Sponsor: Sanofi **Drug substance(s):** isatuximab/SAR650984	**Study Identifiers:** UTN: U1111-1195-6028 NCT03733717 **Study code:** TED15085
Title of the study: An open-label, multi-center study to evaluate the pharmacokinetics, safety, and preliminary efficacy of isatuximab in Chinese patients with relapsed and/or refractory multiple myeloma (TED15085)	
Study center(s): 3 study centers in China	
Study period: Study Initiation Date (first patient enrolled): 22 October 2018 Primary Completion Date: 06 September 2020	
Phase of development: Phase 1	
Objectives: Primary objective: • To evaluate the pharmacokinetics (PK) of isatuximab at 20 mg/kg in Chinese patients with relapsed and/or refractory multiple myeloma (MM). Secondary objectives: • To evaluate the safety and tolerability of isatuximab at 20 mg/kg in Chinese patients with relapsed and/or refractory MM. • To assess the preliminary antitumor effect of isatuximab at 20 mg/kg in Chinese patients with relapsed and/or refractory MM. • To evaluate the immunogenicity of isatuximab in Chinese patients.	
Methodology: This was an open-label, nonrandomized, single arm, multi-center Phase 1 study of isatuximab administered by intravenous (IV) infusion as a single agent in Chinese adult patients with relapsed and/or refractory MM	
Number of participants: Planned: 20 Enrolled: 26 Treated: 21 **Evaluated:** Efficacy: 21 Safety: 21 Pharmacokinetics: 20	

Diagnosis and criteria for inclusion: Patients had to have a known diagnosis of symptomatic MM; patients had to have received at least 2 prior lines of therapies which must include treatment with at least 1 of an immunomodulatory drug (IMiD) or a progression inhibitor (PI) (the patients had to have received an IMiD or a PI for ≥2 cycles or ≥2 months of treatment); patients had to have been responsive to at least 1 prior line of therapy (minimal response or better); refractory to the most recently received IMiD or PI included therapy; for patients who had received more than 1 type of IMiD or PI, their disease had to be refractory to the most recent one; patients with measurable disease defined as at least 1 of the following: serum M-protein ≥0.5 g/dL (≥5 g/L); urine M-protein ≥200 mg/24 hours.
Study products **Investigational medicinal product(s):** Isatuximab Formulation: Solution for injection Route(s) of administration: Intravenous infusion Dose regimen: 20 mg/kg once every week (QW) in Cycle 1 (4 weeks) followed by 20 mg/kg once every 2 weeks (Q2W) in subsequent cycles
Premedications prior to isatuximab infusion: Methylprednisolone (or equivalent) along with diphenhydramine (or equivalent), ranitidine (or equivalent), and acetaminophen Route(s) of administration: intravenous or oral Dose regimen: Methylprednisolone 100 mg (or equivalent), diphenhydramine 25 to 50 mg (or equivalent), ranitidine 50 mg (or equivalent), and acetaminophen 650 to 1000 mg

Duration of treatment:

All patients received isatuximab at 20 mg/kg, administered IV QW in Cycle 1 followed by Q2W in subsequent cycles. Each cycle had a duration of 4 weeks.

Duration of observation:

The duration of the study for an individual patient included a period to assess eligibility (screening or baseline period) of up to 21 days, a treatment period of repeated 28-day cycles of study treatment, and a follow-up period.

Criteria for evaluation:

Efficacy: All efficacy endpoints were defined as secondary endpoints. The following efficacy endpoints were derived for the study: overall response rate (ORR), duration of Response (DOR), time to first response (TT1R), time to best response (TTBR), time to progression (TTP), progression free survival (PFS), and overall survival (OS).

Safety: The safety profile was assessed from the findings of physical examination, laboratory tests, and reports of AEs, etc, and was based on incidence, severity (as graded by the NCI-CTCAE version 4.03).

Pharmacokinetics: Following isatuximab PK parameters were derived from plasma concentrations observed after the first administration: C_{eoi}: concentration observed at the end of an IV infusion; C_{max}: maximum observed concentration; t_{max}: time to reach C_{max}; $Clast$: last concentration observed above the lower limit of quantitation; t_{last}: time of Clast; AUC_{last}: area under the plasma concentration versus time curve calculated using the trapezoidal method from time zero to t_{last}; AUC_{tau}: area under the plasma concentration versus time curve calculated using the trapezoidal method over the dosing interval, ie, 168h. AUC_{tau} corresponds to $AUC_{0\text{-}168h}$.

Additionally, C_{trough} (concentration observed just before investigational medicinal product [IMP] administration during repeated dosing) and C_{eoi} were provided beyond the first administration and up to Cycle 10 and Cycle 4, respectively.

Immunogenicity: The presence of human antidrug antibodies (ADA) against isatuximab was assessed throughout the study.

Pharmacokinetic/Pharmacodynamics sampling times and bioanalytical methods:

Blood samples for analyses PK of isatuximab were collected Cycle 1 Day 1 at predose (start infusion), end of infusion (EOI), and 4 hours post EOI, 24h (Day 2), 48h (Day 3), 72h (Day 4). At predose on Day 8, Day 15, and Day 22. At predose and EOI at Cycle 2 Day 1 then at predose at Cycle 2 Day 15; Cycle 3 Day 1 and Day 15. At Cycle 4 Day 1, at predose, EOI and 1h after EOI, and predose on Day 15; subsequent cycles up to Cycle 10 at predose on Day 1 and Day 15.

Isatuximab concentrations were determined in plasma with an immunoassay using a Gyrolab Platform with a lower limit of quantification (LLOQ) of 5.00 µg/mL (DOH1586).

Statistical methods:

Analysis population included the following:

The all treated/safety population included all patients who had given their informed consent and who had received at least one dose (even incomplete) of isatuximab. This population was the primary population for the analyses of efficacy and safety parameters.

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

The ADA evaluable population included all treated/safety population with at least one ADA assessment during the ADA on-study observation period with a reportable result.

Safety:

All safety analyses were performed on the treated/safety population, unless otherwise specified, the baseline value was defined as the last available value before the first isatuximab administration. The primary focus of adverse event (AE) reporting was on treatment-emergent adverse events (TEAEs). Pre-treatment and post-treatment AEs were described separately. All TEAEs, TEAEs related to isatuximab, treatment-emergent serious adverse events (TESAEs) related to Isatuximab, TEAEs leading to permanent treatment discontinuation, TEAEs leading to death and Infusion reactions (IRs) were summarized or listed separately.

Efficacy:

All analyses of efficacy endpoints were performed using the all treated/safety population. Overall response rate was summarized with descriptive statistics. Kaplan-Meier estimates such as 25th, 50th, and 75th percentiles and 95% CIs, and Kaplan-Meier curves were provided for DOR for patients who had a response (≥partial response [PR]), TTP, PFS, and OS.

Analysis for TT1R and TTBR was descriptive only. Response endpoints including M-protein quantification in serum and 24-hour urine and serum free light chain (FLC) were summarized using descriptive statistics.

Pharmacokinetics:

Pharmacokinetic parameters of isatuximab were summarized by descriptive statistics (such as mean, geometric mean, median, standard deviation, standard error of mean, coefficient of variation, minimum, and maximum).

Immunogenicity:

Using the ADA evaluable population, the number (%) of patients was planned to be provided for the following if at least one positive observed: pre-existing ADA, ADA negative at baseline, on study ADA (including treatment-induced ADA, persistent ADA, transient ADA, indeterminate ADA, treatment boosted ADA), ADA positive subject, ADA prevalence, and ADA incidence.

Summary Results: The data cut-off date as defined in the protocol (1 year after last patient treated) was 06 September 2020. The results at the time of this analysis are presented in this core part clinical study report.

Population characteristics:

A total of 26 patients were screened from three sites in China. Among them, 21 patients received at least one dose of study treatment.

The median age of patients was 58 years (range 46 to 72 years) and the majority of patients were <65 years. More than half (52.4%) of the patients were female. Six patients (28.6%) had an Eastern Cooperative Oncology Group performance status (ECOG PS) 0, 12 patients (57.1%) had an ECOG PS 1, and 3 patients (14.3%) had an ECOG PS 2. The median number of prior regimens was 6.00 (range: 2.0-17.0). The median number of prior lines of treatment was 4.00 (range: 2.0-11.0).

Nineteen out of 21 patients (90.5%) discontinued treatment. The reasons for study treatment discontinuation were progressive disease (15 patients, 71.4%), withdrawal by subject (3 patients, 14.3%), and AE (1 patient, 4.8%). Two patients were still receiving treatment at time of the analysis date.

Safety results:

A total of 21 patients with relapsed and/or refractory MM were treated with isatuximab in this study and were included in the safety population.

The overall median number of cycles started was 3 cycles (range: 1 cycle to 18 cycles). Median duration of exposure was 11.14 weeks, and the median total cumulative dose was 142 mg/kg. Cycle delays occurred in 35.0% of patients. Dose interruptions occurred in 57.1% of patients and all of them were due to IR. The median relative dose intensity of Cycle 1 and subsequent cycles were approximate 101% and 99%, respectively.

All patients had at least 1 TEAE (any grade), 47.6% of patients had Grade ≥3 TEAEs. The most common (in >25%) TEAEs of any grade and regardless of relationship with study treatment consisted of infusion related reaction (61.9%), upper respiratory tract infection (42.9%), weight decreased (28.6%), and pneumonia (28.6%).

Four patients (19.0%) died within 30 days of their last study treatment administration in total: 1 patient died due to TEAE (Grade 5 pneumonia), 2 patients died due to progressive disease (PD), and 1 patient died due to other unknown reason. During the post-treatment period, 5 additional patients died due to PD and 2 patients died due to other unknown reasons. TEAEs leading to death occurred in 4 patients (19.0%) with preferred terms (PTs) of pneumonia, death, disease progression, and multiple organ dysfunction syndrome.

Seven patients (33.3%) had TESAEs. The most frequently reported treatment-emergent SAEs were pneumonia (3 patients, 14.3%). Treatment-emergent SAEs were considered to be related in 1 (4.8%) patient with pneumonia and 1 (4.8%) patient with bacterial sepsis.

One patient (4.8%) experienced a TEAE (Grade 5 pneumonia) leading to discontinuation, and this TEAE was a fatal SAE related to the study treatment. TEAEs of pneumonia also resulted in dose delay in 3 patients. Dose interruptions due to infusion related reactions were reported in 57.1% of patients.

Infusion reactions were reported in 61.9% of patients and none of the events was ≥Grade 3 severity. All these patients had only 1 episode of IR and all the events occurred during the first cycle. All IRs were resolved within 1 day. The symptoms of IR most frequently reported were chest discomfort, chills, and nausea (14.3% each).

The most frequently reported respiratory infection TEAEs (all grades) were upper respiratory tract infection (42.9%) and pneumonia (28.6%).

During the on-treatment period, the most frequently reported hematological abnormalities in all grades consisted of white blood cell decrease (100%), lymphocyte count decreased (95.0%), and anemia (90.0%); Grade 3 or 4 liver function abnormalities occurred infrequently except: Grade 3 aspartate aminotransferase increased and alanine aminotransferase increased in one patient (5.0%) for each parameter. During the on-treatment period, Grade 3 and 4 hyperuricemia occurred in 12 patients (60.0%). Grade 3 or 4 electrolyte abnormalities occurred infrequently except 4 hyponatremia (Grade 3 or 4, 25.0%); 3 hypokalemia (Grade 3, 15.0%); 2 hypercalcemia (Grade 3 or 4, 10.0%).

Potentially clinically significant abnormalities in vital signs occurred infrequently except that 57.1% of patients had ≥5% weight decrease from baseline prior to study administration. Weight decreased in 6 patients (28.6%) were reported as AEs, all these events were non-serious, not related to IMP, and did not lead to action with IMP.

Among the 20 patients evaluable for immunogenicity, no patient developed ADA response against isatuximab under isatuximab treatment.

Pharmacokinetic results:

Mean isatuximab PK parameters observed after the first intravenous infusion of isatuximab 20 mg/kg are presented in the Table below:

Summary statistics of isatuximab PK parameters observed after the first intravenous infusion of isatuximab at 20 mg/kg (N=20)

Isatuximab PK parameters – Isatuximab 20 mg/kg Mean ± SD [Geometric Mean] (CV%)	
Dose (mg/kg)	19.8 ± 0.455 [19.8] (2)
Infusion duration (h)[a]	6.05 (3.85-9.47)
C_{eoi} (µg/mL)	396 ± 106 [384] (27)
C_{max} (µg/mL)	402 ± 113 [388] (28)
t_{max}[a](h)	7.63 (3.93-46.7)
C_{last} (µg/mL)	132 ± 59.8 [113] (46)
t_{last}[a] (h)	167 (144-195)
AU_{Clast} (µg.h/mL)	37200 ± 12900 [35200] (35)
AUC_{tau}[b] (µg.h/mL)	37000 ± 12000 [35100] (33)

a Median (min-max) values

b tau is the dosing interval, ie, 168h. AUC_{tau} corresponds to AUC_{0_168h}

After a first intravenous infusion of isatuximab at 20 mg/kg in Chinese patients, the mean isatuximab maximum observed concentration (C_{max}) and area under the concentration versus time curve over the first 1-week dosing interval (AUC_{tau}) was 402 µg/mL and 37000 µg·h/mL, respectively, with low to moderate variability (coefficient of variance [CV%] for C_{max} and AUCtau: 28% and 33%, respectively). About 3-fold increase in exposure (C_{trough}) was observed at the end of the weekly administration (QW) compared to the first administration. Thereafter, the exposure was remained within the same magnitude during every 2-week administration (Q2W).

Efficacy results:

All efficacy endpoints were defined as secondary endpoints in this study.

The ORR as per investigator assessment was 19.0% (4 patients), including 1 patient (4.8%) with complete response (CR) and 3 patients (14.3%) with PR. The clinical benefit rate (CBR) (including minimal response or better response) was 33.3% (7 patients).

Among 4 patients with ORR, the median DOR was 12.52 months. The median TT1R by investigator was 2.83 months. The median TTBR by investigator was 3.71 months. As of the analysis cut-off date, the median TTP by investigator assessments was 1.91 months when including symptomatic deterioration and was 7.36 months when ignoring symptomatic deterioration; the median PFS by investigator assessments was 1.97 months when including symptomatic deterioration and was 3.06 months when ignoring symptomatic deterioration. At the analysis cut-off date (06 September 2020), the median OS was 6.80 months.
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