrolyte abnormalities during treatment reported in more than 2 patients consisted of hypophosphatemia (Grade 3 or 4: 34.1%), hyponatremia (Grade 3: 20.5%; no Grade 4), and hypokalemia (Grade 3 or 4: 3.4%).

Overall, the laboratory analyses of abnormalities of liver enzymes, renal function, metabolism, electrolytes, and analyses of heart rate, pulse rate, QRS, QTc Bazett, and QTc Fridericia intervals do not show apparent dose dependency.

Immunogenicity results:

Of the 88 evaluable patients, 1 patient was positive for ADAs before his first isatuximab administration, and 7 patients were positive for ADAs post-treatment. Therefore, the incidence of ADAs was calculated as 8.0% and the prevalence was calculated as 9.1 %. Among the 8 patients with positive ADA status, 1 patient was considered non-treatment-induced transient positive ADA; 5 patients had transiently positive ADAs, and 2 patients had persistently positive ADAs.

Efficacy results:

In the assessment of ORR in the AT MM population at doses 1 mg/kg or higher (74 patients), 1 patient (1.4%) had CR and 21.6% of the patients had PR resulting in an ORR of 23.0%. The patient with CR was in the 10 mg/kg QW DL. The ORR was similar at doses ≥ 10 mg/kg, with responses occurring in general after two 2-week cycles and that were durable. In the 10 mg/kg Q2W-HR DL, the ORR was 16.7% with durable responses and long stable disease (5 patients with duration of exposure >24 weeks).

The median DOR was 7.16 months (range 1.4 to 23.4 months) and was similar across all DLs (including the 10 mg/kg Q2W-HR DL) with the exception of 1 patient with a DOR of 20.21 months in the 1 mg/kg Q2W DL and 2 patients with a median DOR of 14.31 months (range 9.0 to 19.6 months) in the 10 mg/kg QW DL. Conversely, DOR was short (<2 months) in 3 patients (2 patients in the 10 mg/kg Q2W-DE+EC1 DL and 1 patient in the 10 mg/kg Q2W-HR DL).

A total of 28.9% of patients experienced a ≥50% reduction in paraprotein and 14.4% of patients showed a >90% reduction.

Pharmacodynamic results:

Of the 56 patients treated at doses 1 mg/kg or higher, 31 (55.4%) patients had <150 000 CD38 RD and 25 (44.6%) patients had ≥150 000 CD38 RD. Of the 31 patients with <150 000 CD38 RD, 6 (19.4%) patients had PR (no CR) for an ORR of 19.4%. Of the 25 patients with ≥150 000 CD38 RD, 4% of patients had CR and 32.0% of patients had PR for an ORR of 36.0%. Three patients were not evaluable (2 [6.5%) patients with <150 000 CD38 RD and 1 [4.0%] patient with ≥150 000 CD38 RD).

Cytokine results:

Following isatuximab administration, higher cytokine levels for IL-1, IL-6, TNF-α, and IFN-γ were noted as compared to baseline: the median peak values (defined as the highest value during the on-treatment period) of IFN-γ, IL-1β, IL-6, and TNF-α were 0.44, 0.34, 6.48, and 24.66 pg/mL, respectively, with median relative change from baseline ranging from 6% to 184% across the 4 cytokines with no evident dose dependency. Peak values were mainly observed 6 h after the completion of the first isatuximab infusion for IFN-γ, IL-1β, and TNF-α, and 24 h after the completion of the first isatuximab infusion for IL-6.

For each cytokine, the median of the peak value was overall similar for patients who never experienced an IAR during the on-treatment and those who developed at least one IAR during the on-treatment period. Therefore, no association between the transient cytokine increases and the occurrence of IARs could be demonstrated.

Pharmacokinetic results:

Assessment of PK by non-compartmental analysis in 88 patients demonstrated that isatuximab exposure was supra-dose proportional over the 1 to 20 mg/kg dose range. A low to high variability was observed for C_{max} (CV%=20% to 67%) and for AUC (AUC_{1week} or AUC_{2weeks}) (CV%=14% to 81%) across all dose range and schedule, after the Cycle 1 and 3. The t_{last} varied between 50 h and 383 h from the lowest to the highest dose level.

Repeated QW dosing resulted in an accumulation of 1.7 to 2.6-fold at Cycle 3 at 10 and 20 mg/kg, and steady state was not reached on the observed period (9 cycles for Q2W schedule and 7 cycles for QW schedule).

A population PK analysis of isatuximab was performed using the data from 75 out of the 89 patients at doses equal or higher than 1 mg/kg. The PK of isatuximab was best described by a 2-compartment structural kinetic model with parallel linear and Michaelis-Menten eliminations from the central compartment (approximation of target mediated – drug disposition model). The typical

estimated linear clearance was 0.00708 L/h (0.170 L/day) and the typical volume of distribution of the central compartment was 4.41 L, resulting in a half-life associated to the linear elimination of 18 days. The maximum binding capacity (V_{max}) was 0.185 mg/L.h (4.4 mg/L.day) and the concentration of isatuximab corresponding to half maximum binding capacity (Km) was 0.142 µg/mL. Interindividual variability for random effects associated with the model parameters ranged from 36.4 % (Vp) to 97.0% (CL). Residual error was low with a proportional part of 25% and an additive part of 0.0047 µg/mL. Derived exposure parameters are consistent to those estimated by NCA. The PK/PDy relationships showed that RO is correlated with the isatuximab concentration measured at end of Cycle 2. The maximal effect (ie, 80% RO) was reached for concentrations corresponding to isatuximab dose of 20 mg/kg.

Issue date: 08-Jul-2024

Sponsor: Sanofi **Drug substance(s):** isatuximab	**Study Identifiers:** U1111-1116-5472, EudraCT: 2013-001418-13, NCT01084252 **Study code:** TED10893

Title of the study:

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 center(s):

17

Study period:

Date first patient enrolled: 02 JULY 2014

Study Status: Completed

Phase of development: Phase 2

Objectives:

PRIMARY OBJECTIVE:

The primary objective was to evaluate the activity of single agent isatuximab at different doses/schedules and to select dose and regimen for Phase 2 Stage 2.

SECONDARY OBJECTIVES:

The secondary objectives were to evaluate single agent isatuximab for 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 isatuximab, Immunogenicity of isatuximab, and Investigate the relationship between CD38 receptor density and CD38 receptor occupancy on multiple myeloma cells and parameters of clinical response.

Methodology:

The Phase 2 Stage 1 part (P2S1) of the trial is an open-label, international multi-center study conducted in 2 stages (1a and 1b) in patients with relapsed or relapsed/refractory multiple myeloma. In Phase 2 Stage 1a patients were randomly assigned to one of 3 treatment arms (3 mg/kg Q2W, 10 mg/kg Q2W, 10 mg/kg Q2W/Q4W) in a 1:1:1 ratio. Patients in Phase 2 Stage 1b were treated at 20 mg/kg QW/Q2W.

The results of P2S1 are presented in this clinical study report (CSR). P2S2 is ongoing and the results will be presented in a separate report.

Number of study participants:	
	Planned: 96
	Enrolled/Randomized: 72
	Treated:97
Evaluated:	
	Efficacy: 97
	Safety: 97
	Pharmacokinetics: 168 for population PK analysis, including 95 from Phase 2 Stage 1
Diagnosis and criteria for inclusion:	
Patients must have a known diagnosis of multiple myeloma with evidence of measurable disease. Patients must have received prior treatment with an alkylating agent, an immunomodulatory drug (IMiD) and a proteasome inhibitor (PI). Patients must have received at least three prior lines of therapy for multiple myeloma.	

Study products

Investigational medicinal product(s): SAR650984 (isatuximab).

Formulation: The cell 1, process 1, formulation 1 (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.

Route(s) of administration: Intravenous (IV) infusion.

Dose regimen: 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

Duration of treatment/participation: Patients were treated until disease progression, unacceptable adverse reaction or other reason for discontinuation.

Duration of observation: Patients were followed for a screening period of up to 3 weeks; study treatment administration and follow-up. Patients with documented disease progression at the end of treatment visit received follow-up visits at 30, 60 and 90 days after the last dose.

Criteria for evaluation:

Efficacy/pharmacodynamic: primary efficacy endpoint was overall response rate as assessed by the Independent Adjudication Committee (IAC). Secondary efficacy variables included best overall response (BOR) as assessed by the IAC from the start of treatment through the entire study excluding any time point following the start of other anti-cancer treatment for MM. The ordering of evaluations from best to worse was stringent complete response (sCR), complete response (CR), very good partial response (VGPR), partial response (PR), stable disease, progressive disease (PD), and not evaluable. Additional efficacy endpoints included clinical benefit rate (CBR), duration of response (DOR), time to response (TTR), follow-up duration (FUD), and best percent change in paraprotein.

Safety: The safety variables included adverse events (AEs), clinical laboratory parameters, physical examinations, vital signs, electrocardiograms (ECG), Karnofsky PS, immunogenicity, and cytokines (tumor necrosis factor alpha [TNF-α], interleukin-6 [IL-6], interleukin-1 β [IL-1 β], and interferon- γ [IFN- γ] for patients with IAR of Grade ≥2). The NCI-CTCAE v. 4.03 was used to grade the severity of AEs and laboratory results.

Immunogenicity: Samples for anti-drug antibodies (ADA) measurement were obtained just before infusion of isatuximab at Cycle 1 Day 1 and 15 and at Day 1 of subsequent cycles; and 30 and 60 days after the last infusion of isatuximab. At 60 days, in the case of a positive ADA sample, every 30 days until the sample was interpretable or negative.

Pharmacokinetics: Population PK analysis: Isatuximab plasma concentrations after single and repeated dose administrations were analyzed using a nonlinear mixed-effects modeling approach with MONOLIX software version 4.4.0 (Lixoft). A basic population PK model was developed and the following PK individual parameters were calculated:

- Cumulative AUC over a 1, 2, or 4 week interval (AUC1W, AUC2W, AUC4W)
- C_{trough} (pre-dose concentration) at 1, 2, or 4 weeks (C_{trough}1W, C_{trough}2W, C_{trough}4W)
- C_{max} at Cycle 1 Day 1, Cycle 2 Day 1 and Cycle 4 Day 1
- Clearance for linear non-specific elimination pathway
- Accumulation ratios: Ceoi ratio at Cycle 4 Day 1 versus Cycle 1 Day 1 for Arm 3 and Arm 4 ; C_{trough} ratio at Cycle 2 Day 1 versus Cycle 1 Day 15 and Cycle 4 Day 1 versus Cycle 1 Day 15 for Arms 1, 2 and 3 ; C_{trough} ratio at Cycle 2 Day 1 versus Cycle 1 Day 8 and Cycle 4 Day 1 versus Cycle 1 Day 8 for Arm 4
- Volumes (V1 and V2) and half-life associated to the linear CL

Pharmacokinetic/Pharmacodynamics sampling times and bioanalytical methods:

Pharmacokinetic/Pharmacodynamics sampling times and bioanalytical methods:

Arms 1 and 2

Blood samples for analyses of PK of isatuximab were collected Cycle 1, Day 1 predose, EOI and EOI+1h; Day 15 predose and EOI, then predose of Day 1 and Day 15 of each subsequent cycles; and 30 and 60 days after last study treatment administration.

Arm 3

Blood samples for analyses of PK of isatuximab were collected Cycle 1 Day 1 and Cycle 4 Day 1 predose, EOI and EOI+1h; Cycle 1 Day 15 predose and EOI; predose of Day 1 and Day 15 of Cycle 2 and 3; then predose of Day 1 of each subsequent cycles and 30 and 60 days after last study treatment administration.

Arm 4

Blood samples for analyses of PK of isatuximab were collected Cycle 1 Day 1 and Cycle 4 Day 1 predose, EOI and EOI+1h; Cycle 1 Day 8 predose, Cycle 1 Day 15 predose and EOI, Cycle 1 Day 22 predose; Cycle 2 and 3 Day 1 and Day 15 predose; then predose of Day 1 and Day 15 of each subsequent cycles and 30 and 60 days after last study treatment administration.

Isatuximab concentrations in plasma were measured using a validated enzyme-linked immunosorbent assay (ELISA) method with a limit of quantitation of 0.500 ng/mL.

Pharmacodynamics: CD38 receptor occupancy (RO) was assessed from bone marrow aspirates before infusion of isatuximab at Cycle 2, Day 1; at the end of treatment visit. CD38 receptor density (RD) was assessed from bone marrow aspirates at screening.

Statistical methods:

Safety

For treatment-emergent AEs (TEAEs), the incidence tables were presented for each DL and overall. Number (%) of patients experiencing TEAEs by primary system organ class and preferred term (PT) (according to MedDRA dictionary) were summarized by CTCAE grade (all grades and Grade ≥3) for the all-treated population. Similar tables were presented for drug-related TEAEs, serious TEAEs, and AEs/SAEs occurring during the pre/post treatment dosing period. Infusion associated reactions were analyzed using both the Investigator reporting and TEAEs occurring within 24 hours after each isatuximab administration. Other significant AEs consisted of respiratory AEs, neutropenic complication, second primary malignancies, symptomatic overdoses, and pregnancies.

The numbers and percentage of patients with abnormal laboratory tests at baseline and during treatment were presented by DL and grade and overall. For patients with multiple occurrences of the same laboratory variable during the on treatment period, the maximum (worst) grade per patient was used. For urate, the number and percentage of patients with a potentially clinically significant abnormality (PCSA) at baseline and during the on-treatment period was summarized by DLs and overall. For vital signs the number of patients with PCSA during the on-treatment period was summarized by DLs and overall. Karnofsky PS was mapped to Eastern Cooperative Oncology Group (ECOG) performance status (PS), and shift tables of baseline ECOG PS (Karnofsky PS) versus best/worst ECOG PS (Karnofsky PS) on treatment values were provided.

Efficacy

Efficacy endpoints were analyzed for the all-treated population. The BOR, ORR, CBR, DOR, TTR as assessed by IAC, and FUD were summarized with descriptive statistics by DL and overall. BOR, ORR and CBR were also summarized using investigator assessment of response. ORR was also summarized for each exploratory biomarker (eg, CD38 RD).

Immunogenicity

A polyethylene glycol precipitation and acid dissociation assay (PandA) was developed and validated to detect ADAs in human serum.

The number (%) of patients who had pre-existing anti-drug antibody (ADA) at baseline, who were 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.

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).

Pharmacokinetics

All individual concentrations and all PK parameters of isatuximab were tabulated using descriptive statistics: arithmetic and geometric mean, median, standard deviation (SD), coefficient of variation, minimum, maximum, for each arm. Maximum drug concentration (C_{max}) ratios and minimum drug concentration (C_{trough}) ratios were calculated between Cycle 2 and first administration of isatuximab and between Cycle 6 and first administration. AUC ratios was also calculated for the Q2W schedule.

Summary Results:

Population characteristics: From July 2014 to April 2015, a total of 97 patients were treated in Phase 2 Stage 1 part of TED10893 study at four different doses and/or schedules of administration. The median age was 62 years. As per inclusion criteria, patients were heavily pretreated as shown by median number of prior lines that was of 5 (2 to 14 lines) with 15 (26.3%) patients having received 8 or more prior lines of treatment. Overall response rate to the most recent treatment line given prior to study entry for RRMM was 28% and included 1 (1.0%) complete response, 7 (7.2%) VGPR, and 19 (19.6%) PR. During the study, median number of isatuximab cycles started was 3.

Duration of Exposure results: The median duration of exposure was 13.0 weeks (range 2-77 weeks). The median duration of exposure was the lowest in the 3 mg/kg Q2W (6.0 weeks) dose group and was consistently ≥14 weeks in ≥10 mg/kg arms

Efficacy results: In the analysis for the all-treated population, the overall ORR based on IAC assessment was 19.6% (19 patients out of 97), including 4.3% for 3 mg/kg Q2W, 29.2% for 10 mg/kg Q2W, 20% for 10 mg/kgQ2W/Q4W, and 24% for 20 mg/kg QW/Q2W. The evaluation of the results between the 4 arms should be performed with cautions with 20 m/kg QW/Q2W arm started after the enrollments in the 3 mg/kg Q2W, 10 mg/kg Q2W and 10 mg/kg Q2W/Q4W arms were completed. Therefore, given the small sample size in each arm, despite 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, no conclusion can be drawn based on ORR at doses ≥ 10 mg/kg. Based on IAC assessment, overall, 11 (11.3%) patients achieved VGPR, and 8 (8.2%) patients achieved PR. Six (25.0%) patients in the 10 mg/kg Q2W group achieved VGPR, and 2 (9.0%) patients in the 20 mg/kg QW/Q2W achieved VGPR. Overall, 28 (28.9%) patients achieved CBR (MR or better). Thirty one (32.0%) patients had SD. In a subgroup analysis, patients <70 years of age had ORR (≥PR) of 16.5% (13 of 79 patients), of which 7 (8.9%) had VGPR, and 6 (7.6%) had PR. For patients >70 years of age, the ORR (≥PR was 33.3% (6 of 18 patients), of which 4 (22.2%) had VGPR, and 2 (11.1%) had PR. Eighty-nine out of 97 patients were refractory to IMiD at study entry. Of these, 19 (21.3%) achieved ORR (≥ PR), of which 11 (12.4%) had VGPR, and 8 (9.0%) had PR. Eight patients was not refractory to IMiD at study entry. Of these, no patient achieved ORR. Eighty-seven out of 97 patients were refractory to PI at study entry. Of these, 17 (19.5%) achieved ORR (≥ PR), of which 10 (11.5%) achieved VGPR, and 7 (8.0%) achieved PR. Ten patients were not refractory to PI at study entry. Of those, 2 (20.0%) achieved ORR (≥ PR), 1 (10.0%) had VGPR, and 1 (10.0%) had PR. Responses were durable at doses >3 mg/kg and generally reported at first disease assessment. Overall, the median duration of response based on IAC assessment was 8.31 months (range 1.9 to 16.6 months) and the median TTR was 1.84 months (range 0.9 to 5.7 months) The median duration of response was 1.91, 14.78, 8.31, and 8.33 months in the 3 mg/kg Q2W, 10 mg/kg Q2W, and 10 mg/kg Q2W/Q4W, and 20 mg/kg QW/Q2W dose groups, respectively, and the median TTR was 0.95, 1.02, 2.07, and 1.43 months, respectively. At the time of analysis, the overall median PFS was 3.6 months (95% CI: 1.91 to 9.20 months) with shorter PFS for the 3 mg/kg dose level. Kaplan-Meier estimates for overall survival were similar between the different dose groups. Medians were not reached in most of the dose groups due to the short follow-up. The highest ORR (60.0%) was observed in FcGR3 V/V variant population. The highest clinical benefit was also observed in the V/V variant (60.0%). The ORR and the clinical benefit were similar among HLA-B/KIR3DL1 variants and among KIR3DS1 variants. Lower absolute counts of TREG and CD4 T-cells were observed in blood samples for responders compared to non-responders patients. Some clinical meaningful improvements were seen in the physical functioning, fatigue and pain scales at given cycles of the HRQL data. However, given the small sample sizes, limited treatment exposure inconsistency in clinical meaningful improvement across cycles, and the lack of a comparator in the study, the HRQL data should be interpreted with caution.

Safety results: In general, the incidence of the AEs does not show an apparent dose dependency, except for drug-related TEAEs (any grade), which were less frequent at the 3 mg/kg Q2W dose level, and appear to have increased progressively in frequency at the other dose levels. The most frequently reported TEAEs by PT of any grade and regardless of causal relationship with study treatment, and across all the dose levels consisted of infusion related reaction (52 patients, 53.6%) followed by nausea (33 patients, 34.0%), fatigue (31 patients, 32.0%), upper respiratory tract infection (28 patients 28.9%), anemia (27 patients 27.8%,), diarrhea and cough (26 patients, 26.8%), headache (23 patients, 23.7%), dyspnea (22 patients, 22.7%). Eight patients died during the treatment period: 3 (3.1%) because of AEs (atrial fibrillation, cerebral hemorrhage, and sudden death) and 5 (5.2%) patients because of progressive disease. None of the AEs leading to death were treatment related. The most frequent serious TEAE consisted of pneumonia (7.2%, all Grade ≥3), followed by disease progression (6 patients, 6.2%), sepsis (5 patients, 5.2%), acute kidney injury (4 patients, 4.1%), upper respiratory tract infection and pathological fracture (3 patients, 3.1%, each), back pain, hyperviscosity syndrome, pleural effusion, asthenia, dehydration (2 patients, 2.1%, each). The distribution of the incidence of serious TEAEs does not show an apparent dose-dependency. Five (5.2%) patients had TEAEs leading to study treatment withdrawal. The most frequent TEAE was infusion related reaction (2 patients, 2.1%).The distribution of the incidence of TEAEs leading to permanent discontinuation does not show an apparent dose-dependency. Overall, IARs of any grade occurred in 50 (51.5%) patients. The majority of the IARs were Grade 2 (44 patients; 45.4%). The incidence of Grade ≥3 IARs was 2.1%, with a Grade 4 IAR in 1 patient. The incidence of IARs was the lowest at the 3 mg/kg Q2W (34.8%), compared with the other dose levels (50.0%, 48.0%, and 48.0% at 10 mg/kg Q2W, 10 mg/kg Q2W/Q4W, and 20 mg/kg QW/QW/Q2W, respectively). No apparent reason could be identified for this finding, which had not been observed in the Phase 1 of study TED10893. Lower respiratory TEAEs occurred in 55 (56.7%) patients, all grades, and 5 (5.2%) Grade ≥3. Twenty-two patients experienced lower respiratory TEAEs for all grades, and 2 patients for Grade ≥3 as IAR, 41 patients for all grades, and 3 patients for Grade ≥3 as non-IAR. Fifty-five (56.7%) patients for all grades, 5 (5.2%) patients for ≥3 grades experienced respiratory, thoracic and mediastinal disorders (HLGT). Twenty-two out of 55 patients experienced lower respiratory TEAEs for all grades, 2 patients for Grade ≥3 as IAR. Out of all 97 patients, 35 patients had respiratory medical history (MH) and 61 patients had no respiratory MH. Treatment-emergent

Grade 3-4 abnormalities, based on the laboratory findings, consisted of lymphopenia (29.0%), anemia (24.7%; no Grade 4), neutropenia (19.4%), and thrombocytopenia (16.1%). Grade 3 febrile neutropenia occurred in 1 patient, and no neutropenic infections were reported.

Pharmacokinetic results: A population PK analysis of isatuximab was performed using the data from 168 patients from Phase 1 and Phase 2 Stage 1 part of the TED10893 study at doses equal to or higher than 1 mg/kg. The PK of isatuximab was best described by a 2-compartment structural kinetic model with parallel linear and Michaelis-Menten eliminations from the central compartment (approximation of target mediated – drug disposition model). The typical estimated linear clearance was 0.00753 L/h (0.181 L/day) and the typical volume of distribution of the central compartment was 4.85 L, resulting in a half-life associated to the linear elimination of 18.6 days. The maximum binding capacity (Vmax) was 0.146 mg/L.h (3.5 mg/L.day) and the concentration of isatuximab corresponding to half maximum binding capacity (Km) was 0.046 µg/mL. Inter-individual variability for random effects associated with the model parameters ranged from 32.1% (V1) to 93.9% (CL). Residual error was low with a proportional part of 24% and an additive part of 0.018 µg/mL. The PK parameters observed in Phase 2 Stage 1 are similar to those obtained during Phase 1 part of the study. Isatuximab C_{max} and AUC 1W increased in a greater than dose-proportional manner over the dose range investigated in 3 to 20 mg/kg (12-fold increase in C_{max} and 8-fold increase in AUC 1W with a 6.67-fold increase in dose), suggesting the presence of target-mediated drug disposition with isatuximab. Repeated dosing resulted in an accumulation of 2.2 and 3.3 at Cycle 2 respectively for C_{max} and C_{trough} for the 20QW-Q2W schedule of administration. Accumulation ratios were similar at Cycle 6, showing that the steady state was reached from Cycle 2 for this administration schedule.

Issue date: 08-Jul-2024

Sponsor: Sanofi **Drug substance(s):** isatuximab	**Study Identifiers:** U1111-1116-5472, EudraCT: 2013-001418-13, NCT01084252 **Study code:** TED10893

Title of the study:

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 center(s):

17

Study period:

Date first patient enrolled: 02 JULY 2014

Study Status: Completed

Phase of development: Phase 2

Objectives:

PRIMARY OBJECTIVE:

The primary objective was to evaluate the activity of single agent isatuximab at different doses/schedules and to select dose and regimen for Phase 2 Stage 2.

SECONDARY OBJECTIVES:

The secondary objectives were to evaluate single agent isatuximab for 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 isatuximab, Immunogenicity of isatuximab, and Investigate the relationship between CD38 receptor density and CD38 receptor occupancy on multiple myeloma cells and parameters of clinical response.

Methodology:

The Phase 2 Stage 1 part (P2S1) of the trial is an open-label, international multi-center study conducted in 2 stages (1a and 1b) in patients with relapsed or relapsed/refractory multiple myeloma. In Phase 2 Stage 1a patients were randomly assigned to one of 3 treatment arms (3 mg/kg Q2W, 10 mg/kg Q2W, 10 mg/kg Q2W/Q4W) in a 1:1:1 ratio. Patients in Phase 2 Stage 1b were treated at 20 mg/kg QW/Q2W.

Number of study participants:

Planned: 96

Randomized: 72

Treated: 97

Evaluated:

Efficacy: 97

Safety: 97

Pharmacokinetics: 168 for population PK analysis, including 95 from Phase 2 Stage 1

Diagnosis and criteria for inclusion:

Patients must have a known diagnosis of multiple myeloma with evidence of measurable disease. Patients must have received prior treatment with an alkylating agent, an immunomodulatory drug (IMiD) and a proteasome inhibitor (PI). Patients must have received at least three prior lines of therapy for multiple myeloma.

Study products

Investigational medicinal product(s): SAR650984 (isatuximab).

Formulation: The cell 1, process 1, formulation 1 (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.

Route(s) of administration: Intravenous (IV) infusion.

Dose regimen: 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

Duration of treatment/participation: Patients were treated until disease progression, unacceptable adverse reaction or other reason for discontinuation.

Duration of observation: Patients were followed for a screening period of up to 3 weeks; study treatment administration and follow-up. Patients with documented disease progression at the end of treatment visit received follow-up visits at 30, 60 and 90 days after the last dose.

Criteria for evaluation:

Efficacy/pharmacodynamic: primary efficacy endpoint was overall response rate as assessed by the Independent Adjudication Committee (IAC). Secondary efficacy variables included best overall response (BOR) as assessed by the IAC from the start of treatment through the entire study excluding any time point following the start of other anti-cancer treatment for MM. The ordering of evaluations from best to worse was stringent complete response (sCR), complete response (CR), very good partial response (VGPR), partial response (PR), stable disease, progressive disease (PD), and not evaluable. Additional efficacy endpoints included clinical benefit rate (CBR), duration of response (DOR), time to response (TTR), follow-up duration (FUD), and best percent change in paraprotein.

Safety: The safety variables included adverse events (AEs), clinical laboratory parameters, physical examinations, vital signs, electrocardiograms (ECG), Karnofsky PS, immunogenicity, and cytokines (tumor necrosis factor alpha [TNF-α], interleukin-6 [IL-6], interleukin-1β [IL-1β], and interferon-γ [IFN-γ] for patients with IAR of Grade ≥2). The NCI-CTCAE v. 4.03 was used to grade the severity of AEs and laboratory results.

Immunogenicity: Samples for anti-drug antibodies (ADA) measurement were obtained just before infusion of isatuximab at Cycle 1 Day 1 and 15 and at Day 1 of subsequent cycles; and 30 and 60 days after the last infusion of isatuximab. At 60 days, in the case of a positive ADA sample, every 30 days until the sample was interpretable or negative.

Pharmacokinetics: Population PK analysis: Isatuximab plasma concentrations after single and repeated dose administrations were analyzed using a nonlinear mixed-effects modeling approach with MONOLIX software version 4.4.0 (Lixoft). A basic population PK model was developed and the following PK individual parameters were calculated:

- Cumulative AUC over a 1, 2, or 4 week interval (AUC1W, AUC2W, AUC4W)
- C_{trough} (pre-dose concentration) at 1, 2, or 4 weeks (C_{trough}1W, C_{trough}2W, C_{trough}4W)
- C_{max} at Cycle 1 Day 1, Cycle 2 Day 1 and Cycle 4 Day 1
- Clearance for linear non-specific elimination pathway
- Accumulation ratios: Ceoi ratio at Cycle 4 Day 1 versus Cycle 1 Day 1 for Arm 3 and Arm 4 ; C_{trough} ratio at Cycle 2 Day 1 versus Cycle 1 Day 15 and Cycle 4 Day 1 versus Cycle 1 Day 15 for Arms 1, 2 and 3 ; C_{trough} ratio at Cycle 2 Day 1 versus Cycle 1 Day 8 and Cycle 4 Day 1 versus Cycle 1 Day 8 for Arm 4

•Volumes (V1 and V2) and half-life associated to the linear CL

Pharmacokinetic/Pharmacodynamics sampling times and bioanalytical methods:

Pharmacokinetic/Pharmacodynamics sampling times and bioanalytical methods:

Arms 1 and 2

Blood samples for analyses of PK of isatuximab were collected Cycle 1, Day 1 predose, EOI and EOI+1h; Day 15 predose and EOI, then predose of Day 1 and Day 15 of each subsequent cycles; and 30 and 60 days after last study treatment administration.

Arm 3

Blood samples for analyses of PK of isatuximab were collected Cycle 1 Day 1 and Cycle 4 Day 1 predose, EOI and EOI+1h; Cycle 1 Day 15 predose and EOI; predose of Day 1 and Day 15 of Cycle 2 and 3; then predose of Day 1 of each subsequent cycles and 30 and 60 days after last study treatment administration.

Arm 4

Blood samples for analyses of PK of isatuximab were collected Cycle 1 Day 1 and Cycle 4 Day 1 predose, EOI and EOI+1h; Cycle 1 Day 8 predose, Cycle 1 Day 15 predose and EOI, Cycle 1 Day 22 predose; Cycle 2 and 3 Day 1 and Day 15 predose; then predose of Day 1 and Day 15 of each subsequent cycles and 30 and 60 days after last study treatment administration.

Isatuximab concentrations in plasma were measured using a validated enzyme-linked immunosorbent assay (ELISA) method with a limit of quantitation of 0.500 ng/mL.

Pharmacodynamics: CD38 receptor occupancy (RO) was assessed from bone marrow aspirates before infusion of isatuximab at Cycle 2, Day 1; at the end of treatment visit. CD38 receptor density (RD) was assessed from bone marrow aspirates at screening.

Statistical methods:

Safety

For treatment-emergent AEs (TEAEs), the incidence tables were presented for each DL and overall. Number (%) of patients experiencing TEAEs by primary system organ class and preferred term (PT) (according to MedDRA dictionary) were summarized by CTCAE grade (all grades and Grade ≥3) for the all-treated population. Similar tables were presented for drug-related TEAEs, serious TEAEs, and AEs/SAEs occurring during the pre/post treatment dosing period. Infusion associated reactions were analyzed using both the Investigator reporting and TEAEs occurring within 24 hours after each isatuximab administration. Other significant AEs consisted of respiratory AEs, neutropenic complication, second primary malignancies, symptomatic overdoses, and pregnancies.

The numbers and percentage of patients with abnormal laboratory tests at baseline and during treatment were presented by DL and grade and overall. For patients with multiple occurrences of the same laboratory variable during the on treatment period, the maximum (worst) grade per patient was used. For urate, the number and percentage of patients with a potentially clinically significant abnormality (PCSA) at baseline and during the on-treatment period was summarized by DLs and overall. For vital signs the number of patients with PCSA during the on-treatment period was summarized by DLs and overall. Karnofsky PS was mapped to Eastern Cooperative Oncology Group (ECOG) performance status (PS), and shift tables of baseline ECOG PS (Karnofsky PS) versus best/worst ECOG PS (Karnofsky PS) on treatment values were provided.

Efficacy

Efficacy endpoints were analyzed for the all-treated population. The BOR, ORR, CBR, DOR, TTR as assessed by IAC, and FUD were summarized with descriptive statistics by DL and overall. BOR, ORR and CBR were also summarized using investigator assessment of response. ORR was also summarized for each exploratory biomarker (eg, CD38 RD).

Immunogenicity

A polyethylene glycol precipitation and acid dissociation assay (PandA) was developed and validated to detect ADAs in human serum.

The number (%) of patients who had pre-existing anti-drug antibody (ADA) at baseline, who were 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.

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).

Pharmacokinetics

All individual concentrations and all PK parameters of isatuximab were tabulated using descriptive statistics: arithmetic and geometric mean, median, standard deviation (SD), coefficient of variation, minimum, maximum, for each arm. Maximum drug concentration (C_{max}) ratios and minimum drug concentration (C_{trough}) ratios were calculated between Cycle 2 and first administration of isatuximab and between Cycle 6 and first administration. AUC ratios was also calculated for the Q2W schedule.

Summary Results:

Population characteristics: From July 2014 to April 2015, a total of 97 patients were treated in Phase 2 Stage 1 part of TED10893 study at four different doses and/or schedules of administration. The median age was 62 years. As per inclusion criteria, patients were heavily pretreated as shown by median number of prior lines that was of 5 (2 to 14 lines) with 15 (26.3%) patients having received 8 or more prior lines of treatment. Overall response rate to the most recent treatment line given prior to study entry for RRMM was 28% and included 1 (1.0%) complete response, 7 (7.2%) VGPR, and 19 (19.6%) PR. During the study, median number of isatuximab cycles started was 3.

Duration of Exposure results: The median duration of exposure was 13.0 weeks (range 2-414 weeks). The median duration of exposure was the lowest in the 3 mg/kg Q2W (6.0 weeks) dose group and was consistently ≥14 weeks in ≥10 mg/kg arms

Efficacy results: In the analysis for the all-treated population, the overall ORR based on IAC assessment was 19.6% (19 patients out of 97), including 4.3% for 3 mg/kg Q2W, 29.2% for 10 mg/kg Q2W, 20% for 10 mg/kgQ2W/Q4W, and 24% for 20 mg/kg QW/Q2W. The evaluation of the results between the 4 arms should be performed with cautions with 20 m/kg QW/Q2W arm started after the enrollments in the 3 mg/kg Q2W, 10 mg/kg Q2W and 10 mg/kg Q2W/Q4W arms were completed. Therefore, given the small sample size in each arm, despite 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, no conclusion can be drawn based on ORR at doses ≥ 10 mg/kg. Based on IAC assessment, overall, 11 (11.3%) patients achieved VGPR, and 8 (8.2%) patients achieved PR. Six (25.0%) patients in the 10 mg/kg Q2W group achieved VGPR, and 2 (9.0%) patients in the 20 mg/kg QW/Q2W achieved VGPR. Overall, 28 (28.9%) patients achieved CBR (MR or better). Thirty one (32.0%) patients had SD. In a subgroup analysis, patients <70 years of age had ORR (≥PR) of 16.5% (13 of 79 patients), of which 7 (8.9%) had VGPR, and 6 (7.6%) had PR. For patients >70 years of age, the ORR (≥PR was 33.3% (6 of 18 patients), of which 4 (22.2%) had VGPR, and 2 (11.1%) had PR. Eighty-nine out of 97 patients were refractory to IMiD at study entry. Of these, 19 (21.3%) achieved ORR (≥ PR), of which 11 (12.4%) had VGPR, and 8 (9.0%) had PR. Eight patients was not refractory to IMiD at study entry. Of these, no patient achieved ORR. Eighty-seven out of 97 patients were refractory to PI at study entry. Of these, 17 (19.5%) achieved ORR (≥ PR), of which 10 (11.5%) achieved VGPR, and 7 (8.0%) achieved PR. Ten patients were not refractory to PI at study entry. Of those, 2 (20.0%) achieved ORR (≥ PR), 1 (10.0%) had VGPR, and 1 (10.0%) had PR. Responses were durable at doses >3 mg/kg and generally reported at first disease assessment. Overall, the median duration of response based on IAC assessment was 8.31 months (range 1.9 to 16.6 months) and the median TTR was 1.84 months (range 0.9 to 5.7 months) The median duration of response was 1.91, 14.78, 8.31, and 8.33 months in the 3 mg/kg Q2W, 10 mg/kg Q2W, and 10 mg/kg Q2W/Q4W, and 20 mg/kg QW/Q2W dose groups, respectively, and the median TTR was 0.95, 1.02, 2.07, and 1.43 months, respectively. At the time of analysis, the overall median PFS was 3.6 months (95% CI: 1.91 to 9.20 months) with shorter PFS for the 3 mg/kg dose level. Kaplan-Meier estimates for overall survival were similar between the different dose groups. Medians were not reached in most of the dose groups due to the short follow-up. The highest ORR (60.0%) was observed in FcGR3 V/V variant population. The highest clinical benefit was also observed in the V/V variant (60.0%). The ORR and the clinical benefit were similar among HLA-B/KIR3DL1 variants and among KIR3DS1 variants. Lower absolute counts of TREG and CD4 T-cells were observed in blood samples for responders compared to non-responders patients. Some clinical meaningful improvements were seen in the physical functioning, fatigue and pain scales at given cycles of the HRQL data. However, given the small sample sizes, limited treatment exposure inconsistency in clinical meaningful improvement across cycles, and the lack of a comparator in the study, the HRQL data should be interpreted with caution.

Safety results: In general, the incidence of the AEs does not show an apparent dose dependency, except for drug-related TEAEs (any grade), which were less frequent at the 3 mg/kg Q2W dose level, and appear to have increased progressively in frequency at the other dose levels. The most frequently reported TEAEs by PT of any grade and regardless of causal relationship with study treatment, and across all the dose levels consisted of infusion related reaction (52 patients, 53.6%) followed by nausea (33 patients, 34.0%), fatigue (32 patients, 33.0%), upper respiratory tract infection (28 patients 28.9%), anemia (28 patients 28.9%,), cough (27 patients, 27 .8%), diarrhea (26 patients, 26.8%) ,headache (24 patients, 24.7%), dyspnea (22 patients, 22.7%). Eight patients died during the treatment period: 3 (3.1%) because of AEs (atrial fibrillation, cerebral hemorrhage, and sudden death) and 5 (5.2%) patients because of progressive disease. None of the AEs leading to death were treatment related. The most frequent serious TEAE consisted of pneumonia (7.2%, all Grade ≥3), followed by disease progression (6 patients, 6.2%), sepsis (5 patients, 5.2%), acute kidney injury (4 patients, 4.1%), upper respiratory tract infection and pathological fracture (3 patients, 3.1%, each), back pain, hyperviscosity syndrome, pleural effusion, influenza, dehydration (2 patients, 2.1%, each). The distribution of the incidence of serious TEAEs does not show an apparent dose-dependency. Five (5.2%) patients had TEAEs leading to study treatment withdrawal.The distribution of the incidence of TEAEs leading to permanent discontinuation does not show an apparent dose-dependency. Overall, IARs of any grade occurred in 50 (51.5%) patients. The majority of the IARs were Grade 2 (44 patients; 45.4%). The incidence of Grade ≥3 IARs was 2.1%, with a Grade 4 IAR in 1 patient. The incidence of IARs was the lowest at the 3 mg/kg Q2W (34.8%), compared with the other dose levels (50.0%, 48.0%, and 48.0% at 10 mg/kg Q2W, 10 mg/kg Q2W/Q4W, and 20 mg/kg QW/QW/Q2W, respectively). Lower respiratory TEAEs occurred in 55 (56.7%) patients, all grades, and 5 (5.2%) Grade ≥3. Twenty-two patients experienced lower respiratory TEAEs for all grades, and 2 patients for Grade ≥3 as IAR, 41 patients for all grades, and 3 patients for Grade ≥3 as non-IAR. Fifty-five (56.7%) patients for all grades, 5 (5.2%) patients for ≥3 grades experienced respiratory, thoracic and mediastinal disorders (HLGT). Twenty-two out of 55 patients experienced lower respiratory TEAEs for all grades, 2 patients for Grade ≥3 as IAR. Out of all 97 patients, 35 patients had respiratory medical history (MH) and 61 patients had no respiratory MH. Treatment-emergent Grade 3-4 abnormalities, based on the laboratory findings, consisted of lymphopenia (29.0%), anemia (24.7%; no Grade 4), neutropenia (19.4%), and thrombocytopenia (16.1%). Grade 3 febrile neutropenia occurred in 1 patient, and no neutropenic infections were reported.

Pharmacokinetic results: A population PK analysis of isatuximab was performed using the data from 168 patients from Phase 1 and Phase 2 Stage 1 part of the TED10893 study at doses equal to or higher than 1 mg/kg. The PK of isatuximab was best described by a 2-compartment structural kinetic model with parallel linear and Michaelis-Menten eliminations from the central compartment (approximation of target mediated – drug disposition model). The typical estimated linear clearance was 0.00753 L/h (0.181 L/day) and the typical volume of distribution of the central compartment was 4.85 L, resulting in a half-life associated to the linear elimination of 18.6 days. The maximum binding capacity (Vmax) was 0.146 mg/L.h (3.5 mg/L.day) and the concentration of isatuximab corresponding to half maximum binding capacity (Km) was 0.046 µg/mL. Inter-individual variability for random effects associated with the model parameters ranged from 32.1% (V1) to 93.9% (CL). Residual error was low with a proportional part of 24% and an additive part of 0.018 µg/mL. The PK parameters observed in Phase 2 Stage 1 are similar to those obtained during Phase 1 part of the study. Isatuximab C_{max} and AUC 1W increased in a greater than dose-proportional manner over the dose range investigated in 3 to 20 mg/kg (12-fold increase in C_{max} and 8-fold increase in AUC 1W with a 6.67-fold increase in dose), suggesting the presence of target-mediated drug disposition with isatuximab. Repeated dosing resulted in an accumulation of 2.2 and 3.3 at Cycle 2 respectively for C_{max} and C_{trough} for the 20QW-Q2W schedule of administration. Accumulation ratios were similar at Cycle 6, showing that the steady state was reached from Cycle 2 for this administration schedule.

Issue date: 08-Jul-2024

Sponsor: Sanofi **Drug substance(s):** isatuximab	**Study Identifiers:** U1111-1116-5472, EudraCT: 2013-001418-13, NCT01084252 **Study code:** TED10893

Title of the study:

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 (TED10893 Phase 2 Stage 2)

Study center(s):

Participants were enrolled and randomized at 45 sites in 16 countries. The countries with the largest enrollment were United States (29 participants), Brazil (17 participants), Greece (17 participants), Italy (15 participants), and Russian Federation (13 participants)

Study period:

Date first patient enrolled: 27 December 2016

Date last participant last study visit: 13 July 2023

Study Status: Completed

Phase of development: TED10893, the first-in-human study of isatuximab, was originally designed as a Phase 1 dose-escalation trial. The study protocol was subsequently amended to include a Phase 2, Stage 1a and 1b parts; and a Phase 2, Stage 2 part. The results of the Phase 1 and Phase 2, Stage 1 parts of the study are presented in 2 separate reports.

Objectives:

Primary:

The primary objective of the Phase 2, Stage 2 part of the study was to evaluate the activity in terms of overall response rate (ORR) of isatuximab at the selected dose/schedule from Phase 2, Stage 1, as a single agent (ISA arm) and in combination with dexamethasone (ISAdex arm) in patients with relapsed or relapsed/refractory multiple myeloma (RRMM).

Secondary:

The secondary objectives of the Phase 2, Stage 2 part of the study were 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)
- Pharmacokinetic profile of isatuximab
- Immunogenicity of isatuximab

Methodology:

The Phase 2, Stage 2 part of the TED10893 study was an open-label, randomized, multicenter study designed to evaluate the activity and safety of isatuximab (cell line 1, process 2, isatuximab formulation 2, [C1P2F2]) with or without dexamethasone in patients with relapsed or RRMM who had previously received an immunomodulatory imide drug (IMiD) and a proteasome inhibitor (PI).

Patients were randomly assigned to one of the 2 treatment arms in a 2:1 ratio. The dose and schedule of isatuximab (ISA arm) were selected from the interim analysis of the Phase 2, Stage 1 part of the study: 20 mg/kg every week for 4 infusions followed by 20 mg/kg every 2 weeks of subsequent cycles (28-day cycle). This dose was determined based on response rate along with safety, PK, pharmacodynamics (PDy), and overall efficacy from Phase 1 and Phase 2, Stage 1. For patients in the ISAdex arm, dexamethasone was administered at a dose of 40 mg/day (20 mg/day for patients ≥75 years) on Days 1, 8, 15, and 22 of each cycle.

Number of study participants:

Planned: 160

Randomized: 165

Treated:164

Evaluated:

Efficacy: 164

Safety: 164

Pharmacokinetics: 161

Diagnosis and criteria for inclusion:

All patients had to be ≥18 years old; have an Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≤2; and have adequate hematologic, renal, and liver function.

In addition to the criteria noted above, all patients must have had a known diagnosis of MM (IgM subtype was not permitted) with evidence of measurable disease as defined by M-protein (serum M-protein of ≥1.0 g/dL or ≥0.5 g/dL in case of IgA disease, or urine M-protein of ≥200 mg [24-hr urine]) or in the absence of measurable M-protein serum immunoglobulin free light chain (FLC) of ≥10 mg/dL, with abnormal serum immunoglobulin kappa lamda FLC ratio (<0.26 or >1.65). Patients were to have received prior treatment with an IMiD and a proteasome inhibitor, and have had received at least 3 prior lines of therapy for MM, or whose disease is double refractory to an IMiD and a PI. Patients were to have received an alkylating agent for ≥2 cycles or ≥2 months either alone or in combination with other MM treatments.

No exposure to prior treatment with anti-CD38 therapy, no other prior anticancer therapy (chemotherapy or surgery) was permitted within 21 days of study treatment except for systemic radiation within 28 days and localized radiation within 7 days. Dexamethasone could be used up to 21 days or within 5 drug half-lives ($t_{1/2}$). Patients who underwent autologous stem cell transplantation (ASCT) within 12 weeks of study entry and/or prior allogeneic transplant within 1 year or had evidence of graft versus host disease (GVHD) requiring >10 mg prednisone were not permitted.

Study products

Investigational medicinal product(s): Investigational medicinal product(s): Isatuximab (SAR650984) process and formulation (cell 1, process 2, isatuximab formulation 2 [C1P2F2]) drug product.

Formulation: Isatuximab 20 mg/mL (500 mg/25 mL) in a 20 mM histidine, 10% (w/v) sucrose, and 0.02% (w/v) polysorbate 80, pH 6.0 buffer.

Route(s) of administration: Intravenous (IV)

Dose regimen: Isatuximab 20 mg/kg on Days 1, 8, 15, and 22 (QW) of Cycle 1 (28-day cycle) followed by 20 mg/kg on Days 1 and 15 (Q2W) of subsequent cycles.

Noninvestigational medicinal product: Dexamethasone

Formulation: Oral dexamethasone was supplied to European and Latin American countries. Commercially available dexamethasone (oral and IV) was used for this study in the United States. In all other countries, commercially available dexamethasone (IV) was used; Investigators were to refer to the United States Product Insert (USPI) or Summary of Product Characteristics (SmPC) for details.

Route(s) of administration: IV or orally (PO)

Dose regimen: Dexamethasone 40 mg/day in patients <75 years old, and 20 mg/day ≥75 years old, on Days 1, 8, 15, and 22 of each 28-day cycle. Administration of dexamethasone was used as part of premedication and followed the premedication rules. (Note: most sites used oral dexamethasone.)

Duration of treatment:

Patients were treated until unacceptable toxicity, disease progression, death, withdrawal of consent, Investigator's decision to withdraw the patient, and/or availability of treatment.

Duration of observation:

Patients were followed for a Screening Period of up to 3 weeks; a Study Treatment Period every week for 4 weeks (28-day cycle) and a Post-Treatment Follow-Up Period of at least 60 days. For patients who discontinued study treatment due to disease progression, follow-up visits were to occur every 3 months until death or end of study, whichever came first. Patients without disease progression were followed-up for efficacy and safety every 4 weeks until disease progression, and then were followed every 3 months until death or cutoff date, whichever came first.

Criteria for evaluation:

Efficacy:

Efficacy assessments included overall response rate (ORR), duration of response (DOR), clinical benefit rate (CBR), progression free survival (PFS), and overall survival (OS).

Safety:

Safety variables included adverse events (AEs), clinical laboratory parameters (blood and urine), vital signs, physical examinations, chest X-ray, tumor lysis syndrome (TLS), and at baseline only, electrocardiograms (ECGs). The National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.03 (NCI CTCAE v. 4.03) was used to grade the severity of AEs and laboratory results. The Observation Period for safety included the Pretreatment Period defined as the time from when the patients gave informed consent to the start of study treatment; the On-Treatment Period defined as the time from first dose of study treatment up to 30 days after the last dose of study treatment; and the Post-Treatment Period defined as the time from 31 days after the last dose of study treatment to the study closure.

Immunogenicity:

Samples for the measurement of anti-drug antibodies (ADAs) were obtained before infusion of isatuximab at Day 1 and Day 15 of Cycle 1; then at predose of Day 1 of subsequent cycles; and 30 days and 60 days after the last infusion of isatuximab. In the case of a positive or inconclusive ADA sample at the end of study, additional assessment of ADA were performed every 30 days until the sample was negative.

Biomarkers:

Biomarker assessments included immune genetic determinants, immune phenotypes, repertoire clonality, and minimal residual disease (MRD).

Pharmacokinetics:

Plasma isatuximab concentrations after single and repeated dose administrations were collected for a population PK analysis using a nonlinear mixed-effects modeling approach with MONOLIX software version 2016 R1 (or more recent version) (Lixoft). Individual estimates of PK parameters were obtained using parameter estimates from the basic population model developed in TED10893 Phase 1 and Phase 2, Stage 1 (POH0458 study) as priors (Empirical Bayes estimates) and individual concentrations. Exposure parameters (maximum concentration [C_{max}], predose concentration [C_{trough}] and cumulated area under the plasma concentration versus time curve [AUC]) were derived using the individual parameters and the following parameters were provided:

- AUC over a 1, 2, or 4 week interval (AUC1W, AUC2W, AUC4W)
- C_{trough} at 1, 2, and 4 weeks (C_{trough} 1W, C_{trough}2W, and C_{trough} 4W)
- C_{max} at Cycle 1 Day 1, Cycle 2 Day 1, and Cycle 4 Day 1
- Clearance (CL) for linear non-specific elimination pathway
- Central (V1) and peripheral (V2) volumes of distribution
- Half-life (T1/2) associated to the linear CL

Accumulation ratios: Observed C_{eoi} ratio at Cycle 4 Day 1 versus Cycle 1 Day 1; Observed C_{trough} ratio at Cycle 2 Day 1 versus Cycle 1 Day 8 and Cycle 4 Day 1 versus Cycle 1 Day 8

Pharmacokinetic/Pharmacodynamics sampling times and bioanalytical methods:

Isatuximab concentrations in plasma were measured using a validated enzyme-linked immunosorbent assay (ELISA) method with a lower limit of quantitation (LLOQ) of 0.500 ng/mL.

Blood samples for analyses of PK of isatuximab were collected Cycle 1 Day 1 and Cycle 4 Day 1 predose, EOI and EOI +1 h; Cycle 1 Day 8 predose, Cycle 1 Day 15 predose and EOI, Cycle 1 Day 22 predose; Cycle 2 and 3 Day 1 predose and EOI, and Cycle 2 and 3 Day 15 predose; then predose of Day 1 and Day 15 of each subsequent cycles and 30 days after last study treatment administration.

Statistical methods:

Four analysis populations were defined for the statistical analysest:

- The Randomized Population included all patients who gave their informed consent and were assigned a randomization number by the interactive voice response system (IVRS)/ interactive web response system (IWRS).
- The All Treated [AT]/Safety Population included all randomized patients who gave their informed consent and who received at least 1 dose (even incomplete) of isatuximab. Patients who received dexamethasone in addition to isatuximab (excluding when given as part of premedication) were included in the ISAdex arm. Nonrandomized but treated patients were not part of the safety population; their safety data were presented separately.
- The PK Population included all patients from the Safety Population who had a PK parameter.
- The ADA Population included all patients from the AT Population with at least 1 ADA assessment with a reportable result during the ADA On-Study Observation Period.

Efficacy**:**

The ORR was summarized with descriptive statistics. A 95% two sided confidence interval was computed using Clopper-Pearson method. In addition, for exploratory purpose, ORR and VGPR or better rate according to IAC assessment between the 2 arms was compared using the Fisher exact test, one sided. For Stage 2, the null hypothesis that the true response rate (ORR) was <15% was tested for each arm using a one-sided exact binomial test with a significance level of 0.025.

Kaplan-Meier estimates such as median and Kaplan-Meier curves were provided for DOR, PFS, and OS. The log rank test (1-sided test) from the comparison of PFS between the 2 arms was provided. The PFS was analyzed based upon all treated population.

Safety**:**

The primary analysis of safety data was based on treatment-emergent adverse events (TEAEs). Summary tables were presented by treatment group (ISA and ISAdex), and overall. The number and (%) of patients experiencing TEAEs were tabulated by primary system organ class (SOC) and preferred term (PT), and coded using the version of Medical Dictionary for Regulatory Activities (MedDRA) version 20.1. Similar tables were presented for drug-related TEAEs, serious TEAEs, and AEs/SAEs occurring during the pre/post treatment dosing period. The severity of TEAEs was assessed according to the NCI CTCAE v. 4.03. Infusion reactions (IRs) were analyzed using both the Investigator reporting and TEAEs occurring within 24 hours after each isatuximab administration. Other significant AEs consisted of symptomatic overdoses, pregnancies, respiratory AEs, and hematological adverse events (neutropenia from laboratory abnormalities, neutropenic infections, and febrile neutropenia).

The numbers of patients with abnormal laboratory tests at baseline and during treatment were presented by all grades and each grade. For patients with multiple occurrences of the same laboratory variable during the on treatment period, the maximum (worst) grade per patient was used. Shift tables showing the number of patients in each grade at baseline by worst grade during the on-treatment period were provided for selected laboratory tests. In the analysis of laboratory parameters, only local results were used. For creatinine clearance, the number (%) of patients by potentially clinically significant abnormality (PCSA) category and by period, as well as a shift table was provided. For urate, chloride, and blood urea nitrogen (BUN), the number of patients with a PCSA during the on-treatment period was summarized.

Shift tables showing the number of patients in each grade at baseline by best grade and worst grade on treatment were provided for ECOG PS. A listing of patients with tumor lysis syndrome (TLS) reported in electronic case report form (eCRF) AE forms (using a Standardized MedDRA Query [SMQ]: tumor lysis syndrome) during the study were provided with clinical chemistry parameters listed to corroborate the report.

Immunogenicity**:**

A polyethylene glycol precipitation and acid dissociation assay (PandA) was developed and validated to detect ADA in human serum. The number (%) of patients who had pre-existing ADA at baseline, treatment-boosted ADA, treatment-induced ADA, transient ADA, persistent ADA, and indeterminate ADA were summarized. ADA response endpoints included:

- An ADA positive patient, defined as a patient with at least 1 treatment-induced or treatment-boosted ADA positive sample at any time during the ADA on-study observation period.
- ADA incidence, defined as the number of ADA positive patients among evaluable patients divided by the number of patients in the ADA evaluable population.

- ADA prevalence, defined as the sum of the number of patients with pre-existing ADA among evaluable patients and the number of patients with treatment-induced ADAs, divided by the number of patients in the ADA Evaluable Population.

Pharmacokinetics**:**

All PK parameters of isatuximab were tabulated using descriptive statistics: arithmetic and geometric mean, median, standard deviation (SD), coefficient of variation (CV), 5^{th} and 95^{th} percentiles. In addition, steady state (based on C_{trough}) was assessed as well as the extent of the accumulation.

A summary (number of patients, mean, and percentage of coefficient of variation [CV]) of observed C_{trough} of isatuximab by visit was provided. A listing of observed C_{trough} for individual patient was also provided. Observed C_{trough} was kept for the descriptive statistics if sampling occurred within 7 days ±1 day after the previous start of infusion for sampling done during Cycle 1 and within 14 days ±3 days after the previous start of infusion for sampling done for subsequent cycles up to Cycle 10.

Summary Results:

Population characteristics:

A total of 164 randomized patients (109 in the ISA arm; 55 in the ISAdex arm) were treated and included in this analysis. The median age was 68.0 years (range 37 to 84 years) in the ISA arm and 66.0 years (range 42 to 85 years) in the ISAdex arm. Patients had been heavily pretreated with a median number of prior lines of therapy that was 4.0 in both arms; in addition, 43 (39.4%) patients in the ISA arm and 21 (38.1%) patients in the ISAdex arm had received ≥5 prior lines of therapy. As per inclusion criteria, 90.8% of patients in ISA arm and 89.1% of patients in ISAdex arm were refractory to their last regimen of anticancer treatment (IMiD, PI, IMiD and PI, IMiD or PI, and alkylating agent).

The median number of cycles was 5.5 (5.0 ISA arm; 7.0 ISAdex arm) with a median duration of exposure of 22.0 weeks (18.86 ISA arm; 30.00 ISAdex arm) as of data cutoff date.

Efficacy results:

The final analysis confirms the efficacy of isatuximab monotherapy in heavily pre-treated patients with RRMM. The addition of dexamethasone increased primary endpoint of overall response rate (ORR), as determined by IAC with 26 (23.9%) patients in the ISA arm and 24 (43.6%) patients in the ISAdex arm achieved ORR. The difference between the ISA arm and the ISAdex arm was considered significant, with a p-value of 0.0083.

Twice as many patients in the ISAdex arm achieved VGPR or better (9.2% patients in ISA arm, 20.0% patients in the ISAdex arm) (p value 0.0460).

The addition of dexamethasone resulted in strong trend in improvement in PFS (median progression free survival (PFS) from 4.86 to 10.15 months (HR=0.677, p-value=0.0743) and Overall Survival (HR=0.799, p-value=0.3808).

Safety results: Over 90% of the patients in both arms experienced at least 1 TEAE (92.7% ISA arm; 92.7% ISAdex arm) and 55.5% had at least 1 Grade ≥3 TEAE (50.5% ISA arm; 65.5% ISAdex arm).

In the ISA arm, TEAEs (≥10%, all grades), regardless of relationship to study treatment, were infusion related reaction (40.4%), diarrhea (21.1%), back pain (19.3%), cough (17.4%), fatigue, and dyspnea (17.4% each), nausea (14.7%), headache (13.8%), and upper respiratory tract infections (12.8%).

In the ISAdex arm, TEAEs (≥10%, all grades), regardless of relationship to study treatment were, infusion related reaction (40.0%), insomnia (25.5%), diarrhea and cough（21.8% each）, fatigue and pain in the extremity (20% each), back pain and upper respiratory tract infections (16.4% each), headache, dyspnea, nausea and pyrexia 14.5% each), nasopharyngitis, pneumonia and asthenia (12.7% each).

Overall, there were 81 deaths reported during the study (56 [51.4.%] ISA; 25 [45.5%] ISAdex); two of the deaths were considered to be related to study treatment.

Serious TEAEs (all grades) were reported in 47.7% in the ISA arm and 49.1% in the ISAdex arm. Serious TEAEs (Grade ≥3) in ISA arm were pneumonia (7.3%) and disease progression (6.4%), acute kidney injury (3.7%), sepsis, infusion related reaction and anemia (2.8% each). In the ISAdex arm, Serious TEAEs (Grade ≥3) were pneumonia (9.1%),bronchitis and acute kidney injury (5.5% each), disease progression, and sepsis (3.6% each).

Overall, the incidence of infusion related reactions (all grades) was 40.4% in the ISA arm and 40.0% in the ISAdex arm. The relative majority of the IRs in both arms were Grade 2 IRs were reported in 31.2% of the patients in the ISA arm and 34.5% in the ISAdex arm; and Grade 3 IRs were reported in 4.6% of the patients in the ISA arm and 1.8% in the ISAdex arm. One Grade 4 IR were reported in the ISAdex arm by Patient. All the IR episodes occurred during the first infusion regardless of treatment arms. In all the patients, the IRs were resolved on the same day that they occurred.

Overall, the incidence of TEAEs (all grades) leading to definitive study treatment discontinuation was 11.9% in the ISA arm and 5.5% in the ISAdex arm.

The addition of dexamethasone did not add major toxicity, showing a similar incidence of serious TEAE, discontinuations due to TEAE, and fatal TEAEs. However, there was a 15%% difference in Grade 3 or higher AE, with 50.5% of patients in the ISA arm experiencing a Grade ≥3 event and 65.5% of ISAdex patients experiencing a Grade ≥3 event. There were no meaningful

differences in all grade or Grade ≥3 infusion reactions, or all grade or Grade ≥3 infections; however, difference in all grade GI AEs, in particular more incidence of vomiting and constipation in ISA arm (12.8% and 10.1% respectively) versus ISAdex arm (5.5% and 7.3% respectively) and all grade psychiatric events, in particular insomnia in 25.5% of patients in the ISAdex arm versus 1.8% of patients in the ISA treatment arm.

Hematological abnormalities on treatment included Grade 3 or 4 hematological abnormalities consisted of Grade 3 (no Grade 4) anemia (22.9% ISA arm; 14.8% ISAdex arm); decreased white blood cell; Grade 3 (12.8% ISA arm; 9.3% ISAdex arm) Grade 4 (0..9% ISA arm; 1.9% ISAdex arm) decreased platelet count Grade 3 (10.1% ISA arm; 3.7% ISAdex arm), Grade 4 (8.3% ISA arm, 11.1% ISAdex arm) decreased lymphocyte count Grade 3 (21.1% ISA arm, 29.6% ISAdex) Grade 4 (6.4% ISA arm, 20.4% ISAdex, and decreased neutrophil count Grade 3 (14.7% ISA arm; 11.1% ISAdex arm), Grade 4 (3.7 ISA arm, 1.9% ISAdex arm).

Overall, the safety profile was consistent between the ISA and ISAdex treatment groups.

Anti-isatuximab antibodies were evaluable in 160 of the 164 patients treated in this study. Of the 160 patient samples tested, 1 (0.6%) patient in the ISA arm had a positive treatment induced ADA sample at Cycle 1, Day 15. The subsequent samples (Cycle 2 up to Cycle 4) were negative and therefore the ADA in this patient was considered transient positive. Overall, both the ADA incidence and ADA prevalence were calculated as 0.6%.

Pharmacokinetic results:

The PK of isatuximab was described by a 2-compartment structural kinetic model with parallel linear and Michaelis-Menten eliminations from the central compartment (approximation of target mediated - drug disposition model). The typical estimated linear clearance was 0.00567 L/h (0.136 L/day) and the typical volume of distribution of the central compartment was 4.13 L, resulting in a half-life associated to the linear clearance of 53.8 days. The maximum binding capacity (V_{max}) was 0.147 mg.L/h (3.53 mg.L/day) and the concentration of isatuximab corresponding to half maximum binding capacity (Km) was 0.0445 µg/mL. Interindividual variability for random effects associated with the model parameters ranged from 52% (V1) to 112% (Q). Residual error was low with a proportional part of 29.8% and an additive part of 0.0087 µg/mL. Steady-state was reached in 43 days (6.1 weeks) for 50% of the patients. PK parameters were similar for ISA and ISAdex arms showing that dexamethasone had no effect on the pharmacokinetics of isatuximab.

Issue date: 08-Jul-2024