Safety and Efficacy of Oral Octreotide in Acromegaly: Results of a Multicenter Phase III Trial

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Background: A novel oral octreotide formulation was tested for efficacy and safety in a phase III, multicenter, open-label, dose-titration, baseline-controlled study for acromegaly.

Methods: We enrolled 155 complete or partially controlled patients (IGF-1 $<$ 1.3 $\times$ upper limit of normal [ULN], and 2-h integrated GH $<$ 2.5 ng/mL) receiving injectable somatostatin receptor ligand (SRL) for $\geq$ 3 months. Subjects were switched to 40 mg/d oral octreotide capsules (OOCs), and the dose escalated to 60 and then up to 80 mg/d to control IGF-1. Subsequent fixed doses were maintained for a 7-month core treatment, followed by a voluntary 6-month extension.

Results: Of 151 evaluable subjects initiating OOCs, 65% maintained response and achieved the primary endpoint of IGF-1 $<$ 1.3 $\times$ ULN and mean integrated GH $<$ 2.5 ng/mL at the end of the core treatment period and 62% at the end of treatment (up to 13 mo). The effect was durable, and 85 % of subjects initially controlled on OOCs maintained this response up to 13 months. When controlled on OOCs, GH levels were reduced compared to baseline, and acromegaly-related symptoms improved. Of 102 subjects completing the core treatment, 86% elected to enroll in the 6-month extension. Twenty-six subjects who were considered treatment failures (IGF-1 $\geq$ 1.3 $\times$ ULN) terminated early, and 23 withdrew for adverse events, consistent with those known for octreotide or disease related.

Conclusions: OOC, an oral therapeutic peptide, achieves efficacy in controlling IGF-1 and GH after switching from injectable SRLs for up to 13 months, with a safety profile consistent with approved SRLs. OOC appears to be effective and safe as an acromegaly monotherapy. **(*J Clin Endocrinol Metab* 100: 0000–0000, 2015)**

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Abbreviations: AE, adverse event; CI, confidence interval; LOCF, last observation carried forward; mITT, modified intent-to-treat; OOC, oral octreotide capsule; PK, pharmacokinetic; SRL, somatostatin receptor ligand; TPE, transient permeability enhancer; ULN, upper limit of normal.

Acromegaly, usually caused by a GH-secreting pituitary adenoma, is an inexorable chronic condition with significant morbidity and mortality (1). Hypersecretion of both GH and its target hormone, IGF-1, leads to acral disfigurement with bony overgrowth; hypertension; cardiac, cerebrovascular, and respiratory disease; arthritis; and tissue swelling (2, 3). In addition to pituitary tumor growth and/or postsurgical recurrence, acromegaly comorbidities occur especially with uncontrolled GH/IGF-1 hypersecretion, and most are ameliorated by aggressively controlling GH/IGF-1 levels (4–6). Acromegaly mortality determinants include GH $>$ 2.5 ng/mL and elevated IGF-1, hypertension, cardiovascular and cerebrovascular disease, requirement for glucocorticoid replacement, and prior pituitary radiation (4, 5, 7, 8). Effective surgical, radiation, and medical strategies to improve comorbidity and mortality require control of GH/IGF-1 (9–13). Treatments exhibit patient-specific efficacy, and each manifests unique side effects (1, 14–16).

Somatostatin inhibits pituitary GH secretion (17). Octreotide was selected as a therapeutic because of its prolonged circulating half-life compared to native somatostatin (2 h vs 2 min) (18), as well as the absence of acute rebound GH hypersecretion (19, 20). Injections of somatostatin analogs acting as somatostatin receptor ligands (SRLs) include sc immediate release, im, or deep sc depot preparations of octreotide and lanreotide (16, 21–23). Both target mainly somatotroph SSTR2 receptors to suppress GH secretion and subsequent peripheral IGF-1 production (17, 24, 25). Currently available parenteral SRLs effectively achieve biochemical control and symptomatic improvement in acromegaly, yet these discomforting injections engender challenges to patients and health care providers. Although attempts to develop oral octreotide have been reported (26, 27), these formulations were not assessed further.

We used oral octreotide capsules (OOCs), which facilitate intestinal octreotide absorption by a novel transient permeability enhancer (TPE) formulation (28). The capsule containing 20 mg nonmodified octreotide acetate formulated with TPE enables transient and reversible paracellular tight junction passage of molecules $<$ 70 kDa. The size limitation and limited permeability duration ensures that luminal pathogens and endobacterial toxins are excluded (28). Ingestion of OOCs by healthy volunteers achieved circulating octreotide levels and exposure comparable to those observed after sc octreotide injection (29).

Because a single 20-mg dose of OOC suppressed basal and GHRH-elicited GH levels in healthy volunteers (29), the drug was tested for efficacy and safety in a phase III, multicenter, open-label, dose-titration, baseline-controlled study in acromegaly. Objectives were to determine OOC effectiveness in maintaining baseline biochemical response for up to 13 months in acromegaly patients in whom prior treatment with an injectable SRL had been effective, ie, to assess the proportion of subjects maintaining baseline response levels after a switch to OOCs.

Subjects and Methods

This open-label, maintenance of response, baseline-controlled withdrawal study was conducted to evaluate OOC safety and efficacy in patients with acromegaly shown to tolerate and respond to injectable SRLs. This Institutional Review Board-approved multicenter international study continued from March 2012 to November 2013 in 37 sites (Supplemental Data) for approximately 15 months and included screening, baseline periods of approximately 2 months, a core treatment period of $\geq$ 7 months, a voluntary 6-month extension for patients who completed the core study, and a follow-up period of 2 weeks.

Patient population

Subjects had confirmed biochemical and clinical evidence for active acromegaly and were required to receive a stable dose of parenteral SRLs for at least 3 months before screening. At screening, patients had to demonstrate complete or partial response to SRLs, defined as IGF-1 $<$ 1.3 $\times$ the upper limit of normal (ULN) for age and integrated GH response over 2 hours of $<$ 2.5 ng/mL.

Patients were excluded if they had received GH antagonists (within $<$ 3 mo) or dopamine agonists (within $<$ 2 mo), received radiotherapy within 10 years, or underwent pituitary surgery within 6 months before screening.

Screening and baseline periods

Screening and baseline periods (median, 42 d) enabled assessment of subject eligibility and establishment of baseline disease control (IGF-1 and GH measurements) while receiving parenteral SRL injections. The first OOC dose was administered $\geq$ 4 weeks after the last SRL injection. On average, the last SRL dose was given approximately 2 weeks after the screening visit and 2 weeks before the baseline visit.

Treatment period

The OOC treatment period lasted $\geq$ 13 months and comprised a dose escalation (2–5 mo) followed by a fixed-dose period (8–11 mo). The fixed-dose period included the time periods up to the completion of the core and extension treatment phases (at 7 and 13 mo, respectively). Enrollment into the extension phase was voluntary. OOC was administered in the morning and evening ($\geq$1 h before a meal and $\geq$ 2 h after a meal).

Dose escalation

The first OOC dose (20 + 20 mg) was dispensed $\geq$ 4 weeks (mean [SD], 33.3 [12.62] d; median [P25, P75], 31.0 [29.0, 35.0] d) after the last SRL injection. OOC dose escalations (to 40 + 20 mg, and if required to 40 + 40 mg) occurred after two successive visits if IGF-1 was inadequately controlled on a stable dose, ie, a $>$20% increase over prior levels, or emergence of acromegaly symptoms. Visits occurred every 14 days for IGF-1 measurements, and results were used to guide dosing decisions at the

subsequent visit. Integrated GH levels (measured 2–4 h after OOC administration) were measured with every dose escalation. Subjects could revert to parenteral SRL therapy at any time, for either safety or efficacy, at the discretion of the site.

Fixed dose

Subjects entered the fixed-dose period when IGF-1 levels were normalized or returned to baseline levels during ≥ two successive visits. Per protocol, adequately controlled subjects completing the core treatment period were offered the option to continue a 6-month extension. At each monthly visit during the core treatment and bimonthly during the extension, IGF-1 was measured and acromegaly symptoms assessed. Integrated GH levels were measured at the beginning and end of the fixed-dose period (core and extension). The optimally effective OOC dose achieved during dose escalation was continued for the duration of the fixed-dose period for up to 13 months.

Endpoints and statistical analysis

The primary efficacy endpoint was descriptive and was defined as the proportion of responders at the end of the core treatment, with an exact 95% confidence interval (CI) in the modified intent-to-treat (mITT) population (ie, all subjects who had ≥ one post-first-dose efficacy assessment). Response was defined, similar to the inclusion criteria, as IGF-1 $< 1.3 \times$ ULN for age and integrated GH < 2.5 ng/mL (utilizing last observation carried forward [LOCF] imputation). At the end of the extension, the primary endpoint was the proportion of responders, of all subjects who entered the extension (extension-intent-to-treat), and for those who entered the extension as responders, with an exact 95% CI. When continuous measures were reasonably symmetric, mean values and SD were used; otherwise, both mean and median values are presented.

Secondary and exploratory descriptive endpoints included the proportion of subjects who achieved categorical response levels at the end of treatment, based on IGF-1 and/or GH levels, and the proportion of subjects who maintained response, ie, who remained responders from the beginning of the fixed-dose phase to the end of the treatment periods.

Acromegaly symptoms (headache, asthenia, perspiration, swelling of extremities, and joint pain) were scored by severity at each visit: absent = 0, mild = 1, moderate = 2, severe = 3. The proportion of subjects with improvement, no change, or worsening in overall scores, as well as those with one, two, or three active symptoms from baseline to the end of treatment was calculated.

Assays

IGF-1 and GH were measured centrally by IDS-iSYS IGF-1 (IS-3900; Immunodiagnostic Systems) (30) and IDS-iSYS hGH (IS-3700; Immunodiagnostic Systems) (31) assays at the Endocrine Laboratory, Universität München, (Munich, Germany) and Solstas Lab (Greensboro, North Carolina). Recombinant standards (98/574 for GH and 02/254 for IGF-1) yielded interassay variability of 4–8.7% (IGF-1) and 1.1–3.4% (GH) and sensitivity of 8.8 ng/mL (IGF-1) and 0.04 ng/mL (GH) (30, 31). Integrated GH levels were calculated from the mean of five samples collected every 30 ± 5 minutes for 2 hours beginning 2 hours after drug dosing (or at time zero at screening and baseline visits) (31). IGF-1 measurements were assayed from a single sample (time zero) and compared to age-related reference ranges (30). Routine laboratory safety assessments were performed centrally, and all samplings were after ≥ 8 hours of fasting .

During the fixed-dose period, 46 subjects at a subset of sites underwent pharmacokinetic (PK) evaluation (Supplemental Data).

Oversight

The protocol was developed by an academic steering committee and the sponsor; independent study oversight was provided by the data-monitoring committee. The first draft was written by the first author, and all authors reviewed the data and participated in preparing the manuscript.

Results

Baseline characteristics

Enrolled subjects had been receiving long-acting SRL injections for 3 months to > 20 years at all dose ranges. Of the 155 subjects enrolled, 95 had IGF-1 $\leq 1 \times$ ULN and GH < 2.5 ng/mL at baseline; of these, 67 (43%) had GH $<$ 1 ng/mL. Forty-two subjects entered the study with $1 <$ IGF-1 $< 1.3 \times$ ULN and GH < 2.5 ng/mL. Although eligible patients had to meet criteria of complete or partial response to injectable SRLs at screening to enter the study, only 88.7% of these subjects were responding to injectable SRLs at baseline, and 17 patients (11%) had IGF-1 $\geq 1.3 \times$ ULN and/or GH ≥ 2.5 ng/mL (Table 1); 81% of subjects had active acromegaly symptoms despite treatment with injectables.

Subject disposition

A total of 235 patients were screened, and most of those failing to meet inclusion criteria had IGF-1 $\geq 1.3 \times$ ULN. A total of 155 subjects (67 males, 88 females) were enrolled, 151 underwent at least one biochemical assessment after the first OOC dose (mITT), 110 (71%) entered the fixed-dose period, 88 elected to continue into the 6-month extension, and 82 completed 13 months of treatment.

Fifty-nine subjects discontinued treatment during the course of the study, most (n = 45; 76%) during the dose-escalation period. Early terminations were due to treatment failure (IGF-1 $> 1.3 \times$ ULN; n = 26; 16.8%), adverse events (AEs) (n = 23; 14.8%), patient choice (n = 7; 4.5%), loss to follow-up (n = 2; 1.3%), and sponsor request (n = 1; 0.6%).

Efficacy

Overall, 65% of all enrolled subjects (mITT population, n = 151; 95% CI, 58.4–74.2), were responders up to 7 months, and 62% were responders up to 13 months (95% CI, 54.9–71.7), as compared to 88.7% at the baseline visit while on injectable SRLs. Sensitivity analysis (Markov Chain Monte Carlo multiple imputation)

Table 1. Baseline Characteristics of All Subjects Enrolled (n = 155)

Demographics	
Age, mean (SD)	54.2 (11.54)
Gender, female	88 (56.8)
Disease characteristics	
Duration of acromegaly, y	
<10	74 (47.7)
10 to <20	53 (34.2)
≥20	28 (18.1)
Pituitary tumor characteristic	
Microadenoma	51 (32.9)
Intrasellar macroadenoma	53 (34.2)
Extrasellar macroadenoma	46 (29.7)
Other	5 (3.2)
Medical treatment	
Previous treatments for acromegaly	
Surgery	121 (78.1)
Medication other than SRLs	61 (39.4)
Radiation	13 (8.4)
Surgery followed by radiation	8 (5.2)
Radiation followed by surgery	1 (0.6)
Previous SRL treatment	
Octreotide LAR, mg[a]	97 (62.6)
10, 20	64 (66% of patients on octreotide)
30, 40, 60	33 (34% of patients on octreotide)
Lanreotide, mg[b]	58 (37.4)
60, 90	27 (47% of patients on lanreotide)
120	31 (53% of patients on lanreotide)
Time receiving parenteral SRLs, y	
<1	21 (13.5)
1 to <5	63 (40.6)
5 to <10	37 (23.9)
≥10	34 (21.9)
Subjects on combination cabergoline/pegvisomant[c]	18 (11.6)
Symptomatic and biochemical control	
Acromegaly symptoms	
Headache	64 (41.3)
Perspiration	65 (41.9)
Asthenia	68 (43.9)
Swelling of extremities	58 (37.4)
Joint pain	87 (56.1)
At least one symptom	125 (80.6)
At least two symptoms	91 (61.3)
At least three symptoms	67 (43.2)
IGF-1 (ULN)	
Mean (SD)	0.94 (0.250)
Median (P25, P75)	0.89 (0.76, 1.07)
GH, ng/mL	
Mean (SD)	0.93 (0.716)
Median (P25, P75)	0.77 (0.44, 1.23)
Biochemical control	
IGF-1 ≤ 1 × ULN and GH < 2.5 ng/mL	95 (61)
IGF-1 ≤ 1 × ULN and GH < 1 ng/mL	67 (43)
IGF-1 ≤ 1 × ULN and 1 ≤ GH < 2.5 ng/mL	28 (18)
1 < IGF-1 < 1.3 × ULN and GH < 2.5 ng/mL	42 (27)
IGF-1 ≥ 1.3 × ULN and/or GH ≥ 2.5 ng/mL	18 (12)

Data are expressed as number (percentage), unless stated otherwise.

[a] Sandostatin LAR.

[b] Somatuline Autogel.

[c] Subjects on combination therapy with cabergoline/pegvisomant within the last 6 months before screening.

showed 65.6% response, consistent with primary LOCF analysis.

The effect was durable because 85 and 89% of subjects who entered the fixed-dose and extension periods, respectively, as responders maintained response for up to 13 months of treatment; 78.4% (95% CI, 68.4, 86.5) of subjects who entered the extension were responders at the end of treatment (up to 13 months). At the beginning of the

Table 2. IGF-1 and Mean Integrated GH Suppression at Baseline and End of Treatment

mITT Population	Baseline	End of Treatment
n	151	151
IGF-1 $<$ 1.3 $\times$ ULN and GH $<$ 2.5 ng/mL	134 (88.7)	93 (61.6)
IGF-1 $\leq$ 1 $\times$ ULN and GH $<$ 1 ng/mL	65 (43.0)	49 (32.5)
IGF-1 $\geq$ 1.3 $\times$ ULN and/or GH $\geq$ 2.5 ng/mL	17 (11.3)	58 (38.4)
IGF-1 $<$ 1.3 $\times$ ULN	138 (91.4)	97 (64.2)
IGF-1 $\leq$ 1.0 $\times$ ULN	96 (63.6)	57 (37.7)
GH $<$ 2.5 ng/mL	145 (96.0)	140 (92.7)
GH $<$ 1.0 ng/mL	100 (66.2)	117 (77.5)
Median IGF-1 levels (Q1-Q3)	0.90 (0.76–1.07)	1.120 (0.870–1.440)
Median GH levels (Q1-Q3)	0.77 (0.44–1.23)	0.488 (0.244–0.870)

Data are expressed as number (percentage), unless stated otherwise. IGF-1 and GH categories at baseline and end of treatment (core + extension) are presented for all enrolled subjects, with at least one efficacy measure on post first OOC dose (mITT population). This analysis also includes the 59 subjects who terminated early in the study. For this analysis, the last concentrations of IGF-1 and GH on treatment were carried forward. Q1-Q3 indicates interquartile range.

Table 3. IGF-1 and Mean Integrated GH Suppression at Beginning of Fixed-Dose Period and End of 13-Month Treatment

Fixed-Dose Population	Beginning of Fixed Dose	End of Treatment
n	110	110
IGF-1 $<$ 1.3 $\times$ ULN and GH $<$ 2.5 ng/mL	91 (82.7)	82 (74.5)
IGF-1 $\geq$ 1.3 $\times$ ULN or GH $\geq$ 2.5 ng/mL	19 (17.3)	28 (25.5)
IGF-1 $<$ 1.3 $\times$ ULN	91 (82.7)	84 (76.4)
IGF-1 $\leq$ 1.0 $\times$ ULN	59 (53.6)	52 (47.3)
GH $<$ 2.5 ng/mL	109 (99.1)	105 (95.5)
GH $<$ 1.0 ng/mL	97 (88.2)	90 (81.8)
Median IGF-1 levels (Q1-Q3)	0.98 (0.79–1.19)	1.04 (0.83–1.26)
Median GH levels (Q1-Q3)	0.40 (0.23–0.66)	0.43 (0.23–0.76)

Data are expressed as number (percentage), unless stated otherwise. IGF-1 and GH categories at baseline and end of treatment (core + extension) are presented for all subjects controlled on OOC and entering the fixed-dose phase. For this analysis, the last on treatment concentrations of IGF-1 and GH were carried forward. Q1-Q3 indicates interquartile range.

fixed-dose phase, 51 of 110 (46%) were treated on 40 mg, 25 of 110 (23%) on 60 mg, and 34 of 110 (31%) on 80 mg. The response up to 13 months, for those patients that entered the fixed-dose phase, was 88% (95% CI, 76.1–95.6), 84% (95% CI, 63.9–95.5), and 47% (95% CI, 29.8–64.9), for 40, 60, and 80 mg, respectively.

Table 2 depicts biochemical response categories at baseline and the end of treatment for all evaluable patients. Integrated GH levels $<$ 2.5 ng/mL were achieved in 93% of mITT subjects at the end of treatment vs 96% at baseline, whereas GH levels $<$ 1 ng/mL were achieved in 78% of subjects vs 66% at baseline. GH levels were decreased from 0.77 ng/mL at baseline to 0.48 ng/mL at the end of treatment. Although GH was maintained or reduced in 93% of subjects enrolled, 64% achieved IGF-1 $<$ 1.3 $\times$ ULN at the end of treatment vs 91% at baseline. Sixty-five subjects (43% of mITT) entered the study with IGF-1 $\leq$ 1 $\times$ ULN and GH $<$ 1 ng/mL, and 49 (32.5%) subjects exhibited this control at the end of treatment.

Table 3 depicts biochemical response categories at the beginning of the fixed-dose phase and the end of 13-month treatment for those 110 subjects stabilized on OOC who entered the fixed-dose phase. Of these subjects, 91 (83%) were responders at the beginning of the fixed-dose phase, and 82 (75%) were responders at the end of treatment (LOCF imputation). During the fixed-dose phase, both GH and IGF-1 responses were largely maintained.

Exploratory analysis showed that the degree of baseline control on injectable SRLs predicted subsequent response to OOCs. The combination of IGF-1 $\leq$ 1 $\times$ ULN/GH $<$ 2.5 ng/mL and low to mid doses of injectable SRLs (octreotide $<$ 30 mg or lanreotide $<$ 120 mg) at screening yielded an OOC response rate of 84.5% (49 of 58 subjects).

Figure 1 shows that mean IGF-1 levels were stably maintained between the beginning and the end of the fixed-dose period, up to 13 months in both the mITT and fixed-dose populations. The slight increase in mean values from baseline toward the end of the dose-escalation period in the mITT population reflects those subjects failing to be controlled on OOCs and discontinuing the study early, all of whom were included in the mITT analysis. Median GH levels at baseline (0.77 ng/mL) were attenuated within 2 hours of the first OOC dose to 0.40 ng/mL and remained suppressed by the end the extension (0.49 ng/mL). In the fixed-dose population, median GH levels were 0.77 ng/mL at baseline and 0.43 ng/mL at the end of treatment.

Eighty percent of subjects entering the fixed-dose phase improved or maintained acromegaly symptoms (26% maintained, 54% improved). The proportion of subjects with at least one, two, or three acromegaly symptoms decreased from 79, 63, and 45%, respectively, at baseline to 68, 48, and 31% at the end of treatment. Acromegaly symptoms improved, as demonstrated by the decline from baseline (on injectables) to the end of treatment (OOC) in the proportion of subjects with active acromegaly symptoms.

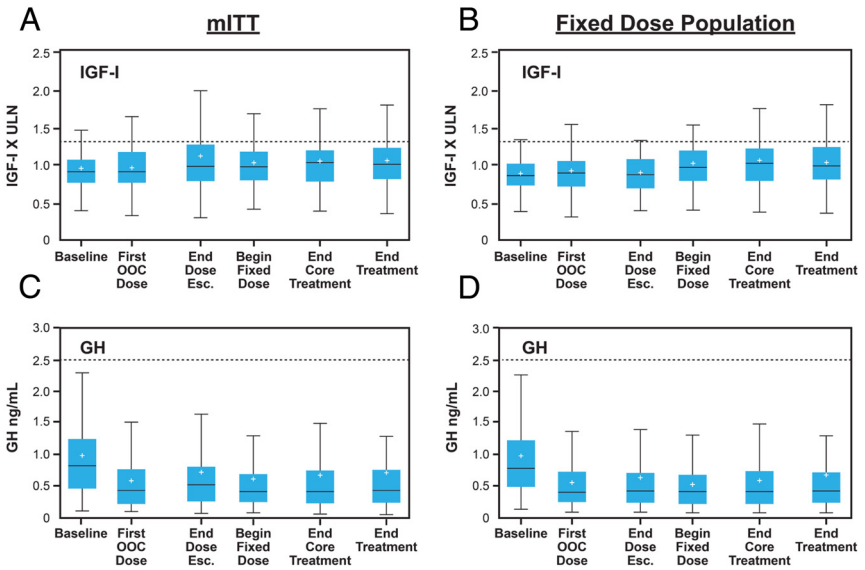

Figure 1. Biochemical control. Boxplots of IGF-1 (× ULN) (A and B) and mean integrated GH concentrations (ng/mL) (C and D) by visit in the mITT (A and C) and fixed-dose (B and D) cohorts. For the mITT population, subjects terminating the trial early during the dose escalation (n = 41) appear at end of dose escalation, and patients terminating early during the fixed-dose phase (n = 8) appear at the end of core. For the fixed- dose population, patients terminating the trial early during the fixed-dose phase (n = 8) and those not continuing into the extension (n = 14) appear at end of core. End treatment indicates end of 13 months. Dotted lines indicate GH and IGF-1 screening and primary endpoints, respectively. Mean, plus sign; median, horizontal line within the box; first quartile, bottom of box; third quartile, top of box; upper fence, third quartile + 1.5 interquartile range; lower fence, first quartile + 1.5 interquartile range. Whiskers are drawn to the most extreme points that lie between fences.

Compliance

Over 94% of subjects fully complied with study drug administration in both the core treatment period and the extension, based on capsule counts, daily diaries, and a general drug administration and food habits questionnaire.

Pharmacokinetics

In 46 subjects studied during the fixed-dose phase, mean plasma octreotide concentrations increased dose-dependently (Figure 2), and mean plasma octreotide trough values (at time zero) were comparable for the 40- and 60-mg regimens, each of which represents a prior 20-mg overnight dose, with a higher mean trough for the 80-mg regimen, which represents a 40-mg prior overnight dose. The steady-state mean apparent elimination half-life ranged from 3.19 ± 1.07 hours (mean ± SD, on 40 mg) to 4.47 ± 2.02 hours (on 80 mg)

Safety

Of 155 subjects in the safety population, 138 (89%) experienced an AE. Ninety-two percent of events were mild to moderate (Supplemental Data). The most commonly reported organ systems included gastrointestinal, neurological, and musculoskeletal, consistent with the known octreotide safety profile (1, 20). Common gastrointestinal AEs (occurring in ≥ 5%) were nausea, diarrhea, dyspepsia, abdominal pain and distention, flatulence, and vomiting, which mostly occurred within the first 2 months of treatment and mostly resolved with treatment continuation (median AE duration, 13 d). Common neurological AEs were headache and dizziness, and in the musculoskeletal system, arthralgia and back pain. Infections related to the gastrointestinal system included a single case of viral gastroenteritis. Hypoglycemia was reported in seven subjects (4.5%), and hyperglycemia was reported in 11 subjects (7%), neither of which led to early discontinuation. Hepatobiliary disorders were reported in 18 subjects (11.6%), with cholelithiasis in 12 (7.7%). Clinically meaningful alterations were not observed in laboratory safety parameters, vital signs, electrocardiogram, or physical examinations. Forty-seven percent of AEs occurred within the first 3 months of treatment, and the incidence significantly decreased with time from the dose escalation to the fixed-dose phase.

Twenty-one subjects (13.5%) experienced 39 serious AEs. Two were considered possibly related to OOC— elevated hepatic transaminases and jaundice occurred in a subject with severe dehydration and a subject with suspected bile duct obstruction. Four malignancies were reported, none of which were considered study drug-related. Serious gastrointestinal infections were not reported.

Twenty-three patients discontinued because of an AE, 19 of which were study drug related, mostly in the first 3 months of treatment; 10 earlier terminations were due to gastrointestinal symptoms, including nausea, diarrhea, and abdominal pain. Two deaths were reported, neither of which was considered OOC-related (Supplemental Data). Overall, OOC safety was consistent with the known octreotide safety profile and acromegaly disease burden, with no new emerging safety signals related to the novel formulation and route of administration.

Discussion

In healthy volunteers, 20 mg OOC yielded systemic drug exposure (area under the curve) comparable to a 0.1-mg sc

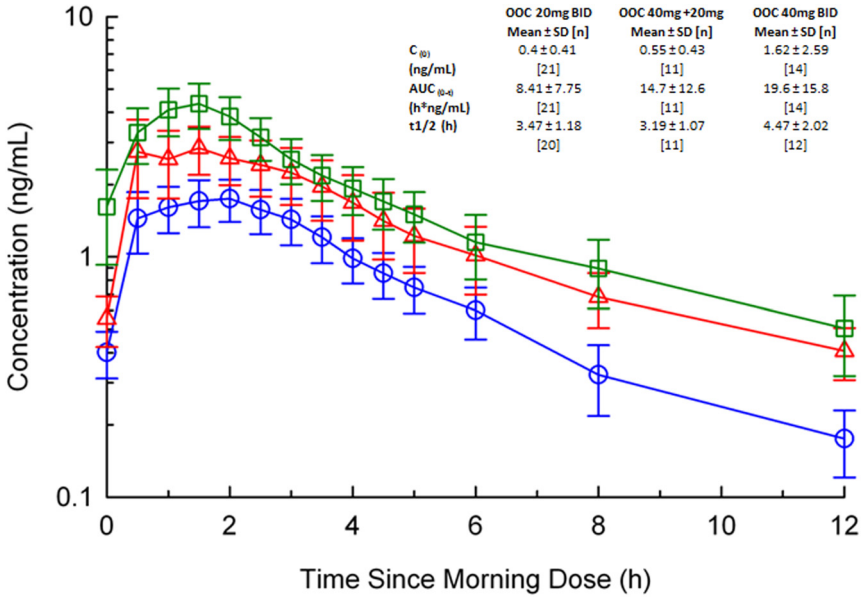

Figure 2. PK analysis in 46 subjects undergoing chronic OOC treatment in their second visit of the fixed-dose phase. PK was assessed after the morning OOC dose for the three tested dosing regimens. Blue circles, A single 20-mg capsule for the 20-mg twice a day regimen (n = 21); red triangles, two capsules of 20 mg (40 mg total) of 40 mg + 20 mg regimen (n = 11); and green rectangles, two capsules of 20 mg (40 mg total) of 40 mg twice a day regimen (n = 14). The arithmetic mean ± SE plasma octreotide concentrations are presented on a logarithmic scale graph, and a summary of PK parameters for octreotide is presented as arithmetic mean ± SD (n).

dose of octreotide (29). We now show clinical utility and unique mode of action of TPE, whereby a therapeutic peptide is effectively and safely delivered orally.

OOC is shown to exhibit efficacy in controlling and maintaining IGF-1 and integrated GH levels for ≥ 13 months in biochemically controlled acromegaly subjects after switching from injectable SRLs. The primary efficacy endpoint was achieved by 65% of subjects at the end of the core treatment and by 62% at the end of 13 months, compared to 89% on injectable SRLs at baseline. The effect was durable, and 85% of the 91 subjects who entered the fixed-dose period as responders maintained this response for up to 13 months. These results are comparable to those reported for 41 acromegaly patients responding to injectable octreotide LAR (IGF-1 ≤ 1.2 × ULN and GH < 2.5 ng/mL); 84% of these maintained baseline IGF-1/GH control at 6 months (32).

Predictors of the degree of OOC responsiveness included good baseline control on injectable SRLs (IGF-1 ≤ 1 × ULN/GH < 2.5 ng/mL) and low to mid doses of injectable SRLs. OOCs also showed efficacy in maintaining clinical response; improved acromegaly symptom severity was noted in subjects who entered the fixed-dose phase.

Because activity and safety of octreotide are well characterized, the primary goal was to assess safety and efficacy of an oral octreotide formulation. Parenteral treatment, shown to be effective, was withdrawn and replaced with OOCs. Because long-term maintenance of response to parenteral octreotide therapy is well established (33) and octreotide tachyphylaxis does not occur in acromegaly, a baseline control of SRL responders shown here reflects an appropriate study design. This design also anticipates clinical practice whereby patients eligible to receive OOCs would be those responding to and tolerating parenteral SRLs and then switched to an oral formulation.

The enrolled patient population is representative of acromegaly patients suitable for OOC therapy. Despite being biochemically controlled by receiving SRL injections as the standard of care, 81% of subjects still exhibited persistent acromegaly symptoms at baseline. The duration of residual IGF-1 suppression after long-acting SRL withdrawal is not known but is not expected beyond 8–12 weeks from withdrawal in a patient with active disease (34). In fact, GH levels may revert between 4 and 6 weeks after octreotide LAR withdrawal (35). Accordingly, SRL was withdrawn 4 weeks before the first OOC test dose, and clinical and biochemical response was measured for ≥ 13 subsequent months. Several additional factors highlight disease activity of the enrolled subjects. Thirty-nine percent had IGF-1 > 1 × ULN at baseline. Of the patients enrolled, 41% were being treated with the highest doses of parenteral octreotide and lanreotide for disease control.

Ninety patients (58%) required > 40-mg OOC doses to maintain response. Furthermore, dose up-titration against rising IGF-1 levels, as well as the observed sustained IGF-1 normalization achieved with OOC over the 13-month duration of the study, allayed the concern of parenteral SRL carryover effect.

OOC doses selected for dose titration to enable optimal IGF-1 control were based on PK modeling to achieve effective therapeutic exposure to octreotide (21, 36). Distribution of the fixed-dose population by OOC dose requirements was similar to the experience with injectable SRLs, where higher doses are not usually required for adequate control (37, 38). PK analyses demonstrated dose proportional exposure to oral octreotide. Octreotide levels measured before the morning dose are reflective of trough levels of the previous night dose and were within

the range shown to effectively inhibit GH secretion (21, 36).

The results show that under fasting conditions, OOC suppressed GH levels in nearly all subjects. However, in contrast to GH inhibition, the proportion of subjects maintaining IGF-1 $< 1.3 \times$ ULN was lower. This suggests that OOC bioavailability was not a cause of nonresponse. Hepatic IGF-1 generation is log-linear with GH levels (39). Octreotide acts primarily on the pituitary to suppress GH secretion, but also directly inhibits hepatic IGF-1 (24, 25), and the observed mild discordant GH and IGF-1 responses are commonly observed with SRL injections. The enhanced response of GH to OOC may also reflect that fasting GH levels were measured within 2–4 hours after the morning OOC dose, and hence may not reflect trough levels. These results underscore that the somatotroph SSTR2 receptor is a primary target for the oral ligand and point to central control of GH hypersecretion by OOC, similar to the primary action of injectables.

The short GH half-life and the pulsatile nature of GH secretion (40, 41) confound the accuracy of assessing GH levels based on a single blood test. The cutoff value of $<$ 2.5 ng/mL (integrated) for GH was chosen to distinguish excess from normal mortality in acromegaly. IGF-1 $<$ $1.3 \times$ ULN was chosen because of the wide variances of IGF-1 values and the challenge of reproducing a rigorous IGF-1 $< 1 \times$ ULN even within individual patients (30, 42).

OOC side effects are largely consistent with underlying acromegaly and are known to be associated with SRLs (16, 20), only with no injection site reactions. Most AEs occurred within the first 60 days, and most resolved on treatment. Fluctuations in circulating octreotide levels (eg, after withdrawal of injectable SRLs and followed by OOC initiation) are known to result in transient AEs (Sandostatin LAR label, http://www.accessdata.fda.gov/drugsatfda_docs/label/2008/021008s021lbl.pdf). Gastrointestinal symptoms associated with octreotide were also largely transient, were reported early in the study, and resolved on continued treatment. AEs were not dose-related. No route of administration-related safety signals or formulation-related AEs were encountered.

Because OOC exhibits GH/IGF-1 control, responders to parenteral SRL injection could be switched to OOCs and avoid the burden of injections. Although compliance with food restrictions might be perceived as challenging for some, the advantages of an oral vs parenteral SRL preparation include convenience with ease of administration, precluding painful injections, and obviating monthly clinic visits and dependence on health care providers and/or family members for injections. Moreover, dose titration and symptomatic control could be achieved more efficiently with an oral SRL than with a 30-day preparation.

This novel TPE technology safely and successfully allowed oral delivery of a therapeutic peptide that achieved systemic endocrine effects. Twice daily OOC appears to offer a safe option for acromegaly monotherapy.

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