A multicenter, phase Ib study of subcutaneous administration of isatuximab in combination with pomalidomide and dexamethasone in patients with relapsed/refractory multiple myeloma

The availability of subcutaneous (SC) formulations for several anticancer, therapeutic agents has improved safety and convenience of treatment in patients with solid tumors as well as hematologic malignancies, including multiple myeloma.[1-3] Compared with intravenous (IV) administration, SC delivery of oncological agents is often preferred by patients and healthcare providers, as it improves comfort and satisfaction for patients and reduces healthcare resource utilization.[2,4-6] To enhance convenience of administration, a SC formulation was developed for the anti-CD38 antibody isatuximab (Isa).[7] Isa is approved for IV use in relapsed/refractory multiple myeloma (RRMM) patients in combination with pomalidomide-dexamethasone (Isa-Pd) after ≥2 prior therapies and with carfilzomib-dexamethasone after one prior therapy.[8-12]

In this first-in-human, multicenter, phase Ib study (ClinicalTrials.gov: NCT04045795), we assessed the safety, tolerability, pharmacokinetics, and efficacy of Isa administered SC at a fixed dose using an infusion pump (IP) or an investigational on-body delivery system (OBDS) compared with IV Isa administration, both in combination with Pd, in RRMM patients who had received ≥2 prior treatment lines.

Patients were randomized 2:1 to Isa SC administration by IP (Crono IP, Cane', Rivoli, Italy) at a dose of 1,000 mg (IP1000; fixed dose) or IV 10 mg/kg (cohort 1) followed by SC Isa administration by IP at a dose of 1,400 mg (IP1400; fixed dose) or IV 10 mg/kg (cohort 2), plus Pd (*Online Supplementary Figure S1A*). In the subsequent expansion cohort, SC Isa was administered via a single-use OBDS (Enable Injections, Inc., Cincinnati, OH, USA) (*Online Supplementary Figure S1B*), at the recommended phase 2 dose (RP2D) of 1,400 mg, plus Pd. SC Isa (10 mL) was delivered by IP or OBDS at a single injection site on the abdomen, which was rotated at each administration. IV and SC Isa were given weekly for 4 weeks and then biweekly in 28-day cycles, with standard doses of pomalidomide and dexamethasone.[8] Patients received premedication with montelukast (10 mg; only in cycle 1), dexamethasone, acetaminophen, and diphenhydramine. Subsequent premedication in patients who did not experience infusion reactions after four consecutive IV or SC Isa administrations was at the investigator's discretion. Treatment with Isa-Pd continued until disease progression, an unacceptable adverse event, or other reason for discontinuation. The study was approved by the Institutional Review Board or Independent Ethics Committee at each center and conducted following the Declaration of Helsinki and International Conference on Harmonization Good Clinical Practice guidelines. All patients provided informed consent.

Primary study endpoints were safety (including dose-limiting toxicity, evaluated in cycle 1, and injection site reactions), and pharmacokinetics. Main secondary endpoints were overall response rate (according to International Myeloma Working Group criteria[13]), progression-free survival (analyzed using the Kaplan-Meier method), and CD38 receptor occupancy (measured in bone marrow plasma cells at screening and day 1 of cycle 2 pre-dose).

Fifty-six patients with RRMM were treated with Isa-Pd: 12 with Isa IV, 12 with Isa IP1000, and 10 with Isa IP1400 (in dose-escalation); 22 patients in the expansion cohort received Isa delivered by OBDS at the RP2D (*Online Supplementary Figure S1C*). Two dose-limiting toxicities were observed during dose-escalation: grade 4 neutropenia (IP1000 group) and grade 3 pneumonia (IP1400 group). Both patients resumed study treatment after supportive therapy and dose modifications (pomalidomide dose reduction for the neutropenia; Isa dose omission and pomalidomide-dexamethasone dose reduction for the pulmonary infection).

The RP2D for SC administration of Isa-Pd in patients enrolled in the expansion cohort was determined based on the safety, pharmacokinetics, CD38 receptor occupancy, and efficacy results observed in the Isa IP1000 and Isa IP1400 cohorts.

At final data cut-off (March 17, 2023), three (25%) patients in the IV group, three (25%) in the IP1000 group, three (30%) in the IP1400 group, and seven (32%) OBDS patients remained on treatment (*Online Supplementary Figure S1C*). The median follow-up was longer in the IV (33.0 months), IP1000 (38.8 months), and IP1400 (33.4 months) groups than in the OBDS (19.4 months) group, because of the sequential accrual.

The patients' baseline characteristics are presented in Table 1. More patients in the IP1000 and OBDS cohorts were refractory to lenalidomide and a proteasome inhibitor than in the IV and IP1400 cohorts. The median relative dose intensity for SC Isa at the RP2D was ≥90% (97%, 95%, 91%, and 93% in the IV, IP1000, IP1400, and OBDS cohorts, respectively, due to dose delays or dose omissions).

The incidence of all-causality grade ≥3 treatment-emergent adverse events was comparable across cohorts (Table 2). Serious treatment-related adverse events occurred in 16.7%, 25.0%, 50.0%, and 13.6% of patients in the IV, IP1000, IP1400, and OBDS cohorts, respectively. No patient prematurely dis-

continued Isa due to a treatment-emergent adverse event. Any-grade, non-hematologic treatment-emergent adverse events reported in ≥25% of patients are listed in *Online Supplementary Table S1*. A grade ≥3 infection occurred in 25%, 25%, 30%, and 36.4% of the IV, IP1000, IP1400, and OBDS patients, respectively, including zero, one (8%), zero, and three (13.6%) patients with grade ≥3 COVID-19 in the corresponding cohorts, due to the concomitance of this trial with the pandemic. Upper respiratory tract infections (all grade 1-2) occurred in 15.6% of patients in the SC cohorts at the RP2D and in 25.0% of patients in the IV cohort with one (8.3%) grade 3 event. Grade 3-4 neutropenia (laboratory abnormality) was observed in 83.3%, 91.7%, 90.0%, and 90.9% of IV, IP1000, IP1400, and OBDS patients, respectively. However, only one (8.3%) patient in the IV cohort, two (20%) in the IP1400 cohort, and two (9.1%) in the OBDS cohort developed febrile neutropenia. Infusion reactions were infrequent. A single grade 2 infusion reaction was reported in the IV, IP1000, and IP1400 cohorts (≤10% of patients), at first Isa administration. Importantly, no infusion/injection reactions were observed in OBDS patients.

The median duration of injections at the RP2D was 12.6 min (range, 2.7-31.0) in IP patients and 10.0 min (range, 6.6-49.5) in OBDS patients. All OBDS injections were completed successfully with no interruptions. The local tolerability of SC Isa administration via OBDS was very good: seven (32%) patients experienced injection site reactions (according to customized MedDRA grouping), all grade 1, in 581 administrations (1.7%; 6 events of erythema, 1 hemorrhage, 1 induration, 1 plaque, 1 puncture site bruise).

Slightly lower exposure (C_{max}, AUC_{last}) was observed during the 1-week dosing period after SC administration than after IV administration, in agreement with slower SC absorption of monoclonal antibodies such as Isa (*Online Supplementary*

Table 1. Patients' demographics and baseline characteristics.[a]

Characteristics	Isa IV 10 mg/kg + Pd N=12	Isa IP1000 + Pd N=12	Isa IP1400 (RP2D) + Pd N=10	Isa OBDS (RP2D) + Pd N=22
Age in years, median (range)	69.5 (46-83)	67.0 (50-78)	72.5 (63-83)	64.5 (43-82)
Weight, kg, median (range)	73.5 (61.3-123)	70.3 (50.4-93.9)	86.9 (54.1-96.3)	71.4 (47.3-104)
ISS stage at study entry, N (%) I II III	 4 (33.3) 6 (50.0) 2 (16.7)	 8 (66.7) 4 (33.3) 0	 4 (40.0) 6 (60.0) 0	 11 (50.0) 9 (40.9) 2 (9.1)
Bone marrow plasma cells at baseline, %, median (range)	7.5 (1-37)	9.0 (0-95)	18.5 (0-43)	10.5 (0-55)
Beta-2 microglobulin, mg/L, median	2.9	2.7	3.6	3.0
Plasmacytoma, N (%)	2 (16.7)	3 (25.0)	1 (10.0)	4 (18.2)
Bone lesions present, N (%)	8 (66.7)	10 (83.3)	9 (90.0)	19 (86.4)
eGFR (MDRD equation), N (%) ≥90 mL/min/1.73 m^2 60≤ eGFR <90 mL/min/1.73 m^2 30≤ eGFR <60 mL/min/1.73 m^2	 4 (33.3) 5 (41.7) 3 (25.0)	 4 (33.3) 6 (50.0) 2 (16.7)	 1 (10.0) 5 (50.0) 4 (40.0)	 2 (9.1) 14 (63.6) 6 (27.3)
Number of prior lines of therapy Median (range) 1, N (%) of patients 2, N (%) of patients ≥3, N (%) of patients	 3.5 (2-7) 0 3 (25.0) 9 (75.0)	 3.0 (2-6) 0 4 (33.3) 8 (66.7)	 2.5 (1-4) 1 (10.0) 4 (40.0) 5 (50.0)	 3.0 (2-6) 0 4 (18.2) 18 (81.8)
Refractory to, N (%) Lenalidomide PI IMiD and PI Daratumumab	 7 (58.3) 7 (58.3) 6 (50.0) 0	 11 (91.7) 9 (75.0) 8 (66.7) 2 (16.7)	 7 (70.0) 5 (50.0) 4 (40.0) 0	 21 (95.5) 16 (72.7) 16 (72.7) 1 (4.5)

[a]Adult patients with relapsed/refractory multiple myeloma with measurable disease were enrolled if they had received ≥2 prior therapies, had experienced disease progression, and had adequate hematologic, liver, and renal functions. Among key exclusion criteria, patients were not enrolled if they had not achieved a minimal response or better to ≥1 previous treatment lines, were refractory/intolerant to anti-CD38 therapy, had progressed after initial response to anti-CD38 therapy, could not tolerate thromboprophylaxis, or had an excess risk of bleeding. Isa: isatuximab; IV: intravenous; Pd: pomalidomide-dexamethasone; IP: infusion pump; RP2D: recommended phase 2 dose; OBDS: on-body delivery system; ISS: International Staging System; eGFR: estimated glomerular filtration rate; MDRD: Modification of Diet in Renal Disease equation; PI: proteasome inhibitor; IMiD: immunomodulatory drug.

Table S2). However, similar or higher trough concentrations (C_{trough}) at the end of the weekly dosing period – the best pharmacokinetic predictor of efficacy after IV Isa administration[14] – were reached with SC Isa 1,400 mg (IP or OBDS) compared with IV Isa 10 mg/kg. Consistently, the mean C_{trough} after multiple dosing was higher in the OBDS than the IV cohort (363 μg/mL and 202 μg/mL, respectively, at day 1 of cycle 3) (*Online Supplementary Table S2*).

High CD38 receptor occupancy saturation was reached by Isa on bone marrow plasma cells in all cohorts. Mean CD38 receptor occupancy (day 1 of cycle 2) was 76.0%, 79.8%, 80.5%, and 77.7% in the IV, IP1000, IP1400, and OBDS patients, respectively. Median decreases in the percentage of cells expressing CD38 *versus* baseline (49.4% for bone marrow plasma cells; 75.3% for bone marrow natural killer cells) and in CD38 receptor density *versus* baseline (85.2% on bone marrow plasma cells and 72.6% on bone marrow natural killer cells) were observed after treatment with Isa (day 1 of cycle 2).

Best overall responses are presented in Table 3. The overall response rate was 66.7% in the IV cohort, 66.7% and 80.0% in the IP1000 and IP1400 groups, respectively, and 72.7% for OBDS patients, with a median progression-free survival of 22.0 months, 17.4 months, not reached, and 20.6 months, respectively.

Our results show that the safety and efficacy of Isa administered SC at the RP2D of 1,400 mg, plus Pd, were consistent with those with IV administration in this study and in the ICARIA-MM trial, with no new safety signals identified.[8] Infusion reactions were infrequent (≤10%), occurring only at the first injection of Isa in the IV and IP cohorts. This incidence rate of infusion reactions was lower than that observed in the IV Isa trials with the same triplet combination (e.g., 38% in ICARIA-MM).[8] Notably, premedication was modified in our study by adding montelukast in the first cycle. No infusion reactions were reported in patients who received SC Isa via OBDS, thus demonstrating the safety of this delivery route in the context of combination treatment with an immunomodulatory drug and low-dose dexamethasone. Furthermore, Isa SC administration via OBDS was very well tolerated locally, with only 1.7% of 581 administrations being associated with injection site reactions (all grade 1).

Isa was administered IV by weight-based dosing and SC as a flat dose. A low-to-moderate variability was observed for all Isa pharmacokinetic parameters regardless of administration route (IV or SC), dose, or SC delivery modality (by IP or OBDS), supporting the feasibility of switching to a flat dose for SC Isa administration. Although evaluated in a few subjects, analysis of patient-reported outcomes showed a high level of confidence and satisfaction after treatment with SC Isa via OBDS (*data not shown*), indicating acceptance of this delivery approach in clinical practice. Further randomized, confirmatory trials in larger numbers of patients, such as the phase III study IRAKLIA (ClinicalTrials.gov NCT05405166),

Table 2. Safety summary.[a]

Adverse events, N (%)	Isa IV 10 mg/kg + Pd N=12	Isa IP1000 + Pd N=12	Isa IP1400 (RP2D) + Pd N=10	Isa OBDS (RP2D) + Pd N=22	Isa OBDS and IP1400 (RP2D) + Pd N=32
Any TEAE[b]	12 (100)	12 (100)	10 (100)	22 (100)	32 (100)
Grade 3 or 4 TEAE	12 (100)	11 (91.7)	9 (90.0)	22 (100)	31 (96.9)
Treatment-related grade 3 or 4 TEAE	10 (83.3)	11 (91.7)	8 (80.0)	18 (81.8)	26 (81.3)
Grade 5 TEAE	0	0	0	2 (9.1)[c]	2 (6.3)
Any serious TEAE	9 (75.0)	9 (75.0)	7 (70.0)	13 (59.1)	20 (62.5)
Any serious treatment-related TEAE	2 (16.7)	3 (25.0)	5 (50.0)	3 (13.6)	8 (25.0)
TEAE leading to definitive treatment discontinuation	0	0	0	2 (9.1)	2 (6.3)
TEAE leading to premature treatment discontinuation	0	2 (16.7)	4 (40.0)	2 (9.1)	6 (18.8)
Isatuximab	0	0	0	0	0
Pomalidomide	0	2 (16.7)	3 (30.0)	0	3 (9.4)
Dexamethasone	0	1 (8.3)	3 (30.0)	2 (9.1)	5 (15.6)

[a]The safety population comprised all patients who received at least one dose or part of a dose of study drugs. [b]Adverse events were monitored and graded by the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5.0. [c]Two patients in the cohort of patients given treatment via an on-body delivery system definitively discontinued treatment due to fatal treatment-emergent adverse events: a cardio-respiratory arrest not related to study treatment and treatment-related Listeria meningitis. Isa: isatuximab; IV: intravenous; Pd: pomalidomide-dexamethasone; IP: infusion pump; RP2D: recommended phase 2 dose; OBDS: on-body delivery system; TEAE: treatment-emergent adverse event.

Table 3. Best overall response with subcutaneous or intravenous isatuximab in combination with pomalidomide and dexamethasone.[a]

Response	Isa IV 10 mg/kg + Pd N=12	Isa IP1000 + Pd N=12	Isa IP1400 (RP2D) + Pd N=10	Isa OBDS (RP2D) + Pd N=22	Isa OBDS and IP1400 (RP2D) + Pd N=32
Overall response rate,[b] %	66.7	66.7	80.0	72.7	75.0
Complete response or better	16.7	25.0	30.0	22.7	25.0
Very good partial response	33.3	16.7	10.0	27.3	21.9
Partial response	16.7	25.0	40.0	22.7	28.1
Very good partial response or better,[c] %	50.0	41.7	40.0	50.0	46.9

[a]The efficacy population included all treated patients who had a baseline and at least one post-baseline efficacy assessment as well as patients with early disease progression. [b]Overall response rate was defined as the proportion of patients with stringent complete response, complete response, very good partial response, and partial response, using the International Myeloma Working Group response criteria. [c]Minimal residual disease negativity rate (at a 10^{-5} sensitivity threshold; exploratory endpoint) was centrally assessed by a next-generation sequencing clonoSEQ assay (Adaptive Biotechnologies, Seattle, WA, USA) in bone marrow aspirates from patients with confirmed very good partial response or better. Minimal residual disease negativity was achieved by one (8.3%) IV patient, none in the IP1000 cohort, two (20.0%) in the IP1400 cohort, and two (9.1%) in the OBDS cohort (4 patients with complete response and 1 with very good partial response). Isa: isatuximab; IV: intravenous; Pd: pomalidomide-dexamethasone; IP: infusion pump; RP2D: recommended phase 2 dose; OBDS: on-body delivery system.

are currently assessing efficacy, safety, and patient-reported outcomes with SC Isa administration via OBDS *versus* IV Isa, plus Pd in RRMM.

In conclusion, our findings show that SC administration of Isa plus Pd is comparable to IV administration and a promising, convenient treatment approach for patients with RRMM.

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Contributions

PM, DS, PC, SM, and FS contributed to the conception/design of this study. All authors contributed to collecting and/or analyzing data, as well as the development and final approval of the manuscript.

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Data-sharing statement

Qualified researchers may request access to patient-level data and related study documents including the clinical study report, study protocol with any amendments, blank case report form, statistical analysis plan, and dataset specifications. Patient-level data will be anonymized and study documents will be redacted to protect the privacy of our trial participants. Further details on Sanofi's data-sharing criteria, eligible studies, and process for requesting access can be found at: *https://www.vivli.org/*.

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