Study Number: IP107-001 [Primary Phase]

Title of Study: Phase III, Open-Label, Multicenter International Study to Evaluate the Efficacy And Safety of an Octreotide Implant Versus Sandostatin LAR® Depot in Patients with Acromegaly [Primary Phase]

Investigators: Each study center had a principal investigator.

Study Center(s): The multi-center study was conducted at 46 centers in 9 countries.

Publications (reference): None

Studied period (years):	**Phase of development**: Phase III
Date first subject enrolled: 14-Nov-2008	
Date last subject completed: 04-Nov-2010	

Objectives: The overall objective of the study was to demonstrate that the octreotide implant provides adequate octreotide levels to suppress growth hormone (GH) and insulin-like growth factor 1 (IGF-1) in subjects with acromegaly who have been successfully treated with a monthly octreotide depot injection (Sandostatin LAR® Depot [S-LAR]).

Primary*:* To evaluate the efficacy, safety, and tolerability of the octreotide implant during 24 weeks of treatment:

- Primary efficacy was assessed via pharmacodynamic (PD) measurements resulting from treatment with the implant (ie, GH and IGF-1 concentration levels). The primary endpoints were the average concentrations of GH and IGF-1 values over the 24-week treatment period compared with pre-treatment concentrations.
- Safety and tolerability resulting from treatment with the implant for 24 weeks was evaluated on the basis of spontaneously-reported adverse events (AEs) and changes in physical examinations, vital signs, 12-lead electrocardiograms (ECG), clinical laboratory data, concomitant medications, pituitary tumor size, and gall bladder ultrasonography outcomes.

Secondary: Included the assessment of the effects of treatment with the implant over 24 weeks on:

- Physician assessment of signs and symptoms scores
- Quality of Life score
- Pituitary tumor size
- Patient Treatment Assessment (a subject-reported assessment of the treatment).

Pharmacokinetics (PK)*:* The PK results of octreotide from the implant were descriptively assessed to the PK results of octreotide resulting from treatment with monthly S-LAR injections.

Methodology: This was a Phase III, open-label, 2-phase (primary and extension) study evaluating the safety and efficacy of an 84-mg octreotide implant in subjects with acromegaly. This study was conducted in 3 stages: Screening (day -60 and day -30), the Primary Treatment Phase (day 1 to week 24), both of which were in the Primary Phase, and the Extension Phase (post week 24 to week 48). Prior to screening, subjects received a stable dose (10 to 40 mg) of monthly octreotide depot injections for a minimum of 3 consecutive months. During Screening, eligible subjects showed a response to octreotide treatment defined as follows:

- mean of day -60 and day -30 IGF-1 levels <20% above the upper limit of normal age-adjusted range
- mean of day -60 and day -30 GH levels ≤2.5 ng/mL.

During the Primary Phase, eligible subjects were randomly assigned treatment in a 3 to 1 ratio to either the 6-month octreotide implant or injections of S-LAR given every 4 weeks. For those subjects assigned

to the S-LAR arm, the dose received before enrollment into the study was to be the same dose received during study treatment.

Protocol Amendment 2 restricted eligibility to GH ≤2.5 ng/mL, based on a directive from the Food and Drug Administration (FDA). Prior to this amendment, the randomization was stratified by GH levels (GH levels ≤2.5 ng/mL or GH levels >2.5 ng/mL). Because this amendment prohibited subjects with GH values >2.5 ng/mL from enrollment, the stratification was not relevant to subjects who enrolled into the study after this amendment.

On day 1 of the Primary Treatment Phase, subjects received the following study treatment:

- Subjects in the octreotide implant arm had one 84-mg octreotide implant inserted subcutaneously in the inner aspect of their upper non-dominant arm under local anesthesia.
- Subjects in the S-LAR arm had their first injection of S-LAR during the study.

Subjects who were randomized to the S-LAR arm were given injections of S-LAR every 4 weeks for a total of 6 injections during the 24-week Primary Treatment Phase.

Each subject returned to the investigational center every 4 weeks (through the 24 weeks of treatment); safety, including local tolerability, and efficacy assessments were performed during these visits. Blood samples were collected monthly for determination of GH, IGF-1, and octreotide serum concentrations. An oral glucose tolerance test (OGTT) was conducted at day -30, and months 3 (week 12) and 6 (week 24) on non-diabetic subjects. Gallbladder ultrasounds and pituitary tumor size were assessed at baseline and at week 24. The final time point for the Primary Phase was the week 24 visit (month 6). A subgroup of subjects in the octreotide implant arm had additional blood samples collected post implantation for the determination of octreotide concentrations.

At completion of the Primary Phase, subject eligibility for entry into the 6-month Extension Phase (post-week 24 through week 48) was evaluated. Eligibility was based upon the average (mean) of the available values from week 4, 8, 12, 16, and 20 concentrations for IGF-1 and GH. To be eligible, at least 4 (of the 5) IGF-1 and GH concentrations must have been available and the following criteria had to be met: 1) average serum IGF-1 values within the age-adjusted normal range or ≤20% above pre-treatment levels (average of 3 pre-treatment levels) and 2) average GH values ≤2.5 ng/mL or ≤20% above pre-treatment levels (average of 3 pre-treatment levels). Subjects who did not meet the eligibility criteria and subjects who chose not to continue did not enter the Extension Phase. Those subjects returned to the study center for a follow-up visit 1 week after their last scheduled Primary Phase visit. All subjects that entered the Extension Phase received an implant.

Number of Subjects (Planned and Analyzed): It was planned that approximately 140 evaluable subjects would be randomized in a 3:1 ratio, with approximately 105 subjects randomized to the octreotide implant arm and approximately 35 subjects randomized to the S-LAR arm. A total of 169 subjects were randomized and 163 subjects received treatment in the Primary Phase. The intent-to-treat population (ITT) consisted of 100 of 126 (79.4%) subjects assigned to receive an implant and 37 of 43 (86.0%) subjects assigned to receive monthly S-LAR injections. The reduction in subject numbers from those randomized who received treatment was due to a protocol amendment based on FDA recommendation, which restricted the eligible subject population based on their GH levels. The original protocol inclusion criteria allowed subjects with GH ≤5 ng/mL. The amended protocol restricted eligibility to GH ≤2.5 ng/mL.

Diagnosis and Main Criteria for Inclusion:

1. Male or female subjects with acromegaly
2. Age ≥18 to ≤80 years
3. Confirmed diagnosis of a growth hormone-secreting tumor based on historical data and meeting at least 1 of the following criteria (a or b):

a. Subjects in whom an OGTT was performed and meeting all of the following (based on previous historical data):
   i. GH value ≥1.0 ng/mL during the OGTT
   ii. IGF-1 value ≥20% above the upper limit of age-adjusted normal value during the OGTT
   iii. Pituitary tumor demonstrable on magnetic resonance imaging (MRI)
b. Subjects in whom an OGTT was not performed and meeting all of the following (based on previous historical data):
   i. IGF-1 value ≥20% above the upper limit of age-adjusted normal value
   ii. Confirmation of a growth hormone-secreting tumor on pathologic examination of tissue removed at surgery
   iii. Pituitary tumor demonstrable on MRI

4. No pituitary tumor present or had a tumor present that was ≥3 mm in distance from the optic chiasm
5. Received a stable dose of monthly octreotide depot injections (10 – 40 mg) for a minimum of 3 consecutive months prior to screening
6. Must have shown a response to octreotide treatment with documented laboratory results at the screening visits (mean of day -60 and day -30 results) defined as follows:
   a. IGF-1 <20% above the upper limit of normal age-adjusted levels and GH ≤2.5 ng/mL
7. Without clinically significant findings on physical exam, laboratory values, and vital signs; or unstable chronic medical conditions, in the opinion of the Investigator
8. Ability to communicate, complete questionnaires independently, provide and sign written informed consent, and willing to participate and comply with study requirements

Criteria for Exclusion:

1. Women who were pregnant, lactating, or of child-bearing potential who were not practicing a medically acceptable method of birth control
2. Pituitary surgery less than 3 months prior to screening
3. Liver disease [eg, cirrhosis, chronic active or persistent hepatitis or persistent abnormalities of ALT, AST (level >2X normal), alkaline phosphatase (level >2X normal), or direct bilirubin (level >1.5X normal)]
4. Other laboratory values considered by the investigator or Sponsor to be clinically significant
5. Unstable angina, sustained ventricular arrhythmias or heart failure (NYHA III and IV)
6. Acute myocardial infarction within 3 months of screening
7. Uncontrolled diabetes defined as having a fasting glucose >150 mg/dL and HbA1c ≥9%
8. Symptomatic cholelithiasis
9. History of drug or alcohol abuse within 6 months of screening
10. Received any investigational drug or participated in another clinical trial within 30 days of screening
11. Received radiotherapy for pituitary tumor or any radiotherapy above the neck at any time before the start of screening
12. Received pegvisomant, lanreotide or a dopamine agonist within 3 months of screening, or at any time during the trial
13. Received a previous octreotide implant
14. History or presence of significant cardiovascular, hepatic, renal, hematologic, gastrointestinal, endocrine, immunologic, dermatologic, neurologic, psychiatric disease, any other severe

coexisting or terminal systemic disease that could limit life expectancy or interfere with the conduct of the study, or subjects who were incarcerated in penal institutions or committed to mental institutions

15. Candidate on a waiting list for surgery while on study
16. Subject who, through completion of the study, would have donated in excess of:
    a. 500 mL of blood in 42 days;
    b. 1500 mL of blood in 180 days; or
    c. 2500 mL of blood in 1 year
17. Received new or non-stable dose of hormone replacement therapy within 3 months of screening

Test Product, Dose and Mode of Administration, Batch Number(s): Octreotide implant (84 mg octreotide acetate) for subcutaneous implantation was used as the investigational product. The implant was inserted subcutaneously into the upper, inner aspect of the subject's non-dominant arm (between the bicep and triceps) using the trocar (insertion device) from the implant kit provided. The batch numbers were 706 and 707.

Duration of Treatment: Planned duration for both treatment arms during the Primary Phase was 24 weeks (6 months).

Reference Therapy, Dose and Mode of Administration, Batch Number(s): Sandostatin LAR® Depot (S-LAR) injection was used as the reference active control therapy. Subjects randomized to receive S-LAR continued to receive the same dosage of S-LAR as they had previously received for a minimum of 3 months prior to entering the study.

Criteria for Evaluation: Outcomes for efficacy, safety, and pharmacokinetics were assessed.

Efficacy/Pharmacodynamics*:* Primary efficacy was evaluated on the basis of IGF-1 and GH. Secondary efficacy assessments included determination of changes in pituitary tumor size, Signs and Symptoms scores, Quality of Life scores, and Patients Treatment Assessment (a subject-reported assessment of the treatment).

Safety*:* The following safety variables were collected: adverse events (AEs) including tolerability, clinical laboratory examinations, physical examinations, body weight and vital signs measurements, 12-lead ECGs, pituitary tumor size and gallbladder ultrasounds.

Pharmacokinetic*:* Blood samples were assessed for octreotide plasma levels during the 6-month treatment period. Area under the plasma concentration-time curve (AUC), average concentration over 24 weeks of treatment period (C_{avg}), maximum concentration (C_{max}) and time to C_{max} (T_{max}) were derived for subjects receiving octreotide implants. For subjects receiving S-LAR, C_{trough} was measured.

Statistical Methods:

Primary Efficacy*:*

The primary hypothesis (for the implant arm) was:

- H_o: The octreotide acetate subcutaneous implant, given once every 6 months, does not provide adequate maintenance of IGF-1 and GH in patients with acromegaly.
- H_a: The octreotide acetate subcutaneous implant, given once every 6 months, does provide adequate maintenance of IGF-1 and GH in patients with acromegaly.

This hypothesis was assessed via the following decision rules for the pharmacodynamic outcomes. A subject must have satisfied both decision rules in order to be determined a "success:"

- Maintenance of mean on-treatment IGF-1 within the age- adjusted normal range or ≤20% above the mean of the 3 values obtained during screening and baseline

- Maintenance of 6 month GH ≤2.5 ng/mL or ≤20% above the mean of the 3 pre-treatment values obtained during screening and baseline

The S-LAR treatment arm was not powered to allow for assessment of the primary hypothesis. However, PD outcomes for the S-LAR arm were descriptively assessed. Subgroup analyses included: sex, age group (<65, ≥65 years), country, history of diabetes and pre-treatment S-LAR dose (10-20 mg, 30-40 mg). The success rate for the subgroup of subjects who entered the study with normal pretreatment concentrations of IGF-1 and GH were calculated where success was defined as mean on-treatment IGF-1 within the age-adjusted normal range and mean on-treatment GH ≤2.5 ng/mL.

***Secondary Efficacy**:*

Secondary efficacy was descriptively assessed for each treatment group for the ITT data set: success rates; physician assessment of signs and symptoms of acromegaly; quality of life Short Form health 36 survey questionnaire (SF-36); 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-1 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. Success was defined as maintenance of mean on-treatment IGF-1 within the age-adjusted normal range or ≤20% above the baseline mean value and; maintenance of mean on-treatment GH ≤5 ng/mL or ≤20% above the baseline mean value.

SUMMARY:

***Pharmacokinetic Results**:*

Following implantation of the octreotide subcutaneous implant, serum octreotide concentrations increased within 8 days and generally peaked between day 14 and day 28. During the first 28 days of the Primary Treatment Phase of the study, C_{max} values for subjects with and without additional samples were 2720 pg/mL (± 762 pg/mL) and 2577 pg/mL (± 2148 pg/mL), respectively. The octreotide serum concentrations decreased modestly by 48.6% (from 1544.09 pg/mL to 793.3 pg/mL) from day 56 to day 168. The mean octreotide C_{avg} for all implanted subjects over the 24-week treatment period was greater than 1280 pg/mL. Higher octreotide concentrations occurred in female subjects compared to the male subjects.

***Efficacy Results**:*

Demographics and Baseline Characteristics of the Safety Population:

One-hundred fourteen (114; 69.94%) of 163 subjects were females with a median of 55 years of age, weight of 83 kg and a BMI of 30 kg/m^2. Sixty nine (69 subjects; 42.33%) of 163 subjects had a history of diabetes or glucose intolerance at baseline. Prior to enrollment, a majority of subjects (82 subjects; 50.31%) had received S-LAR 20 mg. The subjects in this study had underlying diseases and conditions associated with acromegaly. As expected, the majority had medical histories related to endocrine/metabolic (109/161 subjects; 67.7%) and hypertension (106/167 subjects; 65.8%).

Primary Efficacy Analyses:

In subjects who received the octreotide implant, success rate for adequate maintenance of IGF-1 and GH was 86% (86 of 100 subjects; 90% CI: 80.3% – 91.7%) over the 24-week treatment period.

Of the 37 subjects who received S-LAR during the study, success rate was 83.8% (31 subjects; 90% CI: 73.8% - 93.8%).

Secondary Efficacy Analyses:

In the implant arm, maintenance of reduced blood levels of GH (mean on-treatment GH values ≤2.5 ng/mL or ≤20% above the baseline) was achieved in 91% of subjects. Maintenance of reduced blood levels of IGF-1 (mean on-treatment IGF-1 values within the age-adjusted normal range or ≤20% above the baseline) was achieved in 94% of subjects in the implant arm.

Treatment with the octreotide implant did not result in any apparent changes in tumor volume or shape. Treatment with the octreotide implant did not result in any apparent changes in the physician assessment of signs and symptoms, patient treatment assessment scales (including treatment pain).

Based on the Subject Treatment Assessment, a majority of subjects (82.5%, n=97) selected the implant as their preferred method of treatment for acromegaly.

All Quality of Life (SF-36) scores obtained during this study, regardless of visit and treatment arm, were <50, as expected in this population of subjects with acromegaly.

Safety Results:

Treatment with the 84-mg octreotide implant was well-tolerated during the 6-month Primary Phase of the study. Approximately, 70% of subjects in each treatment arm reported AEs during the study with a majority being mild to moderate in severity. Six (6) subjects, all in the implant arm, were withdrawn due to AEs, of which 4 were due to administration site conditions. The most frequently reported AEs in the implant arm were diarrhea (12 subjects; 9.8%) and headache (12 subjects; 9.8%). The most frequently reported treatment-related AEs in the implant arm were cholelethiasis (9 subjects; 7.4%) and diarrhea (8 subjects; 6.6%). There were 10 SAEs in the implant arm; however, none were considered treatment-related.

The most frequently reported AEs in the S-LAR arm were hypertension (n=6; 14.6%) and cholecystitis (n=5; 12.2%). The most frequently reported treatment-related AEs in the S-LAR arm were cholecystitis (n=5; 12.2%) and cholelithiasis (n=3; 7.3%). No subject was withdrawn due to AEs. Three (3) subjects experienced SAEs. Two (2) SAEs of bile duct stone and cholecystitis, experienced by the same subject, were considered possibly related to study medication.

No deaths occurred during the Primary Phase of the study.

There were no clinically significant changes in clinical chemistry, hematology, vital signs, ECGs, physical examinations, thyroid hormone, glucose and HbA1c levels. There were no clinically significant changes in number of gallstones in the implant arm based on ultrasound analyses.

In the non-diabetic group of subjects, glucose levels remained within the acceptable range for an OGTT at each visit for the majority of subjects in both the implant and the S-LAR arm of the study.

All 122 implants were inserted per the study protocol. One subject's implant was broken during implantation and 1 subject's implant was broken during the treatment phase. Four (4) subjects had incomplete removal of their implants at the time of explantation. During the time of explantation, 32/122 explants were broken. In all cases, implant breakages or incomplete removals were not associated with any significant safety related events. The incidence of overall local tolerability AEs was 13.1% and was primarily due to implant site reaction, pain and pruritus.

Study Number: IP107-001 [Extension Phase]	
Title of Study: Phase III, Open-Label, Multicenter International Study to Evaluate the Efficacy and Safety of an Octreotide Implant Versus Sandostatin LAR® Depot in Patients with Acromegaly [Extension Phase]	
Investigators: A total of 39 investigators were involved in this multicenter study.	
Study Center(s): The study was conducted in 39 sites internationally.	
Publications (reference): None	
Studied period (years): Date first patient enrolled: 28-Apr-2010 Date last patient completed: 19-Apr-2011	**Phase of development**: Phase 3
Objectives: The overall objectives of this 24-week extension phase were to evaluate safety and tolerability, efficacy, and pharmacokinetics of the 84-mg subcutaneous implant. The primary phase of the study completed after 24 weeks of treatment. This synopsis presents results of the extension phase (post Week 24 of treatment). Results from the first 24 weeks of the study are presented separately.	
Methodology: The extension phase was a continuation from the Phase 3, open-label study to evaluate the efficacy and safety of an 84-mg octreotide implant versus Sandostatin LAR® Depot (S-LAR) in patients with acromegaly. During the primary treatment phase, subjects were treated with octreotide delivered by implant or S-LAR in a 3:1 ratio. During the extension phase, eligible and consenting subjects received a second 84-mg octreotide implant (if treated with an implant during the primary treatment phase) or received a first 84-mg octreotide implant (if treated with S-LAR during the primary treatment phase). Eligibility for the extension phase was based on the means of at least 4 available concentrations of each of growth hormone (GH) and insulin-like growth factor-1 (IGF-1) obtained from Weeks 4, 8, 12, 16, and 20 (as collected during the primary treatment phase). Eligibility for the extension phase required mean serum IGF-1 concentration to be within the age-adjusted normal range or ≤20% above the primary treatment phase baseline (average of 3 pre-treatment measurements) and mean GH concentration to be ≤2.5 ng/mL or ≤20% above the primary treatment phase baseline (average of 3 pre-treatment measurements). Eligible subjects who consented to participate in the extension phase were to be implanted at Week 24 (immediately following explantation of the first implant if previously implanted). Subjects who received S-LAR during the primary treatment phase received their first 84-mg octreotide implant approximately 1 month after their last S-LAR dose. Clinical laboratory data (hematology, chemistry, and urinalysis) were measured at baseline and at Weeks 24, 36, and 48. Thyroid measures of free T4 hormone (FT4) and thyroid stimulating hormone (TSH) were measured at Baseline, Week 24, and Week 48.	
Number of Subjects (Planned and Analyzed): Approximately 140 evaluable patients were planned for the primary treatment phase. The sample size for the extension phase was limited by the number of subjects from the primary treatment phase who met the eligibility inclusion/exclusion criteria requirements and consented to participate in the extension phase. Of the 163 subjects who received treatment during the primary treatment phase, 135 entered the extension phase.	
Diagnosis and Main Criteria for Inclusion: The key inclusion criteria included male or female subjects with acromegaly, ≥18 to ≤80 years and with a confirmed diagnosis of a growth hormone-secreting tumor. Enrollment into the extension phase required pre-specified GH and IGF-1 levels as previously outlined.	

Test Product, Dose and Mode of Administration, Batch Number(s): Octreotide implant (84-mg octreotide acetate) for subcutaneous implantation was used as the investigational product. The implant was inserted subcutaneously into the upper, inner aspect of the subject's non-dominant arm (between the bicep and triceps) using the trocar (insertion device) from the implant kit provided. The lot numbers were 706 and 707.

Duration of Treatment: Planned duration during the extension phase was 24 weeks (6 months).

Reference Therapy, Dose and Mode of Administration, Batch Number(s): There was no reference therapy.

Criteria for Evaluation: Outcomes for safety, efficacy, and pharmacokinetics were assessed.

Safety: These variables were adverse events (AEs) including tolerability, clinical laboratory examinations, physical examinations, body weight and vital signs measurements, 12-lead electrocardiograms (ECGs), pituitary tumor size, and gallbladder ultrasounds.

Efficacy: Primary efficacy was evaluated on the basis of IGF-1 and GH.

Pharmacokinetic: Blood samples were assessed for octreotide plasma levels during the 6-month treatment period. Area under the plasma concentration-time curve (AUC), average concentration over 24 weeks of treatment period (C_{avg}), maximum concentration (C_{max}), and time to maximum concentration (T_{max}) were derived for subjects receiving octreotide implants.

SUMMARY:

SAFETY RESULTS:

Treatment with the 84-mg octreotide implant was well tolerated during the 6-month extension phase study. Overall, 70 of 135 subjects (51.9%) had AEs during the extension phase with most events being mild (39 subjects; 28.9%) to moderate (22 subjects; 16.3%) in severity. The most frequently reported AEs were headache (12/135 subjects; 8.9%), nasopharyngitis (11/135 subjects; 8.1%), and diarrhea (8/135 subjects; 5.9%).

Overall, 28 of 135 subjects (20.7%) had AEs that were considered drug-related by the Investigator. The most common treatment-related AEs reported in ≥3% of subjects were diarrhea (5/135 subjects; 3.7%), cholelithiasis (5/135 subjects; 3.7%), implant site reaction (4/135 subjects; 3.0%), and acute cholecystitis (4/135 subjects; 3.0%).

Eleven (11) of the 135 subjects (8.1%) in the extension phase had serious adverse events (SAEs). Six (6) SAEs were considered related to the study medication by the Investigator: 1 case of cholecystitis, 4 cases of acute cholecystitis, and 1 case of implant site infection. All SAEs resolved during the study.

All 133 implants were inserted and explanted according to the protocol during the extension phase. There were no reported implant breakages during the implantation procedure. There was 1 suspected breakage that occurred during or shortly after implantation but on inspection of the implant at explantation, it was not broken. Two (2) subjects had incomplete removal of their implants at the time of explantation. One (1) of the subjects had the retained fragment removed during the long-term extension study. During the time of explantation, 33 of 133 explants were broken. In all cases, implant breakages or incomplete removals were not associated with any significant safety related events.

Local tolerability AEs occurred in 10 of 135 subjects (7.4%) and most of these events were implant site reactions (4/135 subjects; 3.0%). There was 1 case each of implant site inflammation, scar, and pain in the extremity. All of these AEs were mild to moderate in intensity. One (1) subject had an SAE of moderate implant site infection which resolved. Implant site reactions included 2 retained implants, 1 partial prolapse, and 1 breakage at explant.

There were no clinically significant changes in clinical chemistry, hematology, vital signs, ECGs, physical examinations, thyroid hormone, glucose, and glycosylated hemoglobin (HbA1c) levels. There were no clinically significant changes in number of gallstones based on ultrasound analyses.

EFFICACY RESULTS:

In subjects who received the second implant in the extension phase, success rates for adequate maintenance of both IGF-1 and GH ranged from 75.6% to 89.5%. At Weeks 28 and 48 the success rate was 85.4% and 76.2%, respectively. Similarly, success rates for subjects who received a first implant ranged from 66.7% to 84.4%. At weeks 28 and 48 the success rate for subjects who received a first implant was 84.4% and 66.7%, respectively. Overall success rates were similar to those observed in the primary phase of the study.

PHARMACOKINETICS RESULTS:

The overall pharmacokinetic profiles of subjects receiving a second implant and those who received their first implant in the extension phase were similar. The only exception was the mean serum octreotide concentrations at Week 28 (corresponding to Week 4 post-implantation in the extension phase) were lower in subjects who received the second implant than in those who received a first implant (1852 pg/mL and 2386 pg/mL, respectively). This is potentially due to the continuing release of octreotide from the S-LAR formulation.