BJCP British Journal of Clinical Pharmacology

DOI:10.1111/bcp.12698

Octreotide s.c. depot provides sustained octreotide bioavailability and similar IGF-1 suppression to octreotide LAR in healthy volunteers

Fredrik Tiberg,[1,2] John Roberts,[3] Camilla Cervin,[1] Markus Johnsson,[1] Severine Sarp,[4] Anadya Prakash Tripathi[5] & Margareta Linden[1]

[1]Camurus AB, Lund, [2]Physical Chemistry, Lund University, Lund, Sweden, [3]Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA, [4]Novartis Pharma AG, Basel, Switzerland and [5]Novartis Healthcare Pvt Ltd, Hyderabad, India

Correspondence
Dr Fredrik Tiberg, Camurus AB, Ideon Science Park, Gamma Building, Sölvegatan 41, SE-223 70 Lund, Sweden.
Tel.: +46 46 286 5730
Fax: +46 46 286 5739
E-mail: fredrik.tiberg@camurus.com

Keywords
depot, FluidCrystal®, formulation, octreotide, subcutaneous, injection

Received
2 January 2015

Accepted
8 June 2015

Accepted Article Published Online
15 June 2015

WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Octreotide is a synthetic somatostatin analogue used clinically for over 25 years in the treatment of acromegaly and neuroendocrine tumours.
- The currently marketed long acting formulation (octreotide LAR) requires a multistep reconstitution procedure and is administered intramuscularly.
- A phase I pharmacokinetic/pharmacodynamic and safety study was conducted to evaluate octreotide s.c. depot, a novel formulation of octreotide based on lipid-crystal technology, the unique characteristics of which potentially offer practical advantages over the existing LAR formulation.

WHAT THIS STUDY ADDS

- Compared with octreotide LAR, octreotide s.c. depot provided greater octreotide bioavailability with stronger and more rapid onset of suppression of IGF-1, as well as similar duration of effect, in healthy volunteers, with a safety profile generally comparable with that of the LAR formulation.

AIMS

The aim was to assess the pharmacokinetics, pharmacodynamics, safety and tolerability of octreotide subcutaneous (s.c.) depot, a novel octreotide formulation.

METHODS

This was a phase I, randomized, open label study. After a single dose of octreotide immediate release (IR) 200 μg, subjects were randomized to one of eight groups to receive three monthly injections of octreotide s.c. depot A 10, 20 or 30 mg, B 30 mg, C 10, 20 or 30 mg or long acting octreotide (octreotide LAR) 30 mg.

RESULTS

One hundred and twenty-two subjects were randomized. For all depot variants, onset of octreotide release was rapid and sustained for up to 4 weeks. The relative octreotide bioavailability of depot variants *vs.* octreotide IR ranged from 0.68 (90% confidence interval [CI] 0.61, 0.76) to 0.91 (90% CI 0.81, 1.02) and, *vs.* octreotide LAR, was approximately four- to five-fold greater: 3.97 (90% CI 3.35, 4.71) to 5.27 ng ml^{-1} h (90% CI 4.43, 6.27). All depot variants showed relatively rapid initial reductions of insulin-like growth factor 1 (IGF-1) compared with octreotide LAR. A trend of octreotide dose dependence was also indicated from the plasma concentrations and suppression of IGF-1. Maximum inhibition of IGF-1 at steady-state was highest for depot B and C. All depot treatments were well tolerated. The most frequent adverse events were gastrointestinal related.

CONCLUSIONS

Octreotide s.c. depot provides greater octreotide bioavailability with a more rapid onset and stronger suppression of IGF-1 than octreotide LAR in healthy volunteers.

Introduction

Somatostatin analogues (SSAs) are the current standard of safe and effective medical therapy for acromegaly and symptom control in gastroenteropancreatic neuroendocrine tumours (GEP-NET) [1–3]. In addition, SSAs show promising antitumour effects and are a management option for tumour control in patients with unresectable NETs [4–6].

Currently marketed somatostatin analogues include octreotide immediate release (IR; Sandostatin®, Novartis) and its long acting formulation octreotide LAR (Sandostatin® LAR®, Novartis), as well as lanreotide (available in two formulations: Somatuline® LA® and Somatuline® Autogel®/Depot®, Ipsen).

Octreotide LAR is a depot formulation based on polymer microsphere technology that is administered as a once monthly intramuscular injection and available as a powder for suspension. The reconstitution procedure requires refrigerated storage and encompasses seven different preparation steps, including very gentle handling to ensure homogenous suspension of the product before it can be administered. Owing to the clinical handling procedure and the intramuscular site of injection, octreotide LAR requires administration by a specially trained healthcare professional. In current clinical practice, many patients are cared for by specialist centres and often have to travel long distances for clinic visits, and the availability of a ready-to-use octreotide formulation that can be self or partner administered would result in added convenience.

Octreotide subcutaneous (s.c.) depot (Novartis Pharma AG, Basel, Switzerland) is a novel, ready-to-use octreotide formulation that has been developed using FluidCrystal® technology (Camurus AB, Lund, Sweden) in order to address the limitations of the LAR formulation. Octreotide s.c. depot is a liquid solution based on naturally occurring lipids, which permits the use of thin needles (22–27 G). When injected into subcutaneous or intramuscular tissue, the depot formulation absorbs interstitial aqueous fluid, resulting in *in situ* transformation from liquid into a highly viscous liquid-crystal gel phase [7, 8]. The formation of the liquid-crystal phase is a spontaneous process resulting from lipid self-assembly that begins immediately upon injection. The immediate onset of gel formation upon injection results in effective encapsulation of the drug compound from the depot matrix, providing a fast initial release (without burst) followed by a slower and consistent release of the drug. The depot is finally biodegraded in the subcutaneous or intramuscular tissue.

We report here an analysis from a phase I study that describes the pharmacokinetics (PK), the pharmacodynamic (PD) effect on secretion of insulin-like growth factor 1 (IGF-1) and the safety and tolerability profiles of three formulation variants of octreotide s.c. depot compared with octreotide LAR in healthy volunteers.

Methods

Subjects

Healthy male and female (not pregnant or lactating) volunteers aged 21–50 years with a body mass index of 19 to $<$30 kg m^{-2} were eligible for enrolment. Subjects were excluded if they used any prescription or non-prescription drugs or dietary supplements within 7 days, insulin or hypoglycaemic drugs within 2 months, oestrogen-containing medication within 2 months, or drugs that may affect growth hormone and IGF-1 levels (e.g. α-adrenergic, β-adrenergic and cholinergic drugs) within 1 month prior to dosing.

The study was approved by an independent ethics committee (Medical Association of North Rhine, approval number 2011310) and complied with the International Conference of Harmonization (ICH) Harmonized Tripartite Guidelines for Good Clinical Practice, the Declaration of Helsinki and local laws. All subjects provided written informed consent.

Study design and treatments

This phase I trial was a randomized, open label, repeat dose, active control, parallel group study (EudraCT number: 2011-001548-31). During a run-in period, subjects (n = 122) had to receive a single dose s.c. injection of octreotide IR 200 μg on day 0 in order to provide a normalizing reference for octreotide bioavailability and IGF-1 response. After a 7 day washout period, subjects were randomized to one of eight groups to receive three repeat once monthly injections on study days 7, 35 and 63: octreotide s.c. depot A 10, 20, 30 mg, octreotide s.c. depot B 30 mg, octreotide s.c. depot C 10, 20, 30 mg or octreotide LAR 30 mg.

The composition of each octreotide s.c. depot variant was based on findings from preclinical pharmacokinetic studies, as well as earlier phase I clinical studies of similar depot formulations. All variants had a 1 : 1 ratio of the functional lipid excipients phosphatidylcholine and glycerol dioleate, but with varying co-solvent levels.

The depot formulations were provided in glass vials for s.c. administration with conventional syringes with 23 G, thin-walled, 16 mm injection needles. Octreotide IR and the octreotide s.c. depot variants were administered as s.c. buttock injections. Octreotide LAR was administered as an intragluteal buttock injection following reconstitution with a 19 G, 38 mm injection needle. For the octreotide s.c. depot 10 mg, 20 mg and 30 mg (octreotide base) formulations, injection volumes administered were 0.5 ml, 1.0 ml and 1.5 ml, respectively. For octreotide LAR 30 mg (octreotide base), the injection volume was 2.5 ml.

Dose selection and timing of injections were based on data from previous studies of octreotide s.c. depot (10, 20 and 30 mg) and the approved summary of product characteristics for octreotide IR 200 μg [9] and octreotide LAR 30 mg [10]. Given the similar composition of the octreotide s.c. depot B and C variants, only one dose of octreotide s.c. depot B was assessed as these variants were expected to have similar PK profiles.

Objectives

The primary objective of the study was to characterize the PK profiles of octreotide following three repeat once monthly injections of octreotide sc depot A, B and C.

Secondary objectives included comparison of the PK and characterization and comparison of the PD profiles following three repeat once monthly injections of octreotide s.c. depot A, B and C *vs*. octreotide LAR, assessment of the safety and tolerability of repeated injections of octreotide s.c. depot A, B and C and octreotide LAR and assessment of the bioavailability of octreotide when administered as octreotide s.c. depot A, B and C compared with octreotide LAR and IR.

Pharmacokinetic assessments

Blood samples for PK analysis of octreotide IR were collected pre-injection (≤45 min before the injection) and at 5, 10, 15, 20, 30, and 45 min and 1, 2, 4, 8, 12, and 24 h post-injection. For randomized treatments, blood samples were collected pre-injection (≤45 min before the injection) and at 0.5, 1, 2, 4, 8, and 12 h post-injection on days 7, 35 and 63, on days 8, 9, 11, 14, 21, 28, 36, 37, 39, 42, 49, 56, 64, 65, 67, 70, 77, 84 and 91 and at the follow-up visit on day 105. Octreotide concentrations were analyzed in plasma containing dipotassium ethylenediaminetetraacetic acid using a validated bioanalytical method (PPD, Richmond, Virginia, USA). A 200 μl matrix aliquot was diluted with 200 μl of 4% phosphoric acid and fortified with 50 μl of 30 ng ml^{-1} internal standard ([$^{13}C_6$Phe$_3$]octreotide) working solution. Analytes were isolated through solid phase extraction by using Oasis WCX μElution plates. The final extract was analyzed by ultra-performance liquid chromatography with column switching and tandem mass spectrometry detection by using positive-ion electrospray detection. The nominal octreotide quantification range was 0.025–25.0 ng ml^{-1}. Precision (CV %) and accuracy (difference from theoretical concentration) were evaluated by replicate analyses of human plasma quality control pools prepared at five concentrations spanning the calibration range. The inter-assay coefficients of variation of the quality controls ranged from 4.0% to 7.6%, with the mean percentage differences from theoretical ranging from 0.8% to 4.7%. For analytical runs which contained diluted subject samples, the appropriate level quality control pool was diluted and analyzed in a similar manner to validate the dilution of study samples. All original and incurred reproducibility samples were analyzed in 75 runs that met the acceptance criteria. Assay reproducibility was good, with 98.2% matching the original results within ≤20%.

Pharmacodynamic assessments

Blood samples for PD analysis of IGF-1 were collected at screening and on day 0 before injection of octreotide IR (≤45 min before the injection) and at 0.5, 1, 4, 12 and 24 h after injection. For subjects in all eight randomized groups, blood samples were collected at the following time points: pre-injection (≤45 min before the injection) and at 1, 4 and 12 h post-injection on days 7, 35 and 63, on days 8, 9, 11, 14, 21, 28, 36, 37, 39, 42, 49, 56, 64, 65, 67, 77, 84 and 91 and at the follow-up visit on day 105. IGF-1 concentrations in serum samples were determined using a validated method based on the Siemens Immulite 2000 IGF-1 assay, which is a solid phase, two site, sequential immunoluminometric assay (PPD Global Central Labs, Zaventem, Belgium). The lower limit of quantitation was 25 ng ml^{-1} and the assay dynamic range was 25–1600 ng ml^{-1}, with a validated precision (CV %) of ≤7.0% at two concentration levels within the calibration range.

Determination of PK and PD parameters

The following PK parameters were determined for octreotide: AUC(0,∞) area under the plasma concentration–time curve (AUC) from time zero to infinity, AUC(0,t_{last}) AUC from time of dosing to last measurable concentration, AUC(0,τ) AUC over the dosing interval, C_{max} maximum plasma concentration from the first and third peaks, $t_{½}$ apparent terminal half-life and t_{max} time to maximum plasma concentration. The randomized treatments had a dosing interval of 28 days. The plasma concentration prior to the next dose, C_{trough}, was measured at 28, 56 and 84 days after drug administration of the sustained release products. The PK parameter estimations were conducted by using the default non-compartmental Model 200 (plasma data from extravascular dose input) in Phoenix WinNonlin (Version 6.3).

Safety analysis

Safety assessments included the evaluation of adverse events (AEs; coded using MedDRA Version 14.0 or later), local tolerability (erythema, swelling and pain), changes in vital sign measurements (pulse rate, respiratory rate, systolic and diastolic blood pressure and body temperature), physical examination findings, electrocardiogram (ECG) and abdominal ultrasound results, time and duration of gastrointestinal AEs and clinical laboratory investigations.

The clinical severity of AEs was classified and defined as mild (usually transient, potentially requiring only minimal treatment or therapeutic intervention, with the event not generally interfering with daily activities),

moderate (usually alleviated with additional specific therapeutic intervention, with the event interfering with daily activities, causing discomfort but posing no significant or permanent risk of harm to the subject) and severe (either interrupts daily activities or significantly affects clinical status or may require intensive therapeutic intervention).

Local tolerability at the injection site was assessed by a physician. Erythema and swelling assessments were based on a four point rating scale (0 = none, 1 = mild, 2 = moderate and 3 = severe) and performed during regularly scheduled AE assessments, as well as 1 and 6 h after injection of the randomized treatments on days 7, 35 and 63. Pain assessments were performed by using a 0 to 10 point numeric rating scale (0 = no pain, 10 = the worst possible pain). Pain was self-assessed by the subject immediately after injection (i.e. assessment of the 'pain on injection') and at 0.5, 1 and 6 h following injection on days 0, 7, 35 and 63.

Statistical analysis

All subjects who received at least one dose of any octreotide treatment were included in the safety population. The PK analysis set included all randomized subjects in the safety population who had at least one post-dose PK measurement. The evaluable (EVAL) population set included all randomized subjects in the safety population who had a complete PK profile for the third dose of randomized treatment. PK and PD analyses were summarized using descriptive statistics. All statistical analyses were performed with SAS® software (Version 9.1.3).

Steady-state conditions were determined by comparing the trough concentrations after the second and third injections for each treatment group using a paired *t*-test. Analysis of dose proportionality and dose linearity was performed for octreotide s.c. depot A and C (only one dose of octreotide s.c. depot B was studied) using a linear regression of the dose-adjusted C_{max} and AUC(0,τ) from the third injection *vs*. dose. AUC was calculated using the linear trapezoidal rule.

The relative bioavailability of the octreotide s.c. depot treatments was assessed using the PK variables (AUC (0,τ)) from the third injection with octreotide LAR as the reference and 90% confidence intervals (CIs) for the ratios of dose-adjusted parameters. Additionally, the relative bioavailability of octreotide when administered as s.c. depot and LAR formulations was assessed from the third injection using octreotide IR as the normalized reference (AUC(0,τ) [AUC(0,∞) for octreotide IR]) with 90% CIs for the ratios of dose-adjusted parameters. The AUC bioavailability of any two treatments was considered equivalent if the 90% CI of the ratio of the dose-adjusted AUCs was entirely within the range 0.75, 1.33.

For the PD analyses, the response (absolute and percentage) in IGF-1 from baseline (before injection on day 7 for randomized treatments) was calculated at all sampling time points. The response values were summarized at each visit for each treatment, with descriptive statistics. Safety and tolerability variables were analyzed and summarized descriptively.

Results

Disposition of subjects

Of the 123 subjects enrolled, 122 were randomized and 105 (85.4%) completed the study. Of the 18 subjects who discontinued, 10 (8.1%) withdrew consent, six (4.9%) discontinued because of an AE, one (0.8%) was withdrawn because of non-compliance with the protocol (subject tested positive for tetrahydrocannabinol) and one non-randomized subject (0.8%) withdrew because of pregnancy. All 123 subjects received at least one dose of octreotide (inclusive of octreotide IR) and were included in the safety population, 122 subjects were included in the PK population and 104 subjects were included in the evaluable population. Table 1 summarizes the demographic and baseline characteristics of the safety population.

Pharmacokinetic analysis

Plasma octreotide concentrations for single dose octreotide IR for each of the treatment arms exhibited a rapid increase in the observed peak concentrations followed by predictable exponential decay during the 24 h post-injection (Figure 1A). Following washout and administration of randomized treatments on day 7, the octreotide s.c. depot formulations and dose groups showed similar plasma concentration profiles, with consistent and rapid increases to C_{max} followed by a slower decrease during the remainder of the 28 day dose interval. Subsequent injections showed qualitatively similar profiles (Figure 1B–D).

Dose-dependent increases in mean plasma concentration were evident for octreotide s.c. depot A (Figure 1B) and C (Figure 1D). By contrast, following the first injection of octreotide LAR 30 mg, an initial short burst-like release of octreotide was observed to an initial peak concentration, which then rapidly declined to undetectable concentrations, followed by a rebound after about 1 week, reaching relatively stable concentrations from day 10. Concentrations then slowly decreased from day 21 post-injection (Figure 1E). Qualitatively similar profiles were seen with subsequent octreotide LAR 30 mg injections, although the initial decay to undetectable concentrations was not observed. Differences in the PK profiles of octreotide s.c. depot B and octreotide LAR were evident following graphical superimposition (Figure 1F).

The mean C_{max} following the 200 μg dose of octreotide IR was 6.95 ng ml^{-1}. The first doses of octreotide s.c. depot and octreotide LAR had mean

Table 1

Demographic characteristics (safety population)

Characteristic	Oct s.c. depot A 10 mg *n* = 17	Oct s.c. depot A 20 mg *n* = 16	Oct s.c. depot A 30 mg *n* = 17	Oct s.c. depot B 30 mg *n* = 14	Oct s.c. depot C 10 mg *n* = 14	Oct s.c. depot C 20 mg *n* = 15	Oct sc depot C 30 mg *n* = 15	Oct LAR 30 mg *n* = 14	Total *n* = 123
Age (years)									
Mean (SD)	33.2 (8.2)	37.1 (8.9)	37.1 (7.4)	40.6 (8.7)	41.9 (7.6)	39.1 (9.7)	39.3 (10.8)	37.8 (9.0)	38.2 (8.9)
Range	23–46	22–50	26–47	22–50	25–50	21–50	22–50	22–50	21–50
Gender, *n* (%)									
Male	8 (47.1)	9 (56.3)	7 (41.2)	9 (64.3)	8 (53.3)	7 (50.0)	6 (40.0)	9 (64.3)	63 (51.2)
Race, *n* (%)									
Caucasian	17 (100.0)	16 (100.0)	16 (94.1)	14 (100.0)	15 (100.0)	14 (100.0)	15 (100.0)	14 (100.0)	122 (99.2)
Asian	0	0	1 (5.9)	0	0	0	0	0	0
BMI (kg m^{-2})									
Mean (SD)	23.7 (2.7)	24.3 (2.3)	24.4 (2.6)	25.9 (2.3)	24.4 (3.3)	24.5 (2.6)	24.2 (1.9)	24.0 (3.0)	24.4 (2.6)
Range	19.0–29.3	20.8–28.3	20.1–29.1	20.9–29.9	19.1–29.3	20.2–29.3	19.7–27.9	19.7–28.1	19.0–29.9

BMI body mass index; Oct octreotide; SD standard deviation

C_{max} values of 7.07–29.13 and 1.04 ng ml^{-1}, respectively (Table 2). Similarly, mean C_{max} values following the third dose of octreotide s.c. depot treatments ranged from 8.9 to 34.5 ng ml^{-1} and it was 1.83 ng ml^{-1} for octreotide LAR. The mean $t_{½}$ for octreotide IR was 3.09 h, while the mean $t_{½}$ following the first dose of octreotide s.c. depot 10, 20 and 30 mg formulations ranged from 151 to 226 h. Median t_{max} values following first injection ranged from 4 to 47 h for the octreotide s.c. depot formulations, compared with 336 h for octreotide LAR. Following the third injection, median t_{max} ranged from 4 to 24 h for the octreotide s.c. depot formulations, compared with 1 h for octreotide LAR. For the third injection, mean AUC(0,τ) values ranged from 962 to 3778 ng ml^{-1} h for the octreotide s.c. depot 10, 20 and 30 mg doses. It was 733 ng ml^{-1} h for octreotide LAR 30 mg. The octreotide s.c. depot A, B and C 30 mg formulations all had similar PK profiles.

Dose linearity and approximately dose-proportional PK were observed for octreotide s.c. depot A and C for the third injection for both C_{max} and AUC(0,τ). C_{max} and AUC(0,τ) values for octreotide s.c. depot B 30 mg were similar to those of octreotide s.c. depot A and C 30 mg. Steady-state was achieved following the second injection for all treatments except for octreotide s.c. depot C 20 mg and octreotide LAR. All treatments achieved steady-state following the third injection (Table 3).

Bioavailability

The establishment of steady-state conditions provided the basis for comparing the bioavailability of randomized treatments. For the third injection, statistically significant differences were found for all dose-adjusted comparisons of AUC(0,τ) and C_{max} for the octreotide s.c. depot formulations *vs*. octreotide LAR. AUC(0,τ) ratios (for the EVAL population) ranged from 4.0 to 5.3, that is, the relative bioavailability for octreotide s.c. depot treatments *vs*. octreotide LAR amounted to 400–530%. C_{max} ratios (for the EVAL population) for octreotide s.c. depot *vs*. octreotide LAR ranged from 13.3 to 18.4. The trough concentrations of octreotide s.c. depot formulations *vs*. octreotide LAR were similar for comparable doses (Table 3).

The relative bioavailability of the randomized octreotide s.c. depot formulations at steady-state was also compared with octreotide IR by assessment of the ratio between the dose-normalized AUC(0,τ) of the randomized groups (at third injection) and the AUC(0,∞) for octreotide IR. The relative bioavailability for octreotide s.c. depot formulations *vs*. octreotide IR ranged from 0.684 to 0.907 (0.839 for the B variant) and was 0.172 for octreotide LAR *vs*. octreotide IR (Table 3). Only the octreotide s.c. depot C 30 mg group did not show a statistically significant difference *vs*. octreotide IR.

Reduction of IGF-1 concentrations

Suppression of mean IGF-1 concentrations was observed during the 24 h post-injection period of single dose octreotide IR for each of the treatment arms (Figure 2A). The PD profiles after each injection of the octreotide s.c. depot formulations showed a relatively rapid initial reduction in IGF-1 concentrations, which gradually increased with time until the next injection (Figures 2B–D). By contrast, octreotide LAR provided a slower and more gradual suppression of IGF-1 (Figure 2E). Generally, the IGF-1 concentrations showed less variation over time for octreotide LAR compared with the octreotide s.c. depot formulations. However, noticeable transient increases of the IGF-1 concentrations were observed during the first few days

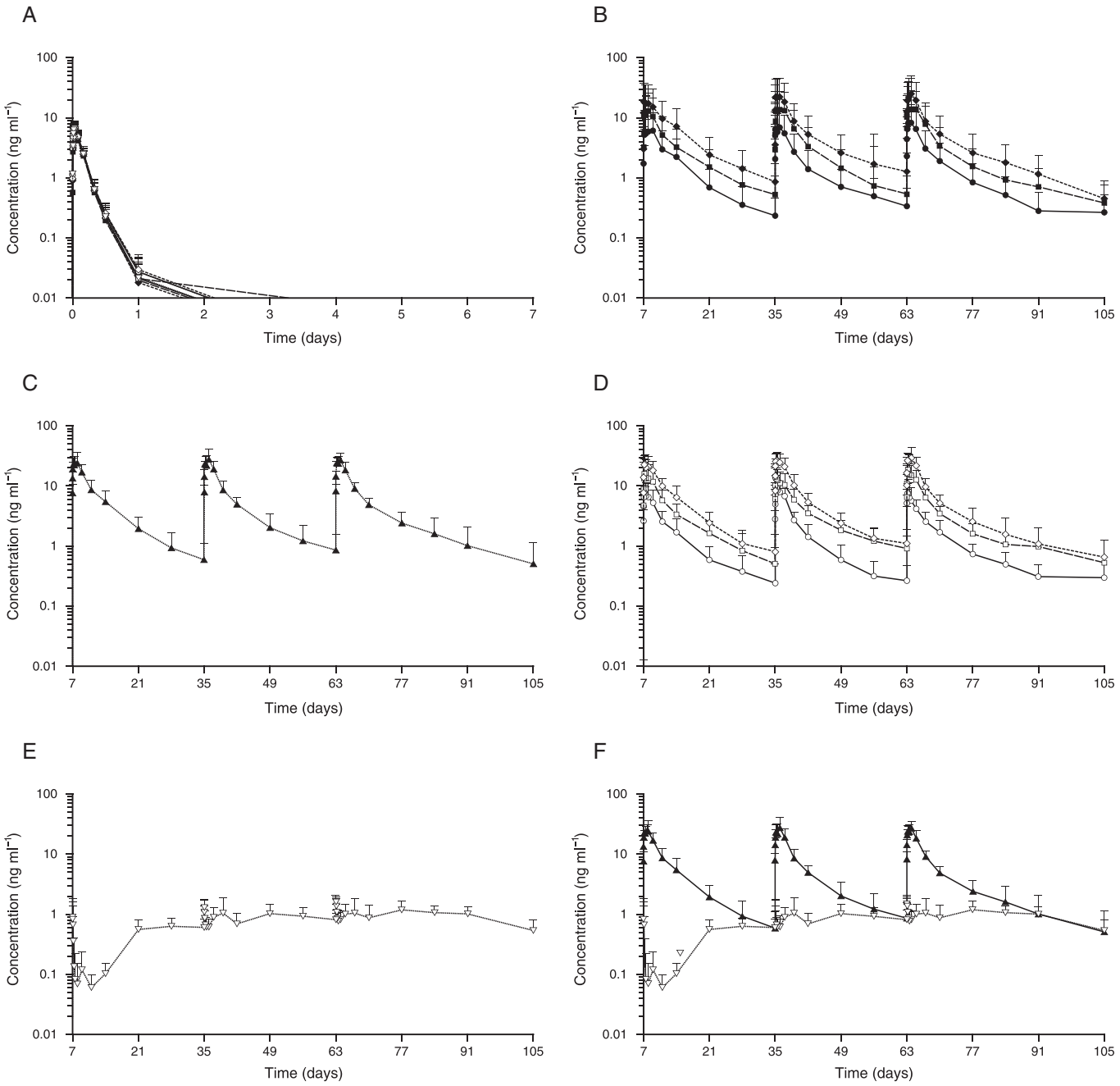

Figure 1

Mean octreotide plasma concentrations by sampling time (PK population) for A) octreotide IR for each of the randomized arms (octreotide IR (200 μg) for each of the following: —●—, octreotide s.c. depot A, 10 mg; —■—, octreotide s.c. depot A, 20 mg; --◆--, octreotide s.c. depot A, 30 mg; ···▲···, octreotide s.c. depot B, 30 mg; —○—, octreotide s.c. depot C, 10 mg; --□--, octreotide s.c. depot C, 20 mg; --◇--, octreotide s.c. depot C, 30 mg; ···▽···, octreotide LAR, 30 mg), B) octreotide s.c. depot A (—●—, octreotide s.c. depot A, 10 mg; —■—, octreotide s.c. depot A, 20 mg; --◆--, octreotide s.c. depot A, 30 mg), C) octreotide s.c. depot B (···▲···, octreotide s.c. depot B, 30 mg), D) octreotide s.c. depot C (—○—, octreotide s.c. depot C, 10 mg; --□--, octreotide s.c. depot C, 20 mg; --◇--, octreotide s.c. depot C, 30 mg), E) octreotide LAR (···▽···, octreotide LAR, 30 mg) and F) octreotide s.c. depot B superimposed with octreotide LAR (···▲···, octreotide s.c. depot B, 30 mg; ···▽···, octreotide LAR, 30 mg)

following the second and third injections of octreotide LAR. Compared with octreotide LAR, all octreotide s.c. depot formulations and doses provided a more rapid and extensive suppression of IGF-1 after the first injection, whereas suppression of IGF-1 was more similar between the eight randomized treatments for the second and third injections (comparison with octreotide s.c. depot B shown for clarity, Figure 2F). For both the first and third injections of octreotide s.c. depot A and C, suppression of IGF-1 was more pronounced

Table 2

Key parameter estimates following a single injection of octreotide IR (run-in period) and following the first and third randomized injections of octreotide s.c. depot A, B, C, and LAR formulations (EVAL population)

	Run-in	Randomized treatments							
PK parameter*	Oct IR Total n = 104	Oct s.c. depot A 10 mg n = 11	Oct s.c. depot A 20 mg n = 12	Oct s.c. depot A 30 mg n = 14	Oct s.c. depot B 30 mg n = 14	Oct s.c. depot C 10 mg n = 14	Oct s.c. depot C 20 mg n = 13	Oct s.c. depot C 30 mg n = 13	Oct LAR 30 mg n = 13
Values following first injection									
C_{max} (ng ml^{-1})	6.95 (1.76)	7.07 (1.72)	16.73 (6.32)	19.54 (7.46)	28.22 (10.99)	9.44 (4.00)	19.04 (9.07)	29.13 (9.75)	1.05 (0.92)
AUC(0,t_{last}) (ng ml^{-1} h)	27.4 (5.5)	1078.4 (221.3)	1990.7 (376.6)	3354.5 (962.0)	3153.1 (765.5)	1002.4 (354.6)	2140.6 (788.4)	3535.4 (984.2)	282.2 (84.4)
AUC(0,τ), (ng ml^{-1} h)	27.6† (5.4)	1080.1 (222.5)	1990.8 (376.6)	3354.6 (962.0)	3153.5 (765.8)	1004.7 (355.4)	2142.0 (788.7)	3535.5 (984.2)	338.4 (43.4)
t_{max} (h)	0.8 (0.3–1.0)	47.3 (4.0–48.7)	12.0 (2.0–48.0)	4.0 (4.0–95.8)	10.0 (2.0–97.0)	8.0 (4.0–47.5)	24.0 (2.0–48.8)	12.0 (2.0–49.0)	336.2 (0.5–671.9)
$t_{½}$ (h)	3.09 (0.84)	210.0 (213.4)	212.8 (66.5)	198.1 (53.2)	157.7 (75.7)	225.6 (198.7)	195.1 (139.8)	151.2 (60.6)	NA†
C_{trough} (ng ml^{-1})‡	0.02 (0.02)	0.24 (0.19)	0.53 (0.28)	0.86 (0.50)	0.60 (0.51)	0.24 (0.27)	0.52 (0.43)	0.82 (0.75)	0.61 (0.23)
C_{max}/C_{trough} (%)	348	29	32	23	47	39	37	36	1.7
Values following third injection									
C_{max} (ng ml^{-1})	–	9.2 (4.6)	16.9 (5.9)	27.2 (9.7)	29.3 (7.1)	8.9 (5.3)	21.1 (8.5)	34.5 (13.1)	1.8 (0.6)
AUC(0,t_{last}) (ng ml^{-1} h)	–	1247.7 (323.6)	2505.9 (748.6)	3853.9 (1123.2)	3708.9 (710.9)	1062.8 (250.2)	2616.3 (597.9)	4048.2 (922.5)	992.7 (304.2)
AUC(0,τ) (ng ml^{-1} h)		1166.7 (353.3)	2314.0 (703.8)	3571.1 (1033.6)	3465.1 (607.6)	962.3 (276.6)	2368.4 (523.9)	3778.3 (821.7)	732.9 (222.1)
t_{max} (h)	–	24.0 (4.0–48.5)	24.0 (2.0–48.8)	12.0 (2.0–24.1)	24.0 (2.0–24.0)	4.0 (2.0–48.8)	4.2 (2.0–49.0)	24.0 (2.0–49.2)	1.0 (0.5–359.9)
$t_{½}$ (h)	–	267.5 (97.5)	442.9 (645.6)	245.3 (160.4)	219.9 (129.1)	303.8 (211.7)	352.5 (488.5)	264.2 (167.3)	NA†
C_{trough} (ng ml^{-1})‡	–	0.28 (0.18)	0.71 (0.60)	1.18 (0.89)	1.03 (1.02)	0.31 (0.19)	1.0 (1.02)	1.08 (0.96)	1.0 (0.32)
C_{max}/C_{trough} (%)	–	33	24	23	28	29	21	32	1.8

*Values are represented as mean (SD); t_{max} is presented as median (range); †$t_{½}$ not reportable owing to limited duration of PK sampling window; ‡Plasma concentrations 24 h after administration of octreotide IR and 28 days after administration of octreotide s.c. depot and LAR formulations; NA, not applicable.

Table 3
Relative bioavailability and test for steady-state (EVAL population)

PK parameter	Randomized treatments						
	Oct s.c. depot A 10 mg	Oct s.c. depot A 20 mg	Oct s.c. depot A 30 mg	Oct s.c. depot B 30 mg	Oct s.c. depot C 10 mg	Oct s.c. depot C 20 mg	Oct s.c. depot C 30 mg	Oct LAR 30 mg/Oct IR 200 µg
Relative bioavailability of octreotide: Oct s.c. depot *vs.* Oct LAR, injection 3, ratio (90% CI)								
AUC(0,τ) ratio	4.762 (3.970, 5.712)	4.739 (3.967, 5.661)	4.898 (4.128, 5.812)	4.872 (4.106, 5.781)	3.973 (3.348, 4.714)	4.931 (4.143, 5.869)	5.270 (4.427, 6.272)	–
***P* value for treatment comparison**	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	–
C_{max} ratio	13.749 (10.441, 18.105)	13.661 (10.439, 17.877)	14.681 (11.334, 19.017)	16.247 (12.543, 21.046)	13.286 (10.257, 17.210)	16.621 (12.770, 21.632)	18.433 (14.163, 23.991)	–
Relative bioavailability of octreotide: Oct s.c. depot injection 3 *vs.* Oct IR, ratio (90% CI)								
AUC(0,τ)* ratio	0.819 (0.725, 0.926)	0.816 (0.725, 0.917)	0.843 (0.755, 0.940)	0.839 (0.752, 0.936)	0.684 (0.613, 0.763)	0.849 (0.758, 0.950)	0.907 (0.810, 1.016)	0.172 (0.152, 0.193)
***P* value for treatment comparison**	0.0076	0.0045	0.0106	0.0085	<0.0001	0.0175	0.1550	<0.0001
Test for steady-state, C_{trough}, mean difference (95% CI)								
$C_{day\ 35}$ *vs.* $C_{day\ 63}$	0.10 (–0.123, 0.325)	0.06 (–0.112, 0.231)	0.35 (–0.059, 0.762)	0.26 (–0.073, 0.596)	0.02 (–0.127, 0.174)	0.38 (0.071, 0.687)	0.26 (–0.384, 0.898)	0.26 (0.046, 0.482)
$C_{day\ 63}$ *vs.* $C_{day\ 91}$	–0.06 (–0.276, 0.164)	0.18 (–0.040, 0.400)	–0.10 (–0.715, 0.515)	0.17 (–0.181, 0.520)	0.05 (–0.032, 0.127)	0.06 (–0.514, 0.630)	–0.03 (–0.394, 0.328)	0.14 (–0.002, 0.276)

*Dose-adjusted AUC(0,τ) (test)/AUC(0,∞) (ref), geometric mean

at the higher dose (30 mg) compared with the lower 10 mg dose (Figure 3). Maximum inhibition after the third injection (steady-state) was highest for octreotide s.c. depot B (30 mg) and octreotide s.c. depot C (20 and 30 mg), with a mean inhibition of ~45% in all cases (Table 4).

Safety

For the randomized treatments, 115 subjects (94.3%) experienced an AE following the start of treatment (Table 5). A total of 109 subjects (89.3%) experienced an AE related to study drug.

During the period of randomized treatment, most AEs were mild or moderate in severity (17 [13.9%] mild, 91 [74.6%] moderate and 7 [5.7%] severe). The most frequent AE was diarrhoea (92 subjects [75.4%] overall), which was reported in similar numbers across the octreotide s.c. depot treatment groups. Headache was the second most frequently reported AE (60 subjects [49.2%], Table 5). AEs were more frequent for the octreotide s.c. depot formulations (85.7–100%) compared with octreotide LAR (71.4%). However, there were no obvious differences in the types of AEs and the frequency of events by dose. Octreotide s.c. depot B and C (20 mg) had the smallest number of drug-related AEs (85.7% and 78.6%, respectively) among the different octreotide s.c. depot formulations. In all randomized subjects, diarrhoea and headache were the most frequent AEs during steady-state (24 [19.7%] and 20 subjects [16.4%], respectively). Gastrointestinal (GI) events were mild to moderate in severity and were generally of short duration.

During the period of randomized treatment, six subjects (4.9%) experienced an AE leading to study discontinuation. Three subjects in the octreotide s.c. depot A (10 mg) group experienced one AE each of the following: syncope (severe, reported as a serious adverse event [SAE] as described below), diarrhoea (moderate) and increased lipase (severe) and blood amylase (moderate). One subject receiving octreotide s.c. depot A 20 mg had decreased thyroid-stimulating hormone (TSH, moderate), while increased lipase (mild) was recorded in one subject in the octreotide s.c. depot C (30 mg) group. Injection site pruritus (two events, one mild and one moderate) and erythema (two events, both mild) were experienced by one subject receiving octreotide s.c. depot A 30 mg. The outcome of all these AEs was reported as recovered. AEs leading to study discontinuation did not occur in subjects receiving octreotide s.c. depot B 30 mg, C 10 or 20 mg or octreotide LAR.

Two subjects (1.6%) presented with a SAE. One subject who received octreotide s.c. depot A 10 mg had a SAE of syncope that was judged 'possibly related' to study drug. On the day of the first injection, the subject experienced a

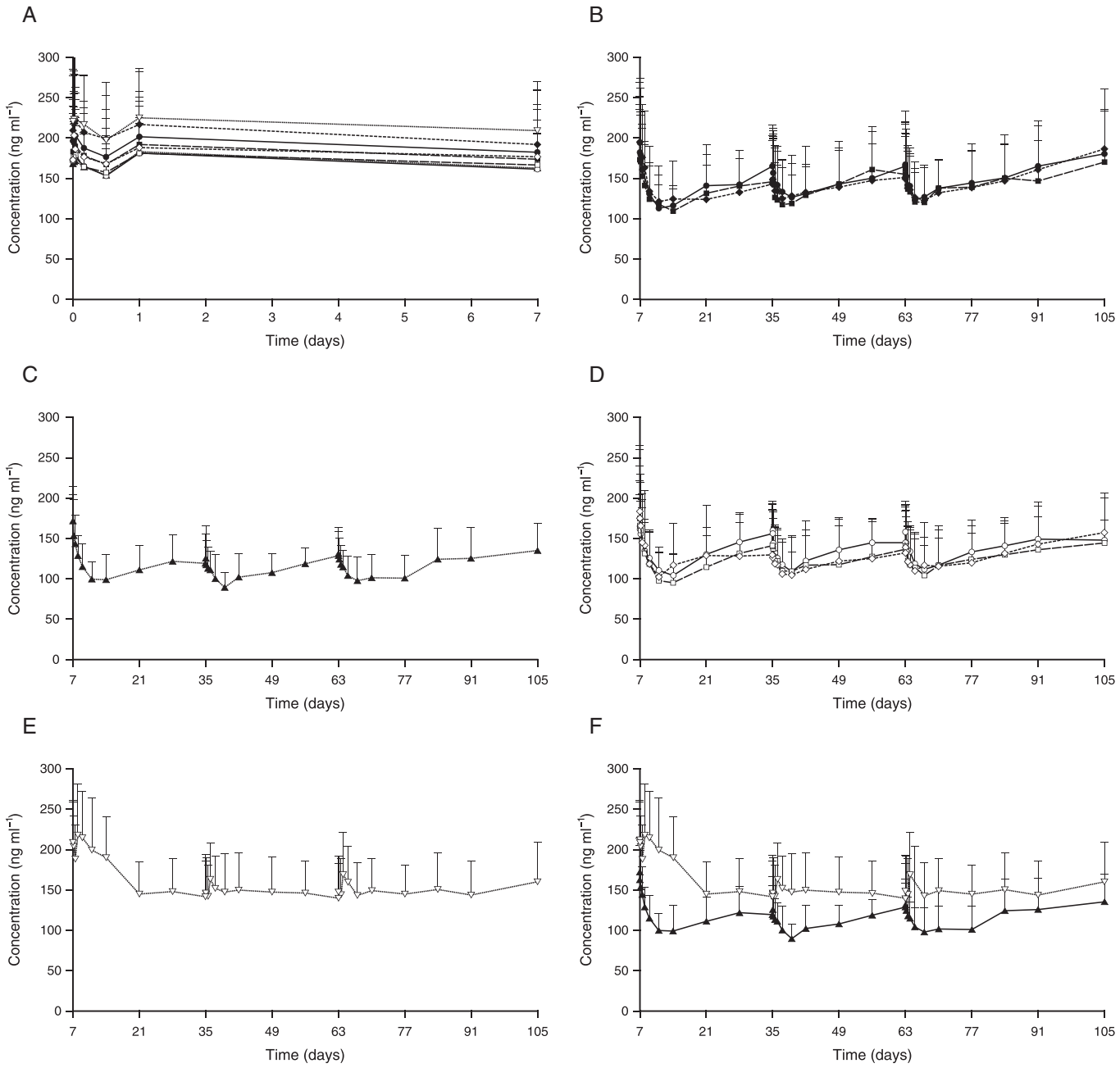

Figure 2

Inhibition of IGF-1 concentrations (absolute values) by sampling time (EVAL population) for A) octreotide IR for each of the randomized arms (octreotide IR (200 μg) for each of the following: —●—, octreotide s.c. depot A, 10 mg; —■—, octreotide s.c. depot A, 20 mg; --◆--, octreotide s.c. depot A, 30 mg; ···▲···, octreotide s.c. depot B, 30 mg; —○—, octreotide s.c. depot C, 10 mg; --□--, octreotide s.c. depot C, 20 mg; --◇--, octreotide s.c. depot C, 30 mg; ···▽···, octreotide LAR, 30 mg), B) octreotide s.c. depot A (—●—, octreotide s.c. depot A, 10 mg; —■—, octreotide s.c. depot A, 20 mg; --◆--, octreotide s.c. depot A, 30 mg), C) octreotide s.c. depot B (···▲···, octreotide s.c. depot B, 30 mg), D) octreotide s.c. depot C (—○—, octreotide s.c. depot C, 10 mg; --□--, octreotide s.c. depot C, 20 mg; --◇--, octreotide s.c. depot C, 30 mg), E) octreotide LAR (···▽···, octreotide LAR, 30 mg) and F) octreotide s.c. depot B superimposed with octreotide LAR (···▲···, octreotide s.c. depot B, 30 mg; ···▽···, octreotide LAR, 30 mg)

headache and developed abdominal pain and nausea followed by diarrhoea on the second day, and then vomiting and subsequent collapse on the third day. The subject was hospitalized the same day, treated and considered to have recovered from the event. The syncopal episode was likely a vegetative reaction attributable to the simultaneous occurrence of abdominal cramps and vomiting or an orthostatic collapse after diarrhoea and vomiting. The other SAE (accidental foot fracture and head lacerations) in a subject who received octreotide s.c. depot C (10 mg) was judged not to be study drug related. No deaths occurred during the study.

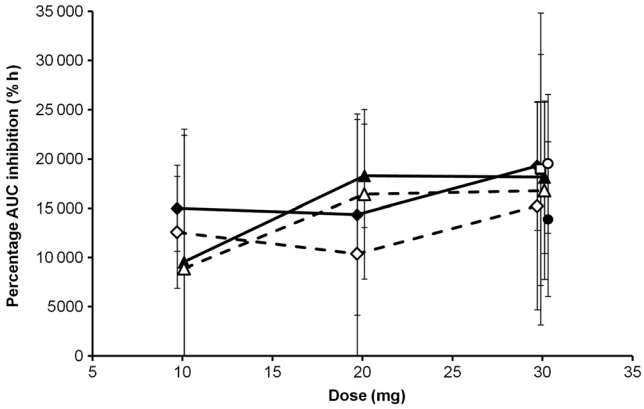

Figure 3

Suppression of IGF-1 concentrations (percentage AUC inhibition) for all doses of randomized treatments after the first and third injections. ⊸, Oct s.c. depot A, first dose; ■, Oct s.c. depot B, first dose; ⊸, Oct s.c. depot C, first dose; ●, Oct LAR, first dose; ⊸, Oct s.c. depot A, third dose; □, Oct s.c. depot B, third dose; ⊸, Oct s.c. depot C, third dose; ○, Oct LAR, third dose

Clinical laboratory evaluations and ECGs

Clinically significant increases in lipase values were observed in eight subjects, seven of whom had mild abnormalities, two in the octreotide s.c. depot A 20 mg group, one each in the octreotide s.c. depot C 10 mg and 20 mg groups, two in the octreotide s.c. depot C 30 mg group (one of whom discontinued the study as a result) and one in the octreotide LAR group. One severe lipase increase in the octreotide s.c. depot-A 10 mg group led to study drug discontinuation and the subject subsequently recovered. One subject receiving octreotide s.c. depot C 30 mg experienced a moderate increase in alanine aminotransferase (ALT) levels. In addition, one subject receiving octreotide s.c. depot A 20 mg had a clinically significant decrease in TSH that resulted in discontinuation (mentioned above). The outcome of all these laboratory abnormalities was reported as recovered. Glucose metabolism did not seem to be affected

Table 4

Concentration of IGF-1: maximum inhibition (percentage) for the first, second, and third randomized injections (EVAL population)

Characteristic	Oct s.c. depot A 10 mg *n* = 17	Oct s.c. depot A 20 mg *n* = 16	Oct s.c. depot A 30 mg *n* = 17	Oct s.c. depot B 30 mg *n* = 14	Oct s.c. depot C 10 mg *n* = 15	Oct s.c. depot C 20 mg *n* = 14	Oct s.c. depot C 30 mg *n* = 15	Oct LAR 30 mg *n* = 14
First injection								
Mean (SD), %	41.9 (6.0)	39.4 (12.0)	42.8 (10.0)	43.8 (16.4)	39.5 (13.0)	44.2 (7.0)	43.3 (12.3)	35.7 (11.2)
Second injection								
Mean (SD), %	37.2 (8.5)	37.5 (18.3)	39.1 (9.9)	46.2 (14.5)	36.3 (10.6)	40.0 (12.5)	45.7 (10.3)	41.2 (12.9)
Third injection								
Mean (SD), %	36.3 (6.4)	33.5 (16.0)	39.3 (12.2)	44.8 (15.7)	35.6 (15.1)	45.4 (10.6)	43.4 (7.4)	41.4 (12.0)

Table 5

Summary of most frequent (>10% in any treatment group) AEs* for randomized treatment injections ordered by decreasing total number (safety population)

Adverse event, *n* (%)	Oct s.c. depot A 10 mg *n* = 17	Oct s.c. depot A 20 mg *n* = 16	Oct s.c. depot A 30 mg *n* = 17	Oct s.c. depot B 30 mg *n* = 14	Oct s.c. depot C 10 mg *n* = 15	Oct s.c. depot C 20 mg *n* = 14	Oct s.c. depot C 30 mg *n* = 15	Oct LAR 30 mg *n* = 14	Total *n* = 122
Any AE	17 (100.0)	16 (100.0)	17 (100.0)	14 (100.0)	14 (93.3)	12 (85.7)	15 (100.0)	10 (71.4)	115 (94.3)
Diarrhoea	15 (88.2)	13 (81.3)	13 (76.5)	11 (78.6)	12 (80.0)	11 (78.6)	12 (80.0)	5 (35.7)	92 (75.4)
Headache	10 (58.8)	8 (50.0)	7 (41.2)	7 (50.0)	8 (53.3)	6 (42.9)	8 (53.3)	6 (42.9)	60 (49.2)
Abdominal pain	7 (41.2)	6 (37.5)	9 (52.9)	5 (35.7)	5 (33.3)	4 (28.6)	4 (26.7)	2 (14.3)	42 (34.4)
Injection site pain	2 (11.8)	4 (25.0)	5 (29.4)	3 (21.4)	3 (20.0)	3 (21.4)	4 (26.7)	3 (21.4)	27 (22.1)
Nasopharyngitis	4 (23.5)	3 (18.8)	1 (5.9)	4 (28.6)	3 (20.0)	4 (28.6)	3 (20.0)	2 (14.3)	24 (19.7)
Injection site pruritis	2 (11.8)	7 (43.8)	4 (23.5)	1 (7.2)	2 (13.3)	3 (21.4)	2 (13.3)	0 (0.0)	21 (17.2)
Injection site induration	3 (17.6)	2 (12.5)	2 (11.8)	3 (21.4)	3 (20.0)	3 (21.4)	2 (13.3)	1 (7.1)	19 (15.6)
Nausea	4 (23.5)	1 (6.3)	5 (29.4)	0 (0.0)	5 (33.3)	0 (0.0)	1 (6.7)	1 (7.1)	17 (13.9)
Flatulence	2 (11.8)	1 (6.3)	3 (17.6)	2 (14.3)	3 (20.0)	1 (7.1)	2 (13.3)	1 (7.1)	15 (12.3)
Injection site erythema	1 (5.9)	3 (18.8)	3 (17.6)	2 (14.3)	0 (0.0)	2 (14.3)	1 (6.7)	0 (0.0)	12 (9.8)
Injection site swelling	0 (0.0)	0 (0.0)	3 (17.6)	3 (21.4)	1 (6.7)	2 (14.3)	1 (6.7)	1 (7.1)	11 (9.0)
Vomiting	3 (17.6)	0 (0.0)	3 (17.6)	0 (0.0)	2 (13.3)	0 (0.0)	0 (0.0)	0 (0.0)	8 (6.6)
Injection site haematoma	0 (0.0)	0 (0.0)	2 (11.8)	0 (0.0)	1 (6.7)	2 (14.3)	3 (20.0)	0 (0.0)	8 (6.6)

*From the signing of informed consent to day 105

by study treatment, with no clinically significant abnormal glucose values reported. Furthermore, only one subject who received octreotide LAR 30 mg had an AE of cholelithiasis (mild).

QT interval increases occurred in 13 subjects, one each in the octreotide s.c. depot A 10 mg and 20 mg, octreotide s.c. depot C 10 mg, 20 mg and 30 mg and octreotide LAR groups, two in the octreotide s.c. depot B 30 mg group and five in the octreotide s.c. depot A 30 mg group, including one subject who only presented with the AE after the injection of octreotide IR and one subject with a right bundle branch block assessed as unlikely to be related to the study drug. All these abnormalities were mildly prolonged QT_c intervals and none of the QT_c interval increases were reported as related to treatment. The analysis of QT_c interval increases showed that the event was recorded in 12 subjects randomized to one of the octreotide s.c. depot formulations (nine males and three females), resulting in a total of 23 AEs. In females, eight measurements of QT_cB were above 450 ms and in males, there were 15 measurements above 450 ms. Considering QT_cF, six occurrences were above 450 ms in females and in males, two measures of QT_cF were above 450 ms. There were no QT_cB/QT_cF values over 480 ms. With regards to the increase from baseline, there were eight QT_cB interval increases of >30 ms, which occurred in two females (among them, one female with three occurrences) and four males. For QT_cF, two measurements of >30 ms from baseline where recorded in one female. There were no QT_cB/QT_cF interval increases from baseline >60 ms. In addition to these data obtained for the octreotide s.c. depot formulations, there was one subject in the octreotide LAR group who had a QT_cB of 480 ms but a pulse of 113 beats min^{-1} (QT_cF 432 ms).

Overall, there were no trends for the occurrence of abnormal laboratory parameters, vital signs, ECG parameters, or physical examinations observed during the study.

Local tolerability

In terms of local tolerability, it should be noted that the octreotide s.c. depot formulations were given by s.c. injection, whereas octreotide LAR was administered by deeper intramuscular injection. Only small numbers of subjects were found to have mild swelling across the treatment groups, with subjects receiving octreotide s.c. depot A 10 mg and octreotide LAR showing no cases of swelling at 1 and 6 h post-injection on days 7, 35 and 63. For the same time points, no cases of erythema were reported in subjects receiving octreotide s.c. depot A 30 mg or octreotide LAR, while instances of mild erythema did not exceed three cases in any of the other treatment groups.

A majority of subjects reported pain at the injection site immediately following injections. However, at the 1 and 6 h post-injection time points for the overall population, ≥87.6% of subjects across treatment groups experienced no pain at the injection site.

Discussion

This phase I study set out to assess the PK, PD and safety and tolerability profiles of three variants of a novel octreotide s.c. depot formulation compared with octreotide LAR in healthy volunteers. The formulations chosen for the present study were selected based on *in vitro* and preclinical assessments to improve the therapeutic index by reducing C_{max} values while increasing C_{trough} values compared with earlier octreotide s.c. depot formulation variants, while at the same time facilitating injectability.

The octreotide s.c. depot formulation variants (A, B and C) showed similar PK profiles, with a consistent and rapid increase to peak concentration, generally by 24–48 h, followed by a slow decay during the remainder of the 28 day dosing interval. The PK characteristics were markedly different for octreotide LAR and octreotide s.c. depot. The onset of octreotide release and therapeutic effect was near immediate after the first dose of the octreotide s.c. depot formulations, in contrast to octreotide LAR. C_{max} for octreotide IR (200 μg) was 7.0 ng ml^{-1}, which was comparable with the mean C_{max} values for the 10 mg doses of the octreotide s.c. depot formulations (approximately 9 ng ml^{-1}). Mean C_{max} for octreotide LAR 30 mg was 1.8 ng ml^{-1}. The establishment of steady-state conditions provided the basis for comparisons of the randomized treatments. Dose-normalized comparisons of AUC(0,τ) after the third injection of the octreotide s.c. depot variants *vs*. octreotide LAR showed that octreotide s.c. depot had approximately four- to five-fold greater bioavailability than octreotide LAR. The corresponding C_{max} ratio ranged from 13.3 to 18.4 at the same dose levels, while dose adjusted C_{trough} concentrations were similar. Octreotide s.c. depot formulation variants showed dose proportionality and linearity over the range 10–30 mg (as observed from A and C).

Although C_{max} for the 30 mg doses of octreotide s.c. depot was higher compared with octreotide LAR 30 mg (27–35 *vs*. 1.8 ng ml^{-1}) and the relative bioavailability of the octreotide s.c. depot formulations was four- to five-fold higher, the tolerability profile appeared comparable. The estimated therapeutic C_{max} and exposure range for the starting clinical dose of octreotide s.c. depot B were comparable with those of prior clinical exposure reports in subjects receiving the marketed octreotide IR formulation (400 μg s.c.) [11]. Single dose C_{max} was estimated to be 23.5 ng ml^{-1} and overall exposure can be extrapolated to multiple dose octreotide IR (400 μg s.c., three times a day) to give an AUC over a 28 day dosing interval of approximately 4416 ng ml^{-1} h, which is above the values reported here for AUC for the 30 mg doses of octreotide s.c. depot. Additionally, the octreotide IR label also

supports even higher doses of 500 μg three times a day, as required in some patients to achieve maximum efficacy.

Mean $t_{½}$ values were, as expected, much longer for octreotide s.c. depot *vs*. octreotide IR (approximately 200 h compared with 3.1 h, respectively). The bioavailability of octreotide LAR *vs*. octreotide IR was significantly lower than for the octreotide s.c. depot formulations *vs*. octreotide IR (0.172 for LAR *vs*. 0.684–0.907 for octreotide s.c. depot formulations), in accordance with the relative bioavailability calculated by comparison of octreotide s.c. depot and octreotide LAR exposures, as discussed above.

For octreotide s.c. depot A and C, there was a trend towards greater reductions in AUC percentage inhibition in IGF-1 with increasing dose. The observed variability in the profiles of depot variants A and C are probably related to differences in the group response, as the octreotide exposures are similar. Compared with octreotide LAR, all octreotide s.c. depot variants and doses provided a more rapid and extensive suppression of IGF-1 after the first injection and during the first 2 weeks after injection. Octreotide s.c. depot B 30 mg consistently demonstrated the lowest mean IGF-1 plasma concentrations (44–46% maximum suppression). The relatively large suppressions of IGF-1 for octreotide LAR 30 mg (36–41% maximum inhibition) observed for relatively low octreotide plasma concentrations may potentially be explained by the high pretreatment mean IGF-1 values measured in the octreotide LAR group.

The three octreotide s.c. depot formulation variants were well tolerated, both locally and systemically. In accordance with the known safety profile of octreotide [1, 9, 10, 12], the most frequent AEs for both the octreotide s.c. depot and LAR formulations were mild to moderate GI events. However, these tended to be of short duration. Injection local tolerability was generally good. Local discomfort was mild and transitory when it did occur.

Octreotide s.c. depot offers several advantages over octreotide LAR, including a rapid onset of therapeutic effect followed by a sustained release of octreotide for up to 4 weeks. By contrast, the lag phase and slow onset of therapeutic octreotide concentrations after the first dose of octreotide LAR may require repeat daily injections of octreotide IR during the first 7–10 days after the first injection. The different PK profiles of the s.c. depot and LAR formulations are likely the result of different drug release characteristics. Octreotide LAR is encapsulated in a polymer formulation that provides controlled octreotide release from an intramuscular site [13]. In contrast, the s.c. depot formulation forms a gel matrix that encapsulates octreotide *in situ* at a subcutaneous site. *In situ* stability of the formulations and the rate and extent of biodegradation, which could be influenced by the composition of the formulation excipients, may then determine the subsequent release characteristics of active octreotide.

The planned availability of octreotide s.c. depot as ready-to-use prefilled syringes combined with s.c. injection is also potentially advantageous *vs*. the multistep reconstitution process and intramuscular injection of octreotide LAR [10]. These features parallel some of the perceived advantages attributed to lanreotide Autogel, which is available in a prefilled syringe and is given subcutaneously rather than intramuscularly. However, the high viscosity of the lanreotide Autogel formulation requires a thick needle (18 or 19 G, length 20 mm) for administration. This is in contrast to octreotide s.c. depot, which permits the use of a thinner needle (needle size 23 G, needle length 16 mm used in the present study).

In conclusion, in healthy volunteers, octreotide s.c. depot provided approximately four- to five-fold greater octreotide bioavailability, with more rapid onset and similar duration of effect in terms of suppression of IGF-1, compared with octreotide LAR. Octreotide s.c. depot is a ready-to-use liquid formulation anticipated to be available in prefilled syringes and administered through a thin needle into the subcutaneous tissue. These unique characteristics offer practical advantages over the existing LAR formulation that may enhance convenience for patients and healthcare providers. Planned and ongoing studies of octreotide s.c. depot *vs*. octreotide LAR in patients with acromegaly and patients with symptoms associated with GEP-NET will provide further insights into the benefits of this novel formulation.

Competing Interests

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare FT, CC, MJ, ML, JR, SS, and APT had support from Novartis for the submitted work, FT, CC, MJ, ML were employees of Camurus and JR, SS and APT were employees of Novartis in the previous 3 years. There are no other relationships or activities that could appear to have influenced the submitted work.

This study was funded by Novartis Pharma AG and Camurus AB. Editorial support was provided by Richard Ogilvy-Stewart PhD, Mudskipper Business Limited and funded by Novartis Pharmaceuticals Corporation.

REFERENCES

1 Anthony L, Freda PU. From somatostatin to octreotide LAR: evolution of a somatostatin analogue. Curr Med Res Opin 2009; 25: 2989–99.

2 Katznelson L, Atkinson JL, Cook DM, Ezzat SZ, Hamrahian AH, Miller KK. American Association of Clinical Endocrinologists medical guidelines for clinical practice for the diagnosis and treatment of acromegaly - 2011 update. Endocr Pract 2011; 17 (Suppl 4): 1–44.

3 Pavel M, Kidd M, Modlin I. Systemic therapeutic options for carcinoid. Semin Oncol 2013; 40: 84–99.

4 Kunz PL, Reidy-Lagunes D, Anthony LB, Bertino EM, Brendtro K, Chan JA, Chen H, Jensen RT, Kim MK, Klimstra DS, Kulke MH, Liu EH, Metz DC, Phan AT, Sippel RS, Strosberg JR, Yao JC. Consensus guidelines for the management and treatment of neuroendocrine tumors. Pancreas 2013; 42: 557–77.

5 National Comprehensive Cancer Network, Inc. NCCN Practice Guidelines in Oncology™ Neuroendocrine Tumors (Version 2.0). 2006. Available at: http://www.nccn.org.

6 Oberg KE. The management of neuroendocrine tumours: current and future medical therapy options. Clin Oncol (R Coll Radiol) 2012; 24: 282–93.

7 Tiberg F, Johnsson M, Jankunec M, Barauskas J. Phase behavior, functions, and medical applications of soy phosphatidylcholine and diglyceride lipid compositions. Chem Lett 2012; 41: 1090–2.

8 Tiberg F, Johnsson M. Drug delivery applications of non-lamellar liquid crystalline phases and nanoparticles. J Drug Del Sci Tech 2011; 21: 101–9.

9 Novartis Pharmaceuticals. Sandostatin® (Octreotide Acetate) Basic Prescribing Information. NJ, USA: East Hanover, 2007.

10 Novartis Pharmaceuticals. Sandostatin® LAR® (Octreotide Acetate) Basic Prescribing Information. NJ, USA: East Hanover, 2012.

11 Kutz K, Nuesch E, Rosenthaler J. Pharmacokinetics of SMS 201-995 in healthy subjects. Scand J Gastroenterol Suppl 1986; 119: 65–72.

12 Yang LP, Keating GM. Octreotide long-acting release (LAR): a review of its use in the management of acromegaly. Drugs 2010; 70: 1745–69.

13 Astruc B, Marbach P, Bouterfa H, Denot C, Safari M, Vitaliti A, Sheppard M. Long-acting octreotide and prolonged-release lanreotide formulations have different pharmacokinetic profiles. J Clin Pharmacol 2005; 45: 836–44.