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

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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/

LETTER TO THE EDITOR

The availability of subcutaneous (SC) formulations for several anti-cancer, therapeutic agents has improved safety and convenience of treatment in patients with solid tumors as well as hematologic malignancies, including multiple myeloma.[1-3] When compared with IV administration, SC delivery of oncologic 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 1 prior therapy.[8-12]

In this first-in-human, multi-center, phase Ib study (NCT04045795), we assessed safety, tolerability, pharmacokinetics (PK), and efficacy of Isa administered SC at 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 with ≥2 prior treatment lines.

Patients were randomized 2:1 to Isa SC administration by IP (Crono IP, Cane', Rivoli, Italy) at 1000 mg (IP1000; fixed dose) or IV 10 mg/kg (cohort 1) followed by SC Isa IP1400 mg (fixed dose) or IV 10 mg/kg (cohort 2), plus Pd (**Figure S1A**). In the subsequent expansion cohort, SC Isa was administered via a single-use OBDS (Enable Injections, Inc., Cincinnati, OH) (**Figure S1B**), at the recommended phase 2 dose (RP2D) of 1400 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/paracetamol, and diphenhydramine. Subsequent premedication in patients who did not experience infusion reactions (IRs) after 4 consecutive IV or SC Isa administrations was at the investigator's discretion. Treatment with Isa-Pd continued until disease progression, unacceptable adverse event (AE), 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 ICH GCP Guidelines. All patients provided informed consent.

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

Fifty-six patients with RRMM were treated with Isa plus 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 (**Figure S1C**). Two DLTs were observed in 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 plus 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 mg and Isa IP1400 mg cohorts.

At final data cut-off (17Mar2023), 3 (25%) IV, 3 (25%) IP1000, 3 (30%) IP1400, and 7 (32%) OBDS patients remained on treatment (**Figure S1C)**. Median follow-up was longer in IV (33.0 months), IP1000 (38.8 months), and IP1400 (33.4 months) than in OBDS (19.4 months) patients, owing to the sequential accrual.

Baseline patient 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).

Incidence of all-causality grade ≥3 treatment-emergent AEs (TEAEs) was comparable across cohorts (**Table 2**). Serious treatment-related AEs 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 discontinued Isa due to a TEAE. Any-grade, non-hematologic TEAEs reported in ≥25% of patients are listed in **Table S1**. 25%, 25%, 30%, and 36.4% of IV, IP1000, IP1400, and OBDS patients, respectively, had a grade ≥3 infection, including 0, 1 (8%), 0, and 3 (13.6%) patients with grade ≥3 COVID-19 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 1 (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 1 (8.3%) patient in the IV cohort, 2 (20%) in IP1400, and 2 (9.1%) in the OBDS cohort developed febrile neutropenia. IRs were infrequent. A single grade 2 IR episode 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.

Median duration of injections at the RP2D was 12.6 min (2.7-31.0) in IP patients and 10.0 min (6.6-49.5) in OBDS patients. All OBDS injections were completed successfully with no interruptions. Local tolerability of SC Isa administration via OBDS was very good: 7 (32%) patients experienced ISRs (per customized MedDRA grouping), all grade 1, in 581 administrations (1.7%; 6 erythemas, 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 versus IV administration, in agreement with slower SC absorption of monoclonal antibodies such as Isa (**Table S2**). However, similar or higher trough concentrations (C_{trough}) at the end of the weekly-dosing period – the best PK predictor of efficacy after IV Isa administration[14] – were reached with SC Isa 1400 mg (IP or OBDS) compared with IV Isa 10 mg/kg. Consistently, mean C_{trough} after multiple dosing was higher in the OBDS than the IV cohort (363 µg/mL and 202 µg/mL, respectively, at cycle 3/day 1) (**Table S2**).

High CD38 RO saturation was reached by Isa on BMPCs in all cohorts. Mean CD38 RO (day 1/cycle 2) was 76.0%, 79.8%, 80.5%, and 77.7% in IV, IP1000, IP1400, and OBDS patients, respectively. Median decreases in the percentage of cells expressing CD38 vs.

baseline (49.4% for BMPCs; 75.3% for BM-NK cells) and in CD38 receptor density vs. baseline (85.2% on BMPCs and 72.6% on BM-NK cells) were observed after treatment with Isa (day 1/cycle 2).

Best overall responses are presented in **Table 3**. The ORR was 66.7% for IV, 66.7% for IP1000, 80.0% for IP1400, and 72.7% for OBDS patients, with a median PFS 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 1400 mg, plus Pd, were consistent with IV administration in this study and in the ICARIA-MM trial, with no new safety signals identified.[8] IRs were infrequent (≤10%), occurring only at first injection of Isa in the IV and IP cohorts. Such an IR incidence rate was lower than observed in the IV Isa trials with the same triplet combination (eg, 38% in ICARIA-MM).[8] Notably, premedication was modified in our study by adding montelukast in first cycle. No IRs were reported in patients receiving SC Isa via OBDS, thus demonstrating the safety of this delivery route in the context of combination treatment with an IMiD and low-dose dexamethasone. Furthermore, Isa SC administration via OBDS was very well tolerated locally, with only 1.7% of 581 administrations associated with ISRs (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 PK parameters regardless of administration route (IV or SC), dose, or SC delivery modality (by IP or OBDS), supporting the feasibility of switching to 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 (NCT05405166), 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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TABLES

Table 1. Patient demographics and baseline characteristics[a].

	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	4 (33.3)	8 (66.7)	4 (40.0)	11 (50.0)
II	6 (50.0)	4 (33.3)	6 (60.0)	9 (40.9)
III	2 (16.7)	0	0	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,				
Median, mg/L	2.9	2.7	3.6	3.0
Plasmacytoma				
n (%)	2 (16.7)	3 (25.0)	1 (10.0)	4 (18.2)
Bone lesions, n (%)				
Yes	8 (66.7)	10 (83.3)	9 (90.0%)	19 (86.4)
eGFR (MDRD equation)				
≥90 mL/min/1.73 m^2	4 (33.3)	4 (33.3)	1 (10.0)	2 (9.1)
60≤ GFR <90 mL/min/1.73 m^2	5 (41.7)	6 (50.0)	5 (50.0)	14 (63.6)
30≤ GFR <60 mL/min/1.73 m^2	3 (25.0)	2 (16.7)	4 (40.0)	6 (27.3)
Number of prior lines, n (%)				
Median (range)	3.5 (2–7)	3.0 (2–6)	2.5 (1–4)	3.0 (2–6)
1	0	0	1 (10.0)	0
2	3 (25.0)	4 (33.3)	4 (40.0)	4 (18.2)
≥3	9 (75.0)	8 (66.7)	5 (50.0)	18 (81.8)
Refractory to, n (%)				
Lenalidomide	7 (58.3)	11 (91.7)	7 (70.0)	21 (95.5)
PI	7 (58.3)	9 (75.0)	5 (50.0)	16 (72.7)
IMiD and PI	6 (50.0)	8 (66.7)	4 (40.0)	16 (72.7)
Daratumumab	0	2 (16.7)	0	1 (4.5)

[a]Adult RRMM patients 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 exlusion criteria, patients were not enrolled if they had not achieved a minimal response or better to ≥1 previous treatment line, were refractory/intolerant to anti-CD38 therapy, had progressed after initial response to anti-CD38 therapy, could not tolerate thromboprophylaxis, or had excess risk of bleeding. eGFR: estimated glomerular filtration rate; IMiD: immunomodulatory drug; IP: infusion pump; Isa: isatuximab; ISS: International Staging System; IV: intravenous; MDRD: Modification of Diet in Renal Disease; OBDS: on-body delivery system; Pd: pomalidomide-dexamethasone; PI: proteasome inhibitor; RP2D: recommended phase 2 dose; RRMM: relapsed/refractory multiple myeloma.

Table 2. Safety summary[a].

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 3–4 TEAE	12 (100)	11 (91.7)	9 (90.0)	22 (100)	31 (96.9)
Treatment-related Grade 3–4 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 1 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) v.5.0. [c]Two patients in the OBDS cohort definitively discontinued treatment due to fatal TEAEs: a cardio-respiratory arrest not related to study treatment and treatment-related Listeria meningitis. IP: infusion pump; Isa: isatuximab; IV: intravenous; OBDS: on-body delivery system; Pd: pomalidomide-dexamethasone; RP2D: recommended phase 2 dose; TEAE: treatment-emergent adverse event.

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

%	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

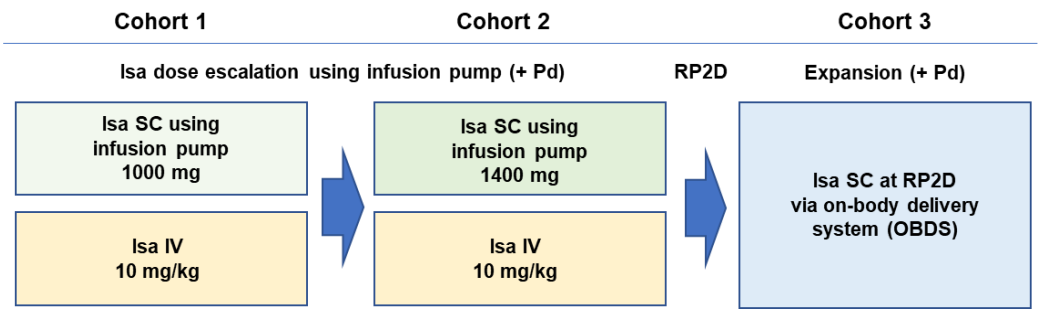
[a]The efficacy population included all treated patients who had a baseline and at least 1 post-baseline efficacy assessment as well as patients with early disease progression. [b]Overall response rate was defined as the proportion of patients with stringent complete response, complete response, very good partial response, and partial response, using the International Myeloma Working Group response criteria. [c]Minimal residual disease (MRD) negativity rate (at 10^{-5} sensitivity threshold; exploratory endpoint), was centrally assessed by next-generation sequencing (NGS) clonoSEQ assay (Adaptive Biotechnologies, Seattle, WA) in bone marrow aspirates from patients with confirmed very good partial response or better. MRD negativity was achieved by 1 (8.3%) IV patient, 0 in the IP1000, 2 (20.0%) in the IP1400, and 2 (9.1%) in the OBDS cohort (4 patients with complete response and 1 with very good partial response). IP: infusion pump; Isa: isatuximab; IV: intravenous; OBDS: on-body delivery system; Pd: pomalidomide-dexamethasone; RP2D, recommended phase 2 dose.

SUPPLEMENTARY INFORMATION

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

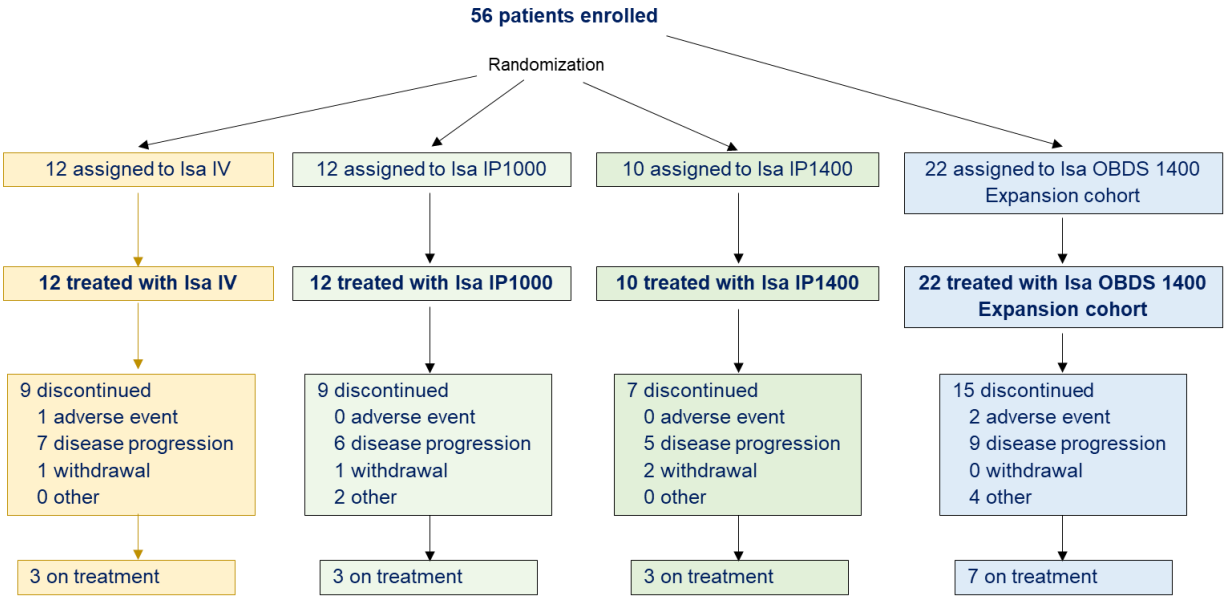
Supplementary Figure S1. Study design, on-body delivery system (OBDS), and patient flow diagram

A



B

C



Footnote

(A) Study design. Patients were randomized 2:1 to SC IP 1000 mg or IV Isa 10 mg/kg in cohort 1 and then to SC IP 1400 mg or IV Isa 10 mg/kg in cohort 2, plus Pd, by a centralized randomization procedure using an interactive response system. Subsequently, patients were

recruited in an expansion cohort for treatment with Isa SC via OBDS at the RP2D of 1400 mg (cohort 3). After determination of the RP2D for SC Isa, 4 patients still on treatment in the IV cohort were allowed by protocol amendment to switch to SC Isa 1400 mg given by infusion pump. Three of these 4 patients switched to SC Isa administration via OBDS at 1400 mg after the final OBDS results became available and a further protocol amendment was implemented to offer more convenience to patients. Both Isa IP1000 mg and IP1400 mg were delivered through an infusion pump (IP) at a 0.8 mL/min flow rate. (B) OBDS applied to the patient's abdomen*. *CAUTION - Investigational device. Limited by Federal (or United States) law to investigational use. (C) Patient flow diagram. IP: infusion pump; Isa: isatuximab; Pd: pomalidomide-dexamethasone; RP2D: recommended phase 2 dose; SC: subcutaneous; IV: intravenous; OBDS: on-body delivery system.

Supplementary Table S1. Any-grade, non-hematologic, treatment-emergent adverse events in ≥25% of patients in any treatment group, by primary system organ class (including selected preferred terms)[a]

	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)	
n (%)	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3
COVID-19	0	0	1 (8.3)	1 (8.3)	4 (40.0)	0	6 (27.3)	3 (13.6)	10 (31.3)	3 (9.4)
Respiratory tract infection	0	0	2 (16.7)	0	2 (20.0)	0	1 (4.5)	0	3 (9.4)	0
Upper respiratory tract infection	3 (25.0)	1 (8.3)	1 (8.3)	0	1 (10.0)	0	4 (18.2)	0	5 (15.6)	0
Insomnia	2 (16.7)	2 (16.7)	4 (33.3)	2 (16.7)	2 (20.0)	2 (20.0)	5 (22.7)	2 (9.1)	7 (21.9)	4 (12.5)
Mood altered	1 (8.3)	1 (8.3)	0	0	3 (30.0)	1 (10.0)	2 (9.1)	2 (9.1)	5 (15.6)	3 (9.4)
Confusional state	0	0	3 (25.0)	0	0	0	0	0	0	0
Dizziness	1 (8.3)	0	3 (25.0)	0	1 (10.0)	0	1 (4.5)	0	2 (6.3)	0
Hypotension	1 (8.3)	0	3 (25.0)	0	1 (10.0)	0	2 (9.1)	0	3 (9.4)	0
Dyspnea	3 (25.0)	0	1 (8.3)	0	2 (20.0)	0	2 (9.1)	1 (4.5)	4 (12.5)	1 (3.1)
Cough	3 (25.0)	0	1 (8.3)	0	1 (10.0)	0	2 (9.1)	0	3 (9.4)	0
Diarrhea	4 (33.3)	0	5 (41.7)	0	6 (60.0)	0	6 (27.3)	0	12 (37.5)	0
Constipation	2 (16.7)	0	7 (58.3)	0	1 (10.0)	0	6 (27.3)	0	7 (21.9)	0
Nausea	4 (33.3)	1 (8.3)	5 (41.7)	0	2 (20.0)	0	3 (13.6)	0	5 (15.6)	0
Vomiting	2 (16.7)	1 (8.3)	5 (41.7)	0	0	0	1 (4.5)	0	1 (3.1)	0
Back pain	5 (41.7)	0	4 (33.3)	1 (8.3)	4 (40.0)	0	6 (27.3)	0	10 (31.3)	0
Muscle spasms	1 (8.3)	0	3 (25.0)	0	2 (20.0)	0	6 (27.3)	0	8 (25.0)	0
Fatigue	5 (41.7)	0	4 (33.3)	0	4 (40.0)	1 (10.0)	6 (27.3)	2 (9.1)	10 (31.3)	3 (9.4)

Injection site erythema	0	0	2 (16.7)	0	5 (50.0)	0	4 (18.2)	0	9 (28.1)	0
Peripheral edema	2 (16.7)	0	4 (33.3)	0	3 (30.0)	0	2 (9.1)	0	5 (15.6)	0
Injection site bruising	0	0	2 (16.7)	0	3 (30.0)	0	0	0	3 (9.4)	0
Pyrexia	4 (33.3)	1 (8.3)	1 (8.3)	0	1 (10.0)	0	2 (9.1)	0	3 (9.4)	0
Basal cell carcinoma	3 (25.0)	0	0	0	0	0	1 (4.5)	0	1 (3.1)	0
Fall	2 (16.7)	1 (8.3)	4 (33.3)	1 (8.3)	2 (20.0)	0	3 (13.6)	1 (4.5)	5 (15.6)	1 (3.1)
Contusion	3 (25.0)	0	1 (8.3)	0	0	0	1 (4.5)	0	1 (3.1)	0
Infusion reaction	1 (8.3)	0	1 (8.3)	0	1 (10.0)	0	0	0	1 (3.1	0

[a]Adverse events were summarized by primary system organ class and preferred terms using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v.5.0. Isa: isatuximab; IP: infusion pump; IV: intravenous; OBDS: on-body delivery system; Pd: pomalidomide-dexamethasone; RP2D: recommended phase 2 dose.

Supplementary Table S2. Isa pharmacokinetic parameters after first intravenous (IV) or subcutaneous (SC) administration at cycle 1 and mean C_{trough} (± SD) after multiple dosing of Isa administered IV or SC, in combination with pomalidomide-dexamethasone[a].

	Isa IV 10 mg/kg + Pd (n=12)	**Isa IP1000 + Pd (n=12)**	**Isa IP1400 + Pd (n=10)**	**Isa OBDS (RP2D) + Pd (n=22)**	**Isa OBDS and IP1400 (RP2D) + Pd (n=32)**
PK parameters at cycle 1					
n	12	12	10	22	32
C_{max}, µg/mL, mean (SD)	234 (66.7)	120 (56.1)	104 (34.8)	145 (71.4)	132 (64.6)
n	11	11	10	21	31
AUC_{last}, µg•h/ml, mean (SD)	18700 (5460)	15200 (7760)	13100 (5080)	18500 (8470)	16700 (7880)
n	12	12	10	22	32
t_{max}, h, median (range)	3.63 (3.33-11.3)	83.2 (44.4-168)	92.6 (68.4-168)	95.1 (46.9-192)	94.7 (46.9-192)
C_{trough} (µg/mL)[b]					
Cycle 2 (day 1)					
n	9	7	6	15	21
Mean (SD)	235 (93.2)	326 (86.2)	338 (120)	343 (158)	341 (145)
Cycle 2 (day 15)					
n	12	10	7	16	23
Mean (SD)	196 (117)	332 (122)	338 (151)	397 (202)	379 (186)
Cycle 3 (day 1)					
n	8	5	7	16	23
Mean (SD)	202 (131)	288 (187)	357 (136)	363 (173)	361 (160)
Cycle 3 (day 15)					
n	10	9	9	18	27
Mean (SD)	210 (111)	329 (93.2)	377 (175)	397 (226)	390 (208)
Cycle 4 (day 1)					
n	9	9	9	13	22
Mean (SD)	244 (139)	361 (154)	385 (149)	353 (118)	366 (129)
Cycle 4 (day 15)					
n	9	9	9	18	27
Mean (SD)	229 (144)	379 (108)	408 (155)	357 (147)	374 (149)
Cycle 6 (day 1)					

n	6	11	8	14	22
Mean (SD)	287 (183)	364 (173)	457 (165)	461 (196)	459 (181)

[a]Isa levels were assessed in plasma by a validated immunoassay using the Gyrolab platform. This quantitative, sandwich immunoassay consisted of biotinylated anti-Isa antibodies bound by streptavidin beads, within the Gyrolab Bioaffy™ CD microstructure (Gyros Protein Technologies, Uppsala, Sweden), for capture and Alexa Fluor® 647-conjugated CD38 antibody for detection, resulting in measurement of functional Isa plasma levels (Isa with ≥1 site available for target binding), with a lower limit of quantitation of 5.0 µg/ml and an upper limit of quantitation of 500 µg/ml. PK parameters were calculated from Isa plasma concentrations by non-compartmental analysis methods using Phoenix WinNonlin® v8.2 (Pharsight, Cary, NC) and summarized with descriptive statistics. [b]From cycle 2, the geometric mean ratios of C_{trough} between each SC cohort and the IV cohort remained constant and above 1, suggesting that a comparable or higher Isa exposure was maintained with SC compared with IV administration over the dosing interval, at the dose range evaluated in the study. AUC_{last}: area under the concentration-time curve from time zero to t_{last}; C_{max}: maximum concentration observed; C_{trough}: trough concentration; h: hours; IP: infusion pump; Isa: isatuximab; IV: intravenous; OBDS: on-body delivery system; Pd: pomalidomide-dexamethasone; PK: pharmacokinetics; RP2D: recommended phase 2 dose; SC: subcutaneous; SD: standard deviation; t_{max}: time to reach C_{max}.