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ORIGINAL ARTICLE

Octreotide SC depot in patients with acromegaly and functioning neuroendocrine tumors: a phase 2, multicenter study

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Abstract

Purpose Octreotide SC depot is a novel, ready-to-use formulation administered via a thin needle. In a phase 1 study in healthy volunteers, this formulation provided higher bioavailability of octreotide with faster onset and stronger suppression of IGF-1 in healthy volunteers versus long-acting intramuscular (IM) octreotide. This phase 2 study evaluated the pharmacokinetics, efficacy, and safety of octreotide SC depot in patients with acromegaly and functioning NETs, previously treated with octreotide IM.

Methods Adult patients with acromegaly or functioning NETs treated for ≥ 2 months with octreotide IM [10/20/30 mg every 4 weeks (q4w)] received the last dose of octreotide IM treatment in study period 0 and were randomized 28 days later to receive octreotide SC depot 10 mg q2w, or 20 mg q4w for 3 months (period 1). The primary objective was to characterize the PK profile of octreotide SC depot after each injection vs PK for octreotide IM (period 0).

Results Twelve patients were randomized to receive octreotide SC depot 10 mg q2w (acromegaly $n=3$; NET $n=1$) or 20 mg q4w (acromegaly $n=4$; NET $n=4$). Plasma levels of octreotide were higher with octreotide SC depot as compared to octreotide IM. Adverse events were reported in 6 and 8 patients during period 0 and period 1, respectively; most common in period 1 were gastrointestinal disorders.

Conclusion Octreotide SC depot provided higher exposure (AUC) than octreotide IM, maintained biochemical control in patients with acromegaly and symptom control in patients with functioning NETs, and was well tolerated with a safety profile consistent with octreotide IM.

ClinicalTrials.gov identifier NCT02299089.

Keywords Octreotide SC depot · Acromegaly · Neuroendocrine tumor (NET) · Carcinoid syndrome · Subcutaneous injection

Introduction

Somatostatin analogs are the mainstay of medical therapy for patients with acromegaly and for control of symptoms related to hypersecretion of bioactive compounds, and proliferation in patients with functioning gastroenteropancreatic neuroendocrine tumors (GEP-NETs) [1–3]. Somatostatin analogs are also used for antiproliferative treatment of patients with advanced unresectable neuroendocrine tumors (NETs) of the midgut or pancreas [4–6]. The currently available somatostatin analogs include octreotide and lanreotide for treatment of patients with acromegaly and NETs and pasireotide for treatment of patients with acromegaly and Cushing's disease. Octreotide and lanreotide bind with high affinity to the sst_2 receptor subtype and with lower affinity to the sst_5 receptor, while pasireotide is a multi-receptor targeted somatostatin analog with high affinity for $sst_{1,2,3}$ and sst_5 [7].

Octreotide has a well-documented efficacy and safety profile for the treatment of patients with acromegaly and GEP-NETs. It is available as immediate release formulation administered as subcutaneous (SC) or intravenous injection/infusion and as long-acting depot formulation administered

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every 4 weeks as intramuscular (IM) injection. The depot formulation is available as powder for suspension, which requires refrigerated storage, and has to be reconstituted for injection. Due to the reconstitution process, which involves several preparation steps before the administration and the IM route of dosage, the administration has to be done by a trained healthcare provider [8].

Octreotide SC depot is a novel, ready-to-use, long-acting, slow-release formulation developed using the FluidCrystal® technology (Camurus AB, Lund, Sweden) [9, 10]. Octreotide SC depot is a liquid formulation based on naturally occurring lipids, which allows the use of thin needles (22–27 G). It is administered subcutaneously using a single conventional syringe, which may encourage and allow for self-administration by patients or administration by care givers, thus reducing the frequency of visits to clinics [5].

In a phase 1 study in healthy volunteers, octreotide SC depot provided greater bioavailability of octreotide with faster onset and stronger suppression of insulin-like growth factor 1 (IGF-1) as compared to octreotide IM [11].

This phase 2, open-label, multicenter, randomized study (NCT02299089) is the first study which evaluated the pharmacokinetics (PK), pharmacodynamics (PD), safety and tolerability of octreotide SC depot in patients with acromegaly, and with well-differentiated functioning neuroendocrine tumors, previously treated with octreotide IM formulation.

Patients and methods

Patients

This study recruited adult patients with two different indications. Male or female patients with acromegaly being treated for at least 2 months with octreotide IM 10 mg, 20 mg or 30 mg every 4 weeks (q4w) before period 0 were included in the study (acromegaly group).

Male or female adult patients with functioning and well-differentiated (grade 1 or 2) NETs with symptoms of carcinoid syndrome (increased number of bowel movements and/or flushing) being treated for at least 2 months with octreotide 10 mg, 20 mg or 30 mg every 4 weeks (q4w) before randomization were included in the study (NET group). Only patients with controlled symptoms were included, i.e., patients who did not require any rescue medication (octreotide immediate release) during the screening phase.

Patients were excluded from the study if they had inadequate bone marrow function, impaired liver or cardiac or renal function, gallbladder or bile duct disease, diabetes with poor glycemic control [glycosylated hemoglobin (HbA_{1c}) > 8.0%] despite therapy, or if they were pregnant or lactating. In addition, patients with NETs were excluded from the study if they had poorly differentiated NETs [12].

The planned enrollment was 24 patients (12 patients with acromegaly and 12 patients with NETs). Sample size assumptions were based on estimated within-patient coefficient of variations (46.2%) of long-acting octreotide 30 mg pre-dose concentrations in RADIANT-2 study in NET patients. There is no information available on within-patient variation for the octreotide SC depot formulation in patients with acromegaly or NET. Assuming a dropout rate of 10%, 14 patients were needed to be randomized in each indication.

The study was conducted in accordance with the Declaration of Helsinki and applicable local regulations. The study protocol and all amendments were reviewed by the independent ethics committee or institutional review board for each center. All patients provided written informed consent to participate in the study.

Study design

This study was a phase 2, open-label, multicenter, randomized trial to assess the PK, PD, efficacy and safety of 2 dosing regimens of octreotide SC depot 10 mg every 2 weeks (q2w), or 20 mg q4w in eligible patients.

The study consisted of four phases/three periods. After a 14-day screening phase, eligible patients entered a 4-week assessment phase (period 0), in which they received their last dose of long-acting IM octreotide (10 mg, 20 mg, or 30 mg; treatment A, B, and C, respectively). In the subsequent 3-month treatment phase (period 1), patients were randomized to receive either octreotide SC depot 10 mg every 2 weeks (treatment D, q2w) or 20 mg q4w (treatment E). After this treatment phase, the patients continued in a 28-day post-treatment follow-up phase (period 2) (Fig. 1). Randomization was stratified by disease (acromegaly or NET) and by long-acting IM octreotide dose at study entry (10 mg, 20 mg or 30 mg).

Octreotide SC depot (20 mg/mL) was supplied as a liquid ready-to-use formulation in 1.5 mL aliquots in glass vials stored at room temperature. Dose was adjusted by volume; 0.5 mL for 10 mg and 1 mL for 20 mg.

The primary objective of the study was to characterize the PK profile of the octreotide SC depot as compared to the PK profile of octreotide IM in patients with acromegaly or NETs.

In the acromegaly group, the secondary objectives were to assess the safety and tolerability of octreotide SC depot, to compare the effect of octreotide SC depot on response rate of IGF-1 normalization and mean growth hormone (GH) levels < 2.5 µg/L in period 1 and period 0, to characterize IGF-1 and GH profiles in period 1 and period 0, and to compare the proportion of patients with GH < 2.5 µg/L and normalized IGF-1 levels in period 1 and period 0. In patients with NETs, the secondary objective was to assess the safety and tolerability of octreotide SC depot.

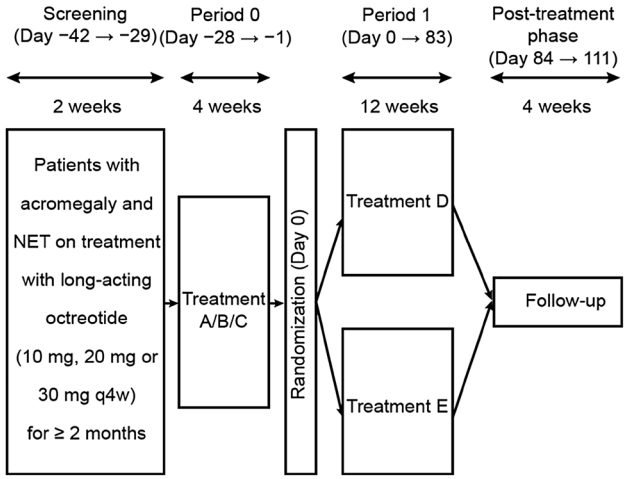

Fig. 1 Study design. Treatment A: long-acting IM octreotide 10 mg; Treatment B: long-acting IM octreotide 20 mg; Treatment C: long-acting IM octreotide 30 mg; Treatment D: octreotide SC depot 10 mg q2w; Treatment E: octreotide SC depot 20 mg q4w

The exploratory objectives in patients with NETs were to assess the symptoms of carcinoid syndrome (number of bowel movements and flushing episodes) in period 1 and period 0, and to assess the use of rescue medication (use of octreotide immediate release) in period 1 vs period 0 using patient diaries.

Assessments

The PK endpoints included the octreotide plasma concentration curve versus time and the PK parameters $AUC_{0–28}$, C_{max}, and C_{trough} for the last dose of long-acting IM octreotide (end of period 0) and for each dose of octreotide SC depot. The steady state PK (expected to be achieved after 3 cycles of administration) was compared between octreotide SC depot (cycle 3 of period 1) and octreotide IM (period 0).

The blood sampling time points and assays used for PK assessments are described in the Supplementary Appendix. Blood samples for assessment of IGF-1 and GH were collected at pre-specified time points during periods 0, 1, and 2. IGF-1 levels were assessed by a validated chemiluminescent method, IDS-iSYS- IGF-1 assay (Quest Diagnostics Clinical Trials) and GH levels were assessed using a validated immunoassay method, IMMULITE 2000 Growth Hormone (hGH) (Quest Diagnostics Clinical Trials). Both parameters were measured in serum. Safety was monitored by collection of adverse events [AEs; assessed according to National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v4.02], ECG recordings, and evaluation of clinical laboratory parameters (hematology, clinical chemistry, and urinalysis). Local tolerability at the injection site was assessed during the first 4 h after each injection. Erythema and swelling assessments were done using a 4-point rating scale (0 = none, 1 = mild, 2 = moderate, and 3 = severe) at 1 h and 4 h after every injection. Pain assessments were done immediately after injection, 30 min, 1 h, and 4 h after every injection using a numeric rating scale (NRS), where 0 = no pain and 10 = the worst possible pain. After the 4-h period, any injection site reaction was collected as an AE.

Statistical analyses

Full analysis set (FAS) included all patients treated with octreotide SC depot. Safety analysis set (SAS) included all patients who received at least one dose of octreotide IM or octreotide SC depot. Pharmacokinetic analysis set (PAS) consisted of patients who received all the doses of octreotide SC depot as scheduled. PAS was used for all PK and PD analyses. SAS was used to summarize safety data by treatment. PK and PD data were summarized using descriptive statistics. The number and percentage of patients with treatment-emergent AEs (new or worsening from baseline) were summarized by system organ class and preferred term.

Results

Patient population

Twelve patients were enrolled and completed the study (acromegaly $n = 7$; NET $n = 5$). Five patients of each indication received all the scheduled doses of octreotide SC depot and were included in the PAS. Two patients with acromegaly (in treatment sequences BE and CE) were excluded from the PAS due to protocol deviations of incorrect dose of treatment (the received dose could not be confirmed). Patient disposition by indication, treatment, and treatment sequence is presented in Table 1.

Baseline characteristics

Baseline characteristics (Table 2) were similar for patients with both indications. The median age was 64.5 years in the overall patient population. The primary site of the NETs was ileum in 4 patients (80%) and ileo-cecal in 1 patient (20%).

Pharmacokinetics

In both patient populations, C_{max} and $AUC_{0–28\ days}$ were significantly higher during treatment with octreotide SC depot 10 mg q2w and q4w (treatments D and E), respectively, than during treatment with long-acting IM octreotide 10 mg, 20 mg and 30 mg, (treatments A, B, and C, respectively) (Fig. 2; Table 3). C_{trough} values were similar between treatments with octreotide SC depot at 10 and 20 mg doses (D

Table 1 Patient disposition by indication, treatment and treatment sequence (FAS)

Acromegaly	Treatment D Octreotide SC depot 10 mg q2w				Treatment E Octreotide SC depot 20 mg q4w				All patients
Disposition	AD	BD	CD	All	AE	BE	CE	All	
	$N=0$	$N=0$	$N=3$	$N=3$	$N=1$	$N=1$	$N=2$	$N=4$	$N=7$
Enrolled and completed the study	0	0	3	3	1	1	2	4	7
NET	Treatment D				Treatment E				All patients
Disposition	AD	BD	CD	All	AE	BE	CE	All	
	$N=0$	$N=0$	$N=1$	$N=1$	$N=0$	$N=1$	$N=3$	$N=4$	$N=5$
Enrolled and completed the study	0	0	1	1	0	1	3	4	5

Treatment A: long-acting IM octreotide 10 mg prior to the first octreotide SC depot injection (reference)

Treatment B: long-acting IM octreotide 20 mg prior to the first octreotide SC depot injection (reference)

Treatment C: long-acting IM octreotide 30 mg prior to the first octreotide SC depot injection (reference)

Treatment D: octreotide SC depot 10 mg q2w (test)

Treatment E: octreotide SC depot 20 mg q4w (test)

N number of patients in the full analysis set (FAS)

Table 2 Baseline demographics by indication (FAS)

Demographic variable	Acromegaly patients $N=7$	NET patients $N=5$	All patients $N=12$
Age (years)			
n	7	5	12
Mean (SD)	61.0 (9.45)	63.6 (4.39)	62.1 (7.59)
Median	65.0	64.0	64.5
Min; max	42; 70	59; 70	42; 70
Sex, *n* (%)			
Female	3 (42.9)	0	3 (25.0)
Male	4 (57.1)	5 (100)	9 (75.0)
Ethnicity, *n* (%)			
Caucasian	3 (42.9)	2 (40.0)	5 (41.7)
Other	0	2 (40.0)	2 (16.7)
Missing	4 (57.1)	1 (20.0)	5 (41.7)
Weight (kg)			
Mean (SD)	76.5 (14.65)	87.5 (14.09)	81.1 (14.87)
Median	78.50	85.00	80.75
Min; max	58.0; 96.0	73.0; 109.0	58.0; 109.0
Height (cm)			
Mean (SD)	168.6 (9.27)	177.6 (4.77)	172.3 (8.76)
Median	166.0	178.0	173.0
Min; max	156; 183	172; 184	156; 184
BMI (mg/m^2)			
Mean (SD)	26.9 (4.41)	27.6 (3.50)	27.2 (3.91)
Median	25.2	26.8	26.3
Min; max	22.5; 35.7	24.7; 33.6	22.5; 35.7

and E) and IM octreotide at 20 and 30 mg doses (B and C). The octreotide exposure ($AUC_{0–28d}$ and C_{trough}) profile (treatment E) was higher in patients with NETs as compared to patients with acromegaly (Table 3).

Pharmacodynamics

Acromegaly

In patients with acromegaly, 3 of 5 (60%) patients who had IGF-1 levels below 1 × upper limit of normal (ULN) at the end of period 0, maintained their IGF-1 levels < 1 × ULN on day 84. Of these 3 patients, 2 were in treatment group D and 1 was in treatment group E. In the 2 patients who had IGF-1 levels above the ULN at the time of switch from treatment with octreotide IM to treatment with octreotide SC depot, IGF-1 levels remained above ULN after 3 months of octreotide SC depot treatment, although the levels improved in one of these patients (Fig. 3a).

Four patients, 2 each in the treatment groups D and E, had GH levels < 2.5 µg/L at all time points during the study. One patient had GH levels > 2.5 µg/L with some fluctuations and IGF levels > ULN at all time points during the study (Fig. 3b).

Neuroendocrine tumors

In patients with NETs, symptoms of carcinoid syndrome were overall well controlled over time in period 1 and were similar or showing some improvement as compared

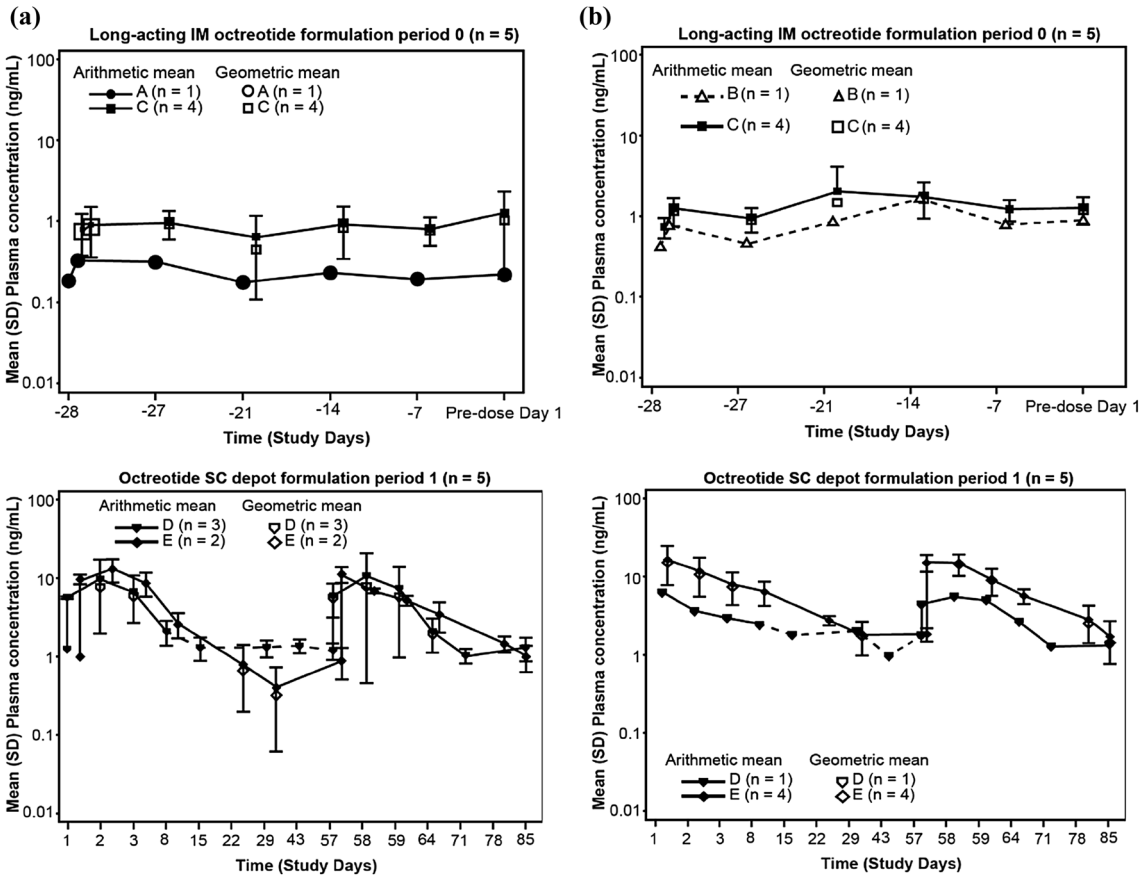

Fig. 2 Plasma concentration of octreotide versus time after injection of octreotide IM and octreotide SC depot in patients with **a** acromegaly and **b** NETs. Treatments: (A) octreotide IM 10 mg (B) octreotide IM 20 mg; (C) octreotide IM 30 mg (D) octreotide SC depot 10 mg q2w; (E) octreotide SC depot 20 mg q4w. The blood samples for PK assessments were collected at: predose, 1 h, and day(s) 1 (24 h), 7, 14 and 21 for period 0; predose, 2 h, and day(s) 1 (24 h), 2 (48 h), 7, 14 (predose), 28 (predose), 42 (predose), 56 (predose), 56 (2 h), 57, 58, 63, 70 (predose) for octreotide SC depot 10 mg q2w; and predose, 2 h, and day(s) 1 (24 h), 2 (48 h), 7, 21, 28 (predose), 56 (predose), 56 (2 h), 57, 58, 63, 77 for octreotide SC depot 20 mg q4w in period 1. Mean (SD) values are presented for $n > 1$; zero concentrations at individual time points are excluded from geometric mean computation; the dotted line represents the period between full treatment cycles

Table 3 Primary pharmacokinetic parameters by indication and treatment (PAS)

Treatment	Profile day[a]	AUC_{0-28d} (day ng/mL) Mean (SD)	C_{trough} (ng/mL) Mean (SD)	C_{max} (ng/mL) Mean (SD)
Acromegaly				
A ($N=1$) Long-acting IM octreotide 10 mg	Day −28	6.2 (–)	0.2 (–)	0.3 (–)
C ($N=4$) Long-acting IM octreotide 30 mg	Day −28	24.1 (11.6)	1.2 (0.6)	1.4 (0.7)
D ($N=3$) Octreotide SC depot 10 mg q2w	Day 56	95.6 (63.3)	1.0 (0.2)	10.6 (10.2)
E ($N=2$) Octreotide SC depot 20 mg q4w	Day 56	78.5 (20.0)	1.0 (0.4)	11.3 (2.6)
NET				
B ($N=1$) Long-acting IM octreotide 20 mg	Day −28	27.8 (–)	0.9 (–)	1.7 (–)
C ($N=4$) Long-acting IM octreotide 30 mg	Day −28	39.9 (20.5)	1.3 (0.5)	2.5 (1.8)
D ($N=1$) Octreotide SC depot 10 mg q2w	Day 56	83.3 (.)	1.3 (.)	5.6 (.)
E ($N=4$) Octreotide SC depot 20 mg q4w	Day 56	135 (34.7)	1.7 (1.0)	15.7 (4.1)

Day −28 is the start of period 0; (parameters refer to the assessment post-last long-acting IM octreotide injection)

Day 56 is the day of the last octreotide SC depot injection (3rd injection, i.e., steady state)

[a]PK profile starts on that day and continue for the next 28 days

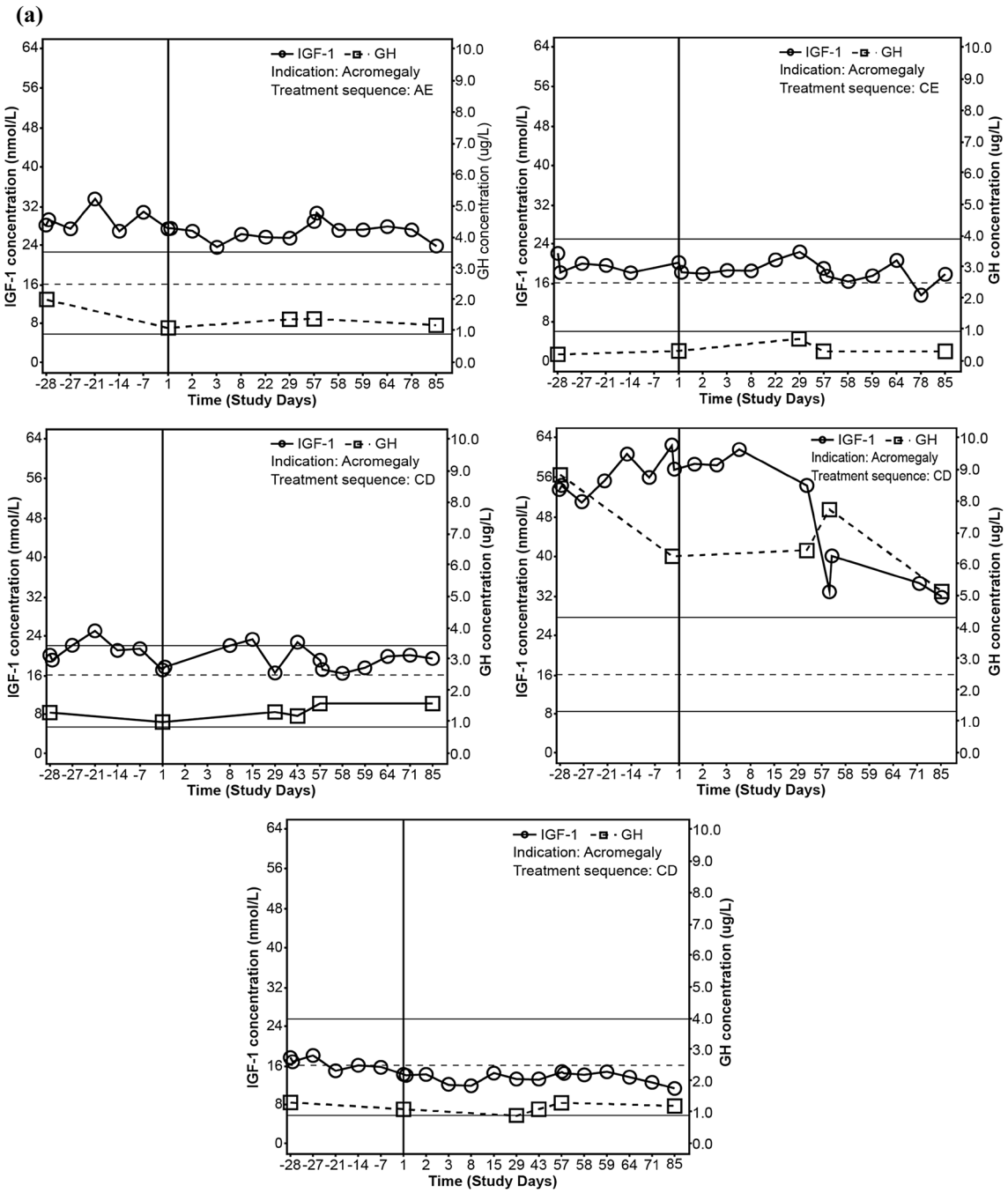

Fig. 3 Individual **a** GH and IGF-1 profiles (per patient) in patients with acromegaly and **b** symptom control profiles for patients with NET. The solid or dotted horizontal lines in **a** are age and gender adjusted normal ranges or values

to period 0 (Fig. 3c). None of the patients needed rescue therapy for symptom control during the study. In 1 patient in the treatment sequence CD (C, long-acting IM octreotide 30 mg; D, octreotide SC depot 10 mg q2w), 2 to 6 bowel movements/ day were reported during period 0 and 1 and no episodes of flushing. In the 20 mg q4w group (treatment E), 1 patient had no sporadic bowel moments or flushing episodes during period 0 or 1. In 1 patient with sporadic flushing episodes in period 0, no new occurrence was reported 28 days after switching to octreotide SC depot 20 mg q4w. In one patient with sporadic flushing episodes and sporadic bowel movements, no episodes of flushing and sporadic bowel movements were reported after 28 days (flushing) and 42 days (bowel movements) of switching to octreotide SC depot 20 mg q4w. One patient

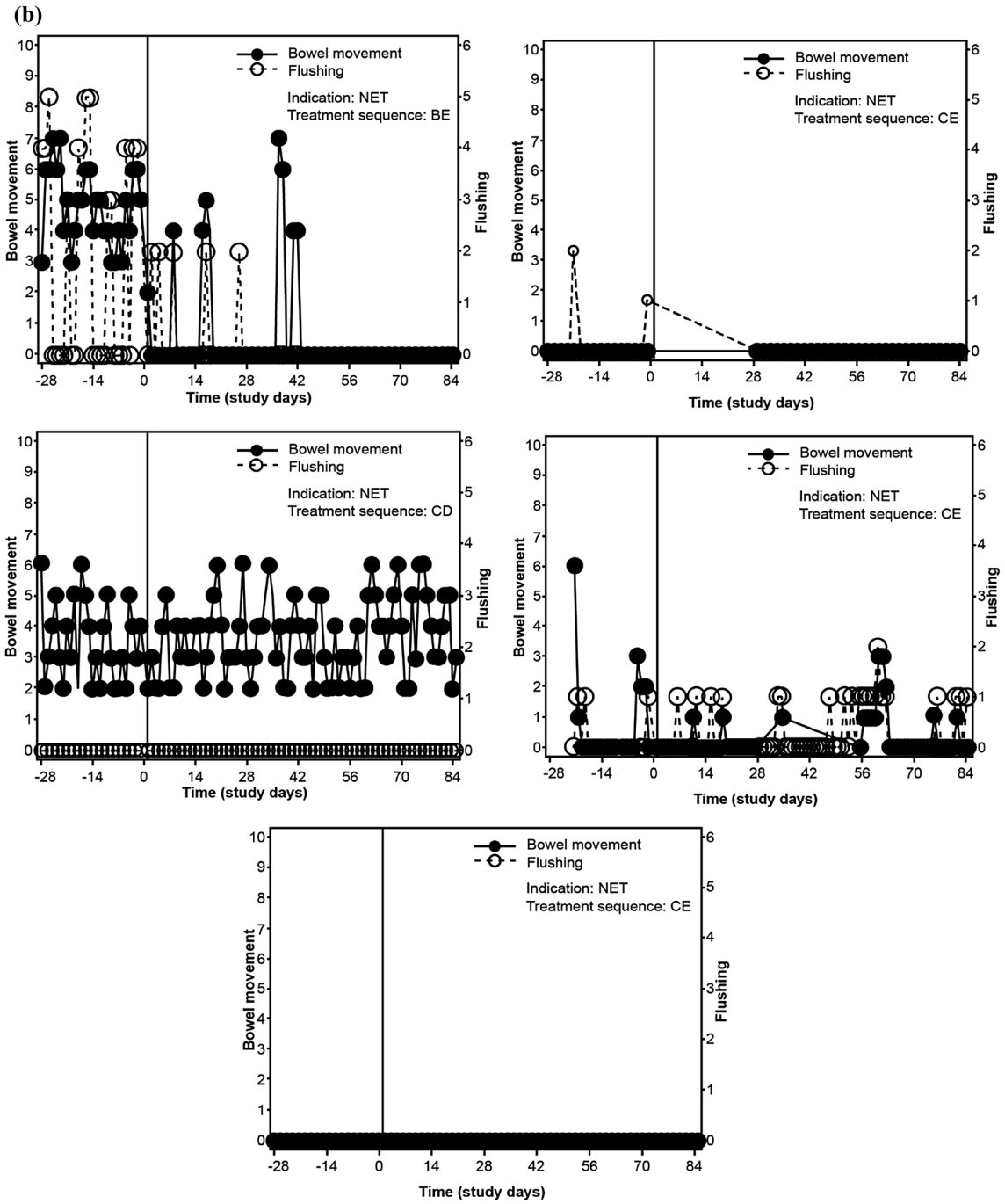

Fig. 3 (continued)

reported sporadic bowel movements and flushing episodes throughout both period 0 and period 1 (Fig. 3c).

Safety and tolerability

Overall, adverse events (AEs) were reported in 6 patients (50%) in period 0 and in 8 patients (67%) in period 1. All AEs were of grade 1–2. Notably, period 0 lasted one month, whereas period 1 lasted 4 months. The most commonly reported AEs in period 1 were gastrointestinal disorders [diarrhea ($n=3$), nausea ($n=1$)], injection site pain ($n=3$) and headache ($n=2$).

AEs in patients with acromegaly

In patients with acromegaly, AEs regardless of study drug relationship were reported in 6 patients (85.7%), all of which were grade 1. In period 0 (octreotide IM), AEs of IGF-1 increased, hyperglycemia, neck pain, osteoarthritis, and throat irritation were reported once each in 4 patients. AEs reported in period 1 were diarrhea and cough ($n=1$ each) in the octreotide SC depot 10 mg ($N=3$) group and vertigo, eyelid disorder, diarrhea, food poisoning, diabetes mellitus, and erythema ($n=1$ each); injection site pain ($n=2$) in the octreotide SC depot 20 mg ($N=4$) group.

AEs suspected to be study drug related were reported in 1 patient (33.3%) during treatment D (grade 1 diarrhea) and in 3 patients (75.0%) during treatment E (two patients had grade 1 injection site pain and one patient had grade 1 diabetes mellitus).

AEs in patients with NETs

In patients with NETs, AEs regardless of study drug relationship were reported in 3 patients (60.0%), all of which were grade 1 or 2. In period 0 (octreotide IM, $N=5$): 1 patient had a grade 2 AE of diarrhea and 1 patient a grade 2 AE of headache. No AEs were reported in period 1 in the octreotide SC depot 10 mg ($N=1$) group. In period 1, a single patient with SAE in the octreotide SC depot 20 mg group had multiple AEs (diverticulum intestinal, hematochezia, hiatus hernia, large intestine polyp, nausea, proctitis, asthenia, fatigue, general physical health deterioration, injection site pain, anastomotic ulcer hemorrhage, decreased appetite, neck pain, basal cell carcinoma, dizziness, headache, altered mood [$n=1$ each]). Decreased weight, diabetes mellitus, and hypertension were reported in one other patient.

AEs suspected to be drug-related were reported in 2 patients (40%) during treatment E (one AE each of nausea, decreased appetite, and diabetes mellitus, all grade 1). No AE lead to study withdrawal, study drug dose change or dose delay.

No grade 3 or 4 AEs were reported. No serious AEs were reported in patients with acromegaly. One serious AE of ulcerous intestine anastomosis bleeding was reported in a patient with NETs, however, it resolved and was not considered to be drug-related.

Local tolerability

Local tolerability assessment during the first 4 h after each injection: In patients with acromegaly, in period 1, few episodes of mild (grade 1) erythema and swelling were reported. Erythema of moderate (grade 2) intensity was observed on day 29 in 1 patient on octreotide SC depot 10 mg dose. Frequency and intensity of erythema and swelling were similar between treatment groups D (octreotide SC depot 10 mg q2w) and E (octreotide SC depot 20 mg q4w). No erythema or swelling was reported in patients with NETs during period 0 or 1. In patients with acromegaly, the highest grade of injection site pain reported on NRS scale (0–10) during periods 0 and 1 was 5 in the 20 mg group and 4 in the 10 mg group. In patients with NETs, the highest grade of injection site pain reported on NRS scale (0–10) during periods 0 and 1 was 4 in the 20 mg group and 3 in the 10 mg group. In patients with NETs, no instance of injection site pain was seen in the octreotide SC depot 10 mg q2w group.

Following the 4-h assessment of local tolerability after each injection, any event of injection site reaction was collected as AE. Two patients in the acromegaly group on treatment E (octreotide SC depot 20 mg q4w) experienced 3 episodes each of injection site pain, all of which were grade 1 and did not require any treatment. One patient with NETs on treatment E (octreotide SC depot 20 mg q4w) experienced an AE of injection site pain of grade 1, which did not require any treatment.

Laboratory abnormalities, liver safety, and vital signs

Two patients with NETs in the treatment group E had pre-existing grade 3 increased gamma-glutamyl transferase (GGT) ($n=1$) and pre-existing grade 3 increased triglyceride ($n=1$), both of which remained as grade 3 during the study. No new events of grade 3 or 4 abnormal laboratory values (including liver/ pancreatic enzymes) were reported in any indication. No patient experienced QTcF interval > 480 ms at ECG during the study.

Discussion

This open-label, randomized, phase 2 study evaluated the PK and PD profile, as well as the efficacy and safety of octreotide SC depot in patients with acromegaly and patients with NETs, previously treated with long-acting IM octreotide. The study showed that octreotide SC depot provided relatively higher bioavailability of octreotide as compared to the long-acting IM formulation and was efficacious in maintaining or improving disease control in both patient populations. Octreotide SC depot was well tolerated during the study and the safety profile was found to be consistent with the previously known safety profile of other octreotide formulations.

Octreotide SC depot is being developed as ready-for-use drug product and can be administered subcutaneously using a prefilled syringe, which may enhance patient convenience and allow self-administration, e.g., in the home setting.

In a phase 1 study in 122 healthy volunteers, octreotide SC depot provided approximately 4 to 5 times higher

bioavailability of octreotide as compared to octreotide IM, with faster onset of action and better suppression of IGF-1 levels [11]. AEs were reported in more than 90% of the healthy volunteers, with gastrointestinal AEs being the most common ones. These AEs were mild to moderate and generally lasted for a short duration. The most common AEs by preferred term were diarrhea (75%), headache (49%) and abdominal pain (34%) [11]. In comparison, the most frequently reported AEs in patients being treated with octreotide IM (occurring in ≥ 20%) were diarrhea, abdominal pain, flatulence in patients with acromegaly and nausea, abdominal pain, and, headache in patients with NET [13].

In the current study, the patients were on their usual dose of octreotide long-acting formulation at a dose of 10–20 mg or 30 mg q4w. The study aimed to compare the PK/exposure/safety of the new SC depot formulation given at 10 or 20 mg dose vs the regular doses of 10–20 or 30 mg q4w of octreotide long-acting IM formulation. In both patient populations, C_{max} and $AUC_{0–28d}$ of octreotide SC depot 10 or 20 mg were significantly higher than long-acting IM octreotide 10, 20, or 30 mg, which is consistent with the findings in the phase 1 study in healthy volunteers [11]. C_{trough}, an established PK indicator of sustained octreotide efficacy in patients with acromegaly, was similar for the two octreotide SC depot doses and octreotide IM 20 and 30 mg doses (treatment B and C). The PK parameters were lowest in one patient who was treated with octreotide IM 10 mg. For octreotide 20 mg q4w, the exposure of octreotide ($AUC_{0–28d}$ and C_{trough}) was higher in patients with NETs compared to patients with acromegaly. This is consistent with the previous reports of higher exposure observed for somatostatin analogs in patients with NETs as compared to acromegaly or healthy volunteers [14–17]. The reason for this phenomenon, however, remains unknown. In period 1, C_{max}, $AUC_{0–28d}$, and C_{trough} were similar after first injection (day 0) and after multiple injections (day 56). These preliminary results are rather interesting and should be interpreted with caution, due to the small number of patients enrolled in this study and also due to the fact that all patients were treated with octreotide IM prior to switch. A statistical model was planned to be used to compare test and reference treatment with respect to $AUC_{0–28d}$, C_{trough} and C_{max} of octreotide. Due to low number of patients, no model-based analysis was performed.

In patients with acromegaly, switching to octreotide SC depot resulted in maintenance of IGF-1 levels either at or below the preswitch values and maintenance of GH levels. In patients with NETs, switching to octreotide SC depot resulted in maintenance of symptom control or improvement of carcinoid symptoms.

Octreotide SC depot was well tolerated and the observed AEs were consistent with the previously known safety profile of octreotide [3, 18] with gastrointestinal disorders being the most commonly reported AEs. In the octreotide SC depot 20 mg q4w group, grade 1 AE of injection site pain was reported in 2 patients with acromegaly (3 episodes each) and in 1 patient with NET, none of which required treatment. No grade 3 or 4 AEs were reported during the study. It is noteworthy that despite significantly higher exposure and bioavailability of octreotide with the SC depot formulation, no increase in the frequency or severity of AEs was observed after switching from long-acting IM octreotide to octreotide SC depot. No new treatment-emergent relevant abnormal laboratory tests were observed during period 0 or 1. No relevant change was recorded in vital signs and ECG. Local tolerability at the injection site, assessed during the first 4 h after each injection, was overall good. A few episodes of erythema and pain were reported in patients with acromegaly and none was reported in patients with NETs. The maximal pain intensity was higher in the 20 mg group as compared to the 10 mg group in patients with acromegaly and could be associated with the higher injection volume in the 20 mg injection (1.0 mL) as compared to the 10 mg injection (0.5 mL). The intensity of pain was higher in patients with acromegaly than in NETs.

A key limitation to the interpretation of the study results is the small sample size; due to difficulties in patient recruitment (screening failures, refusal of patients to participate, available patients switching to other treatment options), only 12 patients could be recruited out of the planned 24.

In conclusion, the exposure to octreotide was higher with octreotide SC depot as compared to octreotide IM. In both the patient populations, efficacy and safety parameters were similar between the two dosing schedules (q2w and q4w) of the SC depot formulation. In patients with acromegaly, switching from octreotide IM to octreotide SC depot resulted in maintenance or improvement of biochemical control in terms of IGF-1 and GH levels. In patients with NETs, the control of carcinoid syndrome during treatment with octreotide SC depot was similar or improved as compared to treatment with long-acting IM octreotide. Further studies are warranted to evaluate the long-term efficacy and safety of the novel octreotide SC depot formulation in patients with acromegaly and NETs.

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Compliance with ethical standards

Conflict of interest MP received honoraria for presentations or advisory board from Novartis, IPSEN, Pfizer, and Lexicon. AC has noth-

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Ethical approval The study was conducted in accordance with the Declaration of Helsinki and applicable local regulations. The study protocol and all amendments were reviewed by the independent ethics committee or institutional review board for each center. All patients provided written informed consent to participate in the study.

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