Efficacy and Safety of an Octreotide Implant in the Treatment of Patients With Acromegaly

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Context: Acromegaly is caused by excessive GH secretion and IGF-I overproduction. The goals of treatment are to reduce GH and IGF-I values to normal and relieve the associated symptoms.

Objective: The purpose of this article was to demonstrate that an octreotide implant (84 mg) is safe and efficacious in patients with acromegaly who were responsive to prior monthly octreotide long-acting release (LAR) injections.

Design: This was a phase 3, open-label study. Before treatment, subjects received a stable monthly dose of octreotide LAR injections (10−40 mg) for ≥3 months. Randomization was in a 3:1 ratio to either a 6-month octreotide implant or monthly octreotide LAR injections.

Setting: This was a multicenter, international study conducted in private or institutional practices.

Subjects: Enrollment included 163 subjects (aged ≥18 years) with acromegaly.

Main Outcome Measure: The efficacy, safety, and tolerability of the octreotide implant during 24 weeks of treatment was evaluated.

Results: After 24 weeks, the success rate of the implant for maintenance of IGF-I and GH levels was 86% (95% confidence interval, 80.3%) compared with a rate of 84% (95% confidence interval, 73.8%) for octreotide LAR. Serum octreotide concentrations after implant insertion increased within 8 days and peaked between days 14 and 28. The overall safety of the octreotide implant and octreotide LAR were similar. Diarrhea and headache were more frequent with the implant, whereas cholecystitis and hypertension were more frequent with octreotide LAR.

Conclusions: In this pivotal phase 3 study, the octreotide implant maintained reduced blood levels of GH and IGF-I with continuous octreotide release over 6 months, which was well tolerated. (***J Clin Endocrinol Metab*** **98: 4047–4054, 2013)**

Acromegaly is a rare, slowly progressive, chronic disorder that is the consequence of excess GH secretion, most commonly caused by a pituitary adenoma. Hypersecretion of GH leads to overproduction of IGF-I, a principal mediator of GH activity in a feedback loop that in turn causes enlargement of bones and soft tissues. Other effects of excessive GH levels are an increased incidence of diabetes and glucose intolerance in patients with acromegaly. Thus, the goal of treatment in acromegaly is to reduce GH and IGF-I to normal levels, decrease or eliminate the associated symptoms, and prevent the comorbidities associated with the disease.

Primary treatment for most patients with acromegaly is surgical excision of the pituitary tumor (1, 2). Radiotherapy can be used as an adjunct to surgery; however, because of its adverse effects, the enthusiasm for radiation has diminished (3). Medical treatment is intended for subjects with acromegaly not adequately treated by surgery, for

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Abbreviations: AE, adverse event; ITT, intent-to-treat; LAR, long-acting release; OGTT, oral glucose tolerance test; SF-36, Short-Form 36; SSA, synthetic somatostatin analog.

subjects in whom surgery is contraindicated, refused by the subject, or poses a high risk, or for subjects waiting for radiotherapy to become effective. Currently available medical therapies consist of somatostatin analogs (ie, octreotide and lanreotide), dopamine agonists (cabergoline and bromocriptine), and a GH receptor antagonist (pegvisomant).

Octreotide is a synthetic derivative of the endogenous hormone somatostatin (4, 5). It inhibits GH secretion and is the most extensively studied and used somatostatin analog (6, 7). Octreotide acetate is currently approved by the US Food and Drug Administration as Sandostatin (octreotide acetate) Injection and as long-acting release (LAR) Sandostatin LAR Depot (octreotide acetate for injectable suspension) (octreotide LAR).

Treatment with multiple daily injections of octreotide acetate and octreotide LAR (every 3−4 weeks) results in relatively high fluctuations of octreotide concentrations over short dosing intervals. A longer-lasting treatment that provides less variable peak-to-trough variation over a longer dosing interval would probably result in more constant octreotide levels, potentially leading to more stable GH and IGF-I concentrations and a better tolerability profile. A long-term treatment option for suppression of GH and IGF-I would be more convenient for the patient vis-à-vis the benefit of less frequent office visits and a significant reduction in the discomfort of monthly IM injections. By extension, the associated health care burden of physician time would be decreased as well.

Implant technologies provide a potential means to achieve continuous drug release while improving convenience by extending the treatment interval. Hydrogel implant technology is currently used in once-yearly GnRH-containing implants for the treatment of advanced prostate cancer (8) and for the treatment of children with central precocious puberty (9). The GnRH hydrogel implant provided more consistent drug release and a longer dosing interval (1 year) than a depot injectable GnRH agonist administered once every 6 months for prostate cancer (10).

With use of this technology, an SC octreotide hydrogel implant (hereafter referred to as the octreotide implant) that contains octreotide in pelletized form within a hydrogel capsule to control the rate of diffusion into the systemic circulation, offering continuous release over 6 months, was developed. The purpose of this study was to determine whether the octreotide implant provides adequate octreotide levels to suppress GH and IGF-I in patients with acromegaly who were previously successfully treated with a monthly octreotide LAR injection.

Subjects and Methods

Subjects

Eligible subjects in this multicenter, international, phase 3 study were ≥18 years of age, with a confirmed diagnosis of acromegaly, defined as a serum IGF-I concentration ≥20% above the upper limit of age-adjusted levels and a serum GH concentration ≥1.0 ng/mL after an oral glucose tolerance test (OGTT) or confirmation of a GH-secreting tumor on pathologic examination of surgically removed tissue. Subjects had demonstrated responsiveness to octreotide treatment (IGF-I <20% above the upper limit of normal age-adjusted levels and GH ≤2.5 ng/mL) during the screening period (~2 months).

All subjects provided informed consent before participation in the study. The study was approved by the independent ethics committee or institutional review board at each center and complied with the Declaration of Helsinki, the Harmonized Tripartite Guideline for Good Clinical Practice from the International Conference on Harmonization, and local laws.

Study design and treatments

This was a phase 3, open-label study evaluating the safety and efficacy of an 84-mg octreotide implant in 163 subjects (safety population) with acromegaly. After a screening period (~2 months), subjects entered a 6-month treatment phase. Before screening, subjects received a stable dose of monthly octreotide depot injections (10−40 mg) for a minimum of 3 consecutive months.

On day 1 of treatment, eligible subjects were randomly assigned in a 3:1 ratio to either the 6-months octreotide implant or octreotide LAR injections given every 4 weeks. Subjects randomly assigned to the implant arm had one 84-mg octreotide implant inserted SC in the inner aspect of their upper nondominant arm under local anesthesia using an insertion tool (trocar device). Subjects in the injection arm started 4-week injections of octreotide LAR at their previous effective and stable dose (i.e., 10−40 mg every 4 weeks). Subjects returned every 4 weeks for safety, efficacy, and pharmacokinetic assessments. Subjects had their implants removed after 6 months under local anesthesia using a hemostat. The implantation and removal procedures were performed by a health care provider.

Efficacy assessments

Blood samples (4 mL) for the measurement of serum IGF-I and GH concentrations were taken at screening, at baseline (just before treatment), and at each visit. Samples were sent to a central laboratory (Esoterix Endocrinology) for analysis of IGF-I and GH concentrations using validated chemiluminescent assays. The coefficient of variation for accuracy of the calibration standards and for the inter- and intraday precision of the quality control samples were all <7% for both methods. Subjects were asked to complete a quality-of-life questionnaire at screening, at month 3, and before implant removal at month 6. The questionnaire was a Short Form-36 (SF-36) health survey of 36 questions (quality-of-life questionnaire) (11). Subjects were also asked to complete a treatment assessment form at screening and before implant removal at month 6. The questionnaire asked subjects specific questions about their satisfaction with their current and previous treatment for acromegaly. At screening, baseline, month 3, and month 6 (before implant removal), the physician assessed the signs and symptoms of acromegaly (ie, headache,

arthralgias, fatigue, perspiration, paresthesias, and soft-tissue swelling). In addition, tumor size was evaluated by magnetic resonance imaging at screening and before implant removal at month 6 by a centralized reader who was unaware of the form of treatment the subjects received.

Safety assessments

Safety was assessed by adverse events (AEs) categorized by severity and relationship to study medication, physical examination, vital signs, electrocardiograms, gallbladder ultrasound, hematology, clinical chemistry, thyroid profiles, and glycosylated hemoglobin. All nondiabetic subjects, regardless of the treatment arm, had an OGTT at screening, month 3, and month 6 (before implant removal) after an overnight fast of at least 12 hours before the test. Blood samples were drawn before and at 30, 60, 90, and 120 minutes after administration of 75 g of glucose for the determination of serum GH and glucose. Subjects with diabetes were excluded from the OGTT and had their IGF-I and GH blood samples drawn in the fasting state.

Pharmacokinetic assessments

Blood samples (4 mL) for the determination of serum octreotide concentrations were collected monthly from all subjects. For subjects in the implant arm only, blood samples were collected on day 1 (before implant insertion [0 hours], at 2 and 6 hours after implant insertion), and at week 24 or early termination (at 2 and 6 hours after implant removal). In addition, a subset of 15 subjects returned for additional blood sampling at 12, 24, 48, and 72 hours after implantation and on days 8, 12, 16, 20, 24, 32, and 40, with a visit window of ± 1 day.

Serum octreotide concentrations were determined by PharmaNet Canada Inc by a validated assay using HPLC with tandem mass spectrometry detection. All samples from each subject were, when possible, analyzed in the same assay. Study samples were analyzed singly with a calibration curve and 4 sets of QC samples were analyzed in duplicate using the same procedure. The validated calibration range for the assay was from 50 to 4000 pg/mL. Values less than 50 pg/mL were reported as <50 and were treated as zero in the pharmacokinetics analysis.

Statistical methods

The intent-to-treat (ITT) population consisted of all randomly assigned subjects who were treated with either the implant or at least one injection of octreotide LAR. They had a baseline mean GH level ≤2.5 ng/mL and a baseline mean IGF-I within 20% above the age-adjusted normal range and had at least 1 on-treatment GH or IGF-I concentration during the treatment phase. Baseline was defined as the mean GH and IGF-I values obtained during screening and pretreatment (basal). Because basal IGF-I and GH levels were not available before treatment, 26 subjects were excluded from the ITT population.

The primary efficacy endpoint of the study was to assess the success rate of treatment based on the average concentrations of GH and IGF-I over the 24-week treatment period compared with pretreatment concentrations in the implant arm. The null hypothesis of this study, assessed for the implant arm only, was that the octreotide acetate SC implant, given once every 6 months, does not provide adequate maintenance of IGF-I and GH in subjects with acromegaly.

This hypothesis was assessed via the following decision rules for the pharmacodynamic outcomes. A subject was required to satisfy both decision rules to be determined a "success": maintenance of mean on-treatment IGF-I within the age-adjusted normal range or ≤20% above the baseline mean value and maintenance of mean on-treatment GH ≤2.5 ng/mL or ≤20% above the baseline mean value.

The primary analysis was performed using the observed cases data from the ITT population. The mean on-treatment IGF-I and GH values over the 24-week treatment period were calculated as the average of the nonmissing IGF-I and GH values at weeks 4, 8, 12, 16, 20, and 24, respectively.

This study was not powered to compare the implant and octreotide LAR arms. Subgroup analyses included sex, age group (<65 or ≥65 years), country, history of diabetes, and pretreatment octreotide LAR dose (10–20 or 30–40 mg). The success rate for the subgroup of subjects who entered the study with normal pretreatment concentrations of IGF-I and GH was defined as the percentage of subjects with mean on-treatment IGF-I within the age-adjusted normal range and mean on-treatment GH ≤2.5 ng/mL. The proportion of subjects deemed a success was derived and a 95% 1-sided confidence interval (CI) (with a lower bound) for that proportion was constructed. If the lower bound of the observed 1-sided CI was ≥75%, the null hypothesis for this study was rejected in favor of the alternative that the implant did provide adequate maintenance of IGF-I and GH in subjects with acromegaly.

Secondary efficacy was descriptively assessed for each treatment group for the ITT data set and included success rates, physician assessment of signs and symptoms of acromegaly, quality-of-life SF-36 questionnaire, SF-36 physical and mental component scores, pituitary tumor size (volume), patient's treatment assessment, maintenance of mean on-treatment GH ≤1 ng/mL and mean on-treatment IGF-I within the age-adjusted normal range or ≤20% above the baseline mean value over the 24-week treatment period. Additional supportive efficacy parameters included success rates over 24 weeks of treatment.

Results

Study population

The study population consisted of 163 subjects (implant, n = 122; octreotide LAR, n = 41) (Table 1). Six subjects in the implant arm and 1 subject in the octreotide LAR arm were withdrawn because of AEs before completing the study. The ITT population consisted of 137 subjects who were treated with either the implant (n = 100) or with at least one injection of octreotide LAR (n = 37), had a starting (days −60, −30, and 0) mean GH level ≤2.5 ng/mL, and had a starting mean IGF-I ≤20% above the age-adjusted normal range with at least one GH or IGF-I concentration measured during treatment. Before enrollment, more than half of the subjects (53%) in the ITT population had received octreotide LAR 20 mg (Table 2).

Efficacy

In the implant arm, the success rate for adequate maintenance of combined IGF-I and GH levels at week 4 for the ITT population was 83% (95% CI, 76.8%), which in-

Table 1. Demographic Characteristics

Parameter	Implant (n = 122)	Octreotide LAR (n = 41)
Age, y		
Mean (SD)	54.3 (11.4)	51.3 (11.9)
Median	55	55
Sex, n (%)		
Male	35 (28.7)	14 (34.2)
Female	87 (71.3)	27 (65.9)
Race, n (%)		
Caucasian	119 (97.5)	41 (100.0)
Asian	2 (1.6)	0
Hispanic	1 (0.8)	0
Weight, kg		
Mean (SD)	85.6 (18.1)	90.2 (28.6)
Median	83	82
BMI, kg/m^2		
Mean (SD)	29.9 (5.0)	30.8 (6.3)
Median	29	30
Diabetes mellitus, n (%)	33 (27.05)	7 (17.07)
Glucose intolerance, n (%)	18 (14.75)	11 (26.83)
Time since diagnosis of acromegaly, y		
Mean (SD)	7.8 (6.2)	6.2 (5.0)
Median	5.4	5.1
Minimum, maximum	0.4, 27.2	0.3, 20.9
Baseline GH level, n (%)[a]		
≤1 ng/mL	42 (34.4)	15 (36.6)
>1 and ≤2.5 ng/mL	62 (50.8)	22 (53. 7)
>2.5 and ≤5 ng/mL	17 (13.9)	4 (9.8)
>5 ng/mL	1 (0.8)	0
Baseline IGF-I level, n (%)[a]		
Below lower limit of age-adjusted normal range	1 (0.8)	2 (4.9)
Within age-adjusted normal range	86 (70.5)	34 (82.9)
Above upper limit of age-adjusted normal range to ≤20% above upper limit of age-adjusted normal range	29 (23.8)	5 (12.2)
>20% above upper limit of age-adjusted normal range	6 (4.9)	0
Baseline mean GH level ≤2.5 ng/mL and baseline mean IGF-I ≤20% above age-adjusted normal range, n (%)		
No	22 (18.03)	4 (9.76)
Yes	100 (81.97)	37 (90.24)

[a] Baseline GH and IGF-I are means of values at days −60, −30, and 1 (pretreatment). Of the 163 subjects in the safety population, 137 were included in the ITT population.

creased to 86% (95% CI, 80.3%) by week 24, as the primary endpoint. In comparison, in the octreotide LAR arm, the success rate for adequate maintenance of combined IGF-I and GH levels was 79% (95% CI, 67.2%) at week 4 and 84% (95% CI:, 73.8%) by week 24. The profiles of mean GH and IGF-I levels in the implant and octreotide LAR arms were similar throughout the 24-week duration of the study (Figure 1). Subgroup analyses by gender, age, baseline BMI, and country showed results similar to those for the overall population in both the implant and octreotide LAR arms (data not shown).

Table 2. Prior Octreotide LAR Dose: ITT Population

Parameter	Implant	Octreotide LAR	Total
No. of subjects	100[a]	37	137
Pretreatment octreotide LAR dose, n (%)			
10 mg	5 (5.0)	5 (13.5)	10 (7.3)
20 mg	51 (51.0)	21 (56.8)	72 (52.6)
30 mg	36 (36.0)	10 (27.0)	46 (33.6)
40 mg	7 (7.0)	1 (2.7)	8 (5.8)

[a] The dose was not recorded for one subject in the implant arm.

There were no significant differences in the efficacy rates between subjects in either treatment arm related to the pretreatment octreotide LAR dose (Table 3).

In addition, there were no observed trends based on reported values or changes from baseline in any of the parameters evaluated that related to the physician assessment of signs and symptoms. A mean score (SD) of 50 (10) in the quality-of-life (SF-36) questionnaire would be expected for the general population. All SF-36 scores obtained during this study, regardless of visit and treatment arm, were <50, as would be expected in this population of subjects with acromegaly. No clinically significant

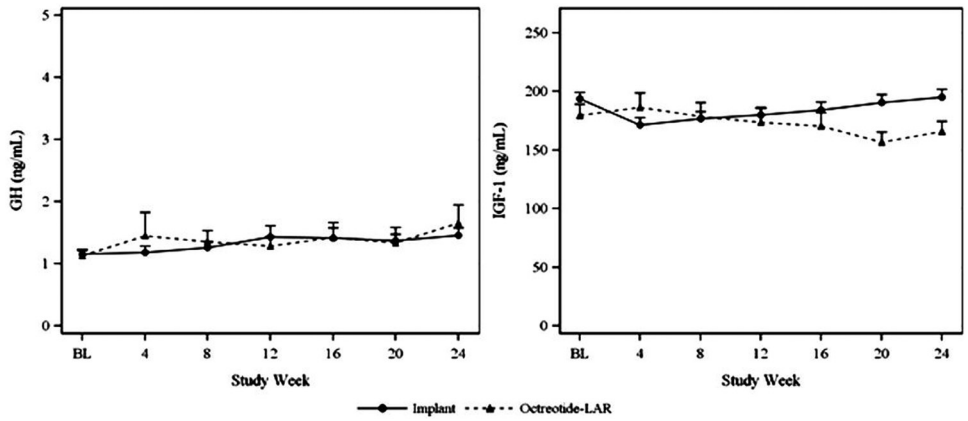

Figure 1. Mean (±SE) serum GH and IGF-I vs time in the ITT population.

changes in tumor volume or shape were observed during the study in either the implant or octreotide LAR arm.

When subjects (n = 97) were asked to select their preferred treatment method for acromegaly, 82.5% (n = 80) selected the octreotide implant for its comfort. No changes from baseline were observed in the scores of other patient treatment assessment scales, including assessment of treatment pain, for either the implant or octreotide LAR arm.

Pharmacokinetics

After insertion of the octreotide SC implant, serum octreotide concentrations increased within 8 days and generally peaked between weeks 2 and 4 (Figure 2). The octreotide concentrations decreased modestly by 48.6% (from 1544 to 93 pg/mL) from week 8 to week 24. The latter value was comparable to the mean serum octreotide concentration before implantation (817 pg/mL). The trough concentrations after octreotide LAR injections for the combined dose groups of 10 + 20 mg and 30 + 40 mg remained relatively constant throughout the 24-week treatment period (Figure 2), suggesting that steady-state conditions had been established. There was a dose-dependent increase in trough octreotide serum concentration between the 2 combined dosing groups. The study was not designed to measure peak octreotide concentrations in subjects receiving monthly octreotide LAR injections.

Higher serum octreotide concentrations were observed in female than in male subjects in the pharmacokinetic population. This occurred irrespective of how octreotide was administered (SC implant or injected IM). In the pharmacokinetic population, approximately 70% of the implant arm and 64% of the octreotide LAR were women.

Table 3. Primary Efficacy Analyses as Related to Pretreatment Octreotide LAR Dose

Pretreatment Octreotide LAR Dose	Statistics/Visit at Weeks 4–24
Implant (n = 100)[a]	
10 mg (n = 5)	5 (100.0)
20 mg (n = 51)	48 (94.1)
30 mg (n = 36)	26 (72.2)
40 mg (n = 7)	6 (85.7)
Octreotide LAR (n = 37)	
10 mg (n = 5)	5 (100.0)
20 mg (n = 21)	17 (81.0)
30 mg (n = 10)	9 (90.0)
40 mg (n = 1)	0

[a] The dose was not recorded for one subject in the implant arm.

Safety

The overall safety profiles of the octreotide implant and octreotide LAR were similar. A summary of AEs reported by ≥5 subjects is presented in Table 4. Diarrhea and headache were more frequently reported in the implant arm, whereas cholecystitis and hypertension were more frequent in the octreotide LAR arm. Except for cholelithiasis, which occurred at the end of the treatment period, there was no apparent temporal relationship to the AE events, nor did the AE severity change over time.

There were no clinically significant changes in clinical chemistry or hematology measures, vital signs, electrocardiograms, physical examinations, or thyroid hormone, glucose, or glycosylated hemoglobin levels. There were no clinically significant changes in the number of gallstones in the implant arm based on ultrasound analyses. However, in the octreotide LAR arm, the percentage of subjects with >10 gallstones increased from 15% at baseline to 22% at the last visit and may have contributed to the increased percentage of cholecystitis AEs in this arm. In the nondiabetic subjects, mean glucose levels during the OGTT remained normal in both treatment arms during the study. No significant changes occurred in glycosylated hemoglobin or in fasting glucose in either nondiabetic or diabetic subjects (Supplemental Table 1 published on The Endocrine Society's Journals Online web site at http://jcem.endojournals.org.).

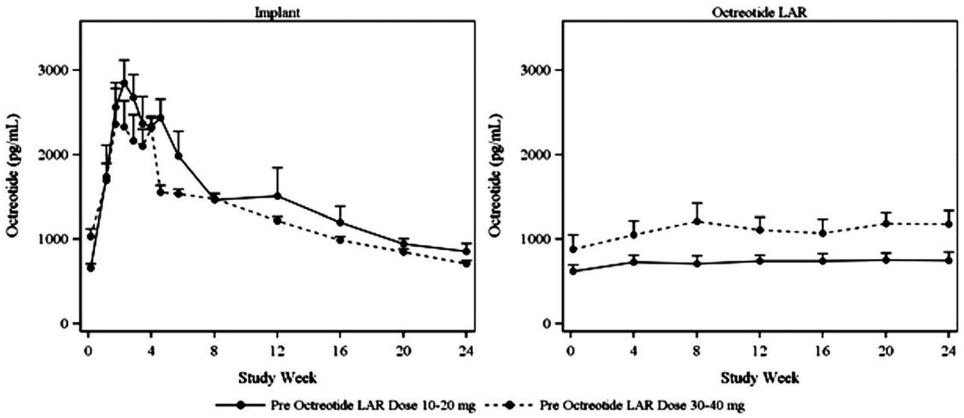

Figure 2. Mean (±SE) serum octreotide vs time in the implant (n = 100) and octreotide LAR (n = 36) arms.

AEs related to local tolerability in the implant arm were reported by 13% of subjects. These events were primarily due to implant site reaction, pain, and pruritus. There was 1 case each of implant site hematoma, hemorrhage, inflammation, necrosis, edema, scar, and injection site pain. All 122 implants used in this study were inserted per the study protocol. Four subjects withdrew because of complications related to the implant. One subject experienced an implant breakage during implantation, and 1 subject had a breakage during the treatment phase of the study. Four subjects had incomplete removal of their implants at the time of explantation. During the time of explantation, 32 of 122 explants were broken. None of the implant breakages or incomplete removals was associated with significant safety-related events. Sixteen (13.1%) subjects had reactions at the implantation site, which were predominantly associated with complications due to the implantation procedure. Because of the breakages that occurred at implantation, the implantation procedure was changed during the study to include the use of a hemostat for creation of a pocket before implant insertion with the insertion tool. After implementation of this procedural change, no breakages occurred at implantations.

Two subjects with implants had higher than expected octreotide concentrations. In 1 subject, high octreotide levels occurred on day 1 (C_{max} = 99,250 pg/mL), suggesting that the implant had broken at the time of implantation. The octreotide concentration decreased by 50% within 4 hours and was <10,000 pg/mL by the next sampling period 8 days later. The octreotide concentration data became available 6 weeks after implantation, and at week 9 the implant was removed, confirming the breakage. GH and IGF-I data for this subject were not collected. A second subject had an elevated octreotide concentration at week 12 (C_{max} = 19,812 pg/mL), suggesting that the implant had broken during the study period and not at the time of implantation. Octreotide concentrations collected 2 hours after implantation for this subject were within the expected range (496 pg/mL), also suggesting that the implant had broken during the study period. An ultrasound examination of the implant site confirmed implant breakage; however, the implant was not removed. This patient completed the 24-week treatment schedule during which preimplantation GH and IGF-I levels were maintained. Octreotide concentrations remained elevated at the next sampling period 4 weeks later (11,442 pg/mL) and then declined to concentrations observed in other subjects. No

Table 4. Summary of AEs Reported by ≥5% of Overall Subjects

	No. (%) Subjects Reporting Events		
System Organ Class Preferred Term	**Implant (n = 122)**	**Octreotide LAR (n = 41)**	**Overall (n = 163)**
Diarrhea	12 (9.8)	3 (7.3)	15 (9.2)
Headache	12 (9.8)	2 (4.9)	14 (8.6)
Hypertension	10 (8.2)	6 (14.6)	16 (9.8)
Cholelithiasis	9 (7.4)	3 (7.3)	12 (7.4)
Nasopharyngitis	9 (7.4)	1 (2.4)	10 (6.1)
Arthralgia	6 (4.9)	3 (7.3)	9 (5.5)
Cholecystitis	1 (0.8)	5 (12.2)	6 (3.7)

associated AEs or other clinically significant safety findings were observed in either subject.

Discussion

The primary goals for the treatment of acromegaly are to suppress levels of GH and IGF-I to the normal range and to minimize the associated symptoms and complications of the disease. Currently, the primary medical treatment for acromegaly is the use of the injectable synthetic somatostatin analogs (SSAs), octreotide or lantreotide. In the current phase 3 study, we have shown that a new implant delivery system of octreotide has an efficacy profile similar to that of octreotide LAR in subjects who were previously treated with the drug.

During the 6-month duration of this study, GH and IGF-I levels were maintained in both the implant and octreotide LAR arms of the study. An advantage of the implant formulation is patient convenience, avoiding monthly IM injections and decreasing discomfort. In the treatment assessment questionnaire, a majority of subjects selected the implant as their preferred treatment method because of its comfort.

Another major potential advantage of the octreotide implant delivery technology is the avoidance of large peak to trough fluctuations in octreotide concentrations as observed with other formulations (12). It can be speculated that a reduction in fluctuations in drug concentrations could be responsible for the observation that both cholecystitis and overall gallbladder-related AEs were lower in the implant arm than in the octreotide LAR arm. The inhibitory effects of somatostatin (and SSAs) on gallbladder contractility and bile flow, if dose dependent, could provide an explanation for this observation.

The pharmacokinetic profile of the 84-mg octreotide implant showed relatively stable and continuous drug delivery over 6 months. Subjects maintained serum octreotide concentrations at or above those immediately before implantation (octreotide LAR trough concentration levels) over the 24-week treatment phase.

The apparent release rate of octreotide from the implant over the total 24-week time course was not constant, appearing higher during the first 2 months than during the last 4 months. Part of the higher octreotide serum concentrations observed during the first 2 months may have been due to the continuing contribution of octreotide from the preimplant octreotide LAR injection. Quantitative assessment of this possibility for the circulating octreotide levels was not evaluated in this study. Regardless, the overall release rate from the implant was sufficient to maintain the mean serum concentration of octreotide above the preimplant concentrations over the total time course of the treatment phase and to achieve overall efficacy in subjects previously maintained on various doses (10–40 mg) of monthly IM injections of octreotide LAR.

There was a lag period from the time of implantation to the time serum octreotide concentrations rose above preimplant levels. Although the precise duration of this lag period was not assessed in this study, the lag period in a previous phase 2 study was found to be approximately 1 week (13). The T_{max} was determined to be approximately 15 days in the present study, which was similar to that reported previously.

There was an apparent sex difference in the serum octreotide concentrations. Female subjects had higher concentrations regardless of the route of administration. The precise mechanism for higher concentrations in women is not known; however, possible causes may be a lower volume of distribution, a lower clearance of octreotide, or a combination of both. Higher octreotide concentrations in women after adjustment for BMI and the octreotide LAR dose have been reported previously (12), and we have observed similar results in preclinical studies in beagle dogs (unpublished data).

Treatment with either the 84-mg octreotide implant or octreotide LAR was well tolerated during this study. The most commonly reported AEs with SSAs have been gastrointestinal disorders, cholelithiasis, headache, and injection site reactions (13, 14). Because SSAs inhibit the secretion of insulin, glucagon, and thyroid-stimulating hormone, changes in glucose metabolism and thyroid function were monitored, and no clinically relevant changes were found.

As expected, in the current study, the most frequently reported AEs in the octreotide implant group were diarrhea, headache, hypertension, cholelithiasis, nasopharyngitis, and arthralgias. There were no significant changes in the number of gallstones in the implant arm.

The cardiac abnormalities observed in this study were consistent with those reported with injectable SSAs. The most frequently reported cardiovascular AE in both the implant and octreotide LAR arms was hypertension. There was no treatment-related edema or clinically significant changes in the 12-lead electrocardiogram parameters in either the implant or the octreotide LAR arm of the study. Relative to the octreotide LAR arm, there was a trend for increased QTcB prolongation in the subjects in the implant arm; however, no subject had prolongations $>$500 ms.

Although there were several implant breakages and incomplete removals, none was associated with any significant safety-related events. Higher than expected serum octreotide concentrations were observed in 2 subjects dur-

ing this study. In a previous phase 2 study, an even higher serum octreotide concentrations was observed in 1 subject (C_{max} = 100,790 pg/mL) (15). No significant AEs were reported in any of these subjects despite the fact that elevated serum octreotide levels may have persisted for several weeks after implant breakage. Based on the prescribing information, Sandostatin Injection has been well tolerated even at high doses (13). IV administration of up to 120 mg did not result in serious adverse effects. However, SC doses of 2.5 mg of Sandostatin Injection have caused hypoglycemia, flushing, dizziness, and nausea. The plasma concentration of octreotide is not reported in the label for these dosing situations, with the exception of the 1-mg IV dose, for which the peak concentration was 2800 pg/mL.

Pharmacokinetic modeling of Sandostatin 30 mg given as an IV infusion over 20 minutes and of Sandostatin 120 mg infused over 8 hours in healthy volunteers, based on the estimated Sandostatin pharmacokinetic parameters provided in the label, resulted in estimated C_{max} concentrations of 1,298,000 and 1,640,000 pg/mL, respectively. These concentrations are 13 to 16.5 times higher than the maximal concentration observed in subjects with implant breakages (~100,000 pg/mL). The >10-fold margin for the maximal serum concentrations may be underestimated, because as stated in the Sandostatin label, the octreotide clearance may be nonlinear, decreasing at doses >600 μg/day.

In this pivotal phase 3 study, octreotide implants had an efficacy profile similar to that of injectable octreotide LAR, maintained normal blood levels of GH and IGF-I with continuous octreotide release over 6 months, and were well tolerated. The efficacy, tolerability, and patient acceptance suggest that the implant is a viable alternative for long term octreotide therapy of acromegaly in patients whose conditions are currently well controlled with other SSAs.

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