Mild, infrequent vaginal bleeding in a 52 yr. old F (patient #4003) who underwent dilatation and curretage. She made an uneventful recovery and the events were considered to be unrelated to LAR.

Cosmetic surgery for jaw reduction in a 50 yr. old M (#4005). He made an uneventful recovery and the event was not considered to be related to LAR.

Slight intermittent vaginal bleeding in a 52 yr. old F (#4006) who was receiving estradiol. The event was not considered to be related to LAR.

Diabetes insipidus secondary to adenectomy in a 40 yr. old M (#5005) who underwent surgical resection due to failure of Sandostatin LAR and sq to normalize IGF-1 and to suppress GH to <5 ug/l. In addition, there was no evidence of tumor shrinkage on LAR. The adverse event was considered to be not related to LAR.

Newly occurring diabetes mellitus in a 59 yr. old F (#5102) who was found to have a fasting blood glucose of _ at the final visit in 202-E-02. The patient subsequently received treatment with metformin and glibenclamide. The adverse event was considered to be a complication of acromegaly and not directly related to LAR.

Adverse events in decreasing order of frequency (note: in some cases, the relationship to LAR as assessed by the investigator, is recorded here):

Any event:	36 (59%)
GI:	14 (23%)
Abdominal pain: 5	
Diarrhea: 4	
Nausea: 4	
Vomiting: 2	

1 each: feces discolored and flatulence

The GI AEs were mild-moderate in severity and did not appear to be dose-dependent. The majority were related to LAR.

Central and peripheral nervous system: 17 (28%)
(most commonly reported were dizziness: possibly or probably related to LAR in 3/7 patients, headache, cramps and paresthesias)

Body as a whole: 15 (25%)
(most commonly reported were fatigue, influenza-like symptoms and surgery)

Skin and appendages: 7 (12%)
(alopecia in 3 patients: regarded as probably related to LAR)

Musculoskeletal system disorders: 6 (10%)
(most commonly reported were arthralgia and arthropathy)

Liver and biliary system disorders: 4 (7%)
(cholelithiasis in 4 patients: probably-possibly related to LAR in all)

Psychiatric: 3 (5%)
(anorexia, anxiety and insomnia in 1 patient each: possibly related to LAR)

Resistance mechanism: 3 (5%)
(note: abscess and cellulitis: 1 patient each- probably related to LAR)

Respiratory system disorders: 3 (5%)
(bronchitis, coughing, rhinitis: 1 patient each- unlikely to be related)

2 patients (3%) reported each of the following AEs:
Injection site disorders: pain in 2
Endocrine disorders:
Diabetes insipidus: 1
Hypothyroidism: 1 (possibly related)
Chest pain: 2 (not related)
Platelet and clotting disorders:
Epistaxsis: 1 (not related)
Non-specific hemorrhage: 1 (unlikely to be related)
Female reproductive:
Vaginal bleeding: 2 (not related/unlikely)

1 patient (2%) reported each of the following AEs (all were reported as not related or unlikely to be related to LAR):
Hypertension
Non-specific ear disorder
Weight increase
Eye abnormality

Injection site disorders:
Pain: 7 patients
Swelling: 1
Rash: 1

Vital signs:

No abnormalities of vital signs were detected which were regarded by the investigators as being of clinical relevance.

Physical exam:

None of the new or worsening abnormalities reported on physical exam were considered related to LAR.

Hematology and biochemistry:

Anemia was the most frequently reported hematological adverse event. It reflected frequent blood sampling.

In 4 patients, the leukocyte count was increased.

Elevated fasting glucose was reported in 9 patients (note: in only 4 of these 9 patients, was the increase in fasting glucose newly occurring in this extension. In 3 of these 4 patients, fasting glucose was normal at baseline). In 1 of these 9 patients (#5116), the increase was clinically notable This patient had a history of type II diabetes for which he was receiving metformin and glibenclamide. His baseline glucose was elevated:

Elevated SGOT and/or SGPT: 4 patients/1 patient; none were clinically notable (i.e. ≥3 x ULN).

Elevated total bilirubin: 6 patients. In 1 of these 6 patients (#5119), the rise was clinically notable In this patient, baseline total bilirubin was elevated and rose at the final visit. Baseline gallbladder ultrasound, normal at baseline, showed sediment while the patient was on LAR. In addition, the patient reported right hypochondrial pain.

Elevated alkaline phosphatase: 4 patients; none were clinically notable.

Elevated HbA_{1C}: 3 patients- (note: HbA_{1C} was also increased in all 3 of these patients in 202-E-02)

#1002 on insulin for diabetes mellitus, baseline

and, at final visit, was

#1005 on glipizide for type II diabetes, baseline:

, and rose , at final visit.

#1010: baseline was and increased

final visit.

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OGGT:

In 13 (21%) of the patients, the OGGT was abnormal. In 2 of these patients, #'s 5004 and 5102, the diabetes was newly occurring.

In 19 (40%), serum GH remained below 2 ug/l or were suppressed to <2 ug/l during the OGTT.

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TFTs:

28 (46%) of patients were receiving concomitant therapy with thyroid hormones. Although fluctuating abnormalities of thyroid function tests were observed throughout the study, there was no consistent or progressive pattern of abnormalities.

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Gallbladder Ultrasound:

Newly occurring or worsening abnormalities in patients with normal baseline ultrasound (note: none of these patients were on bile acid dissolution agents):

Gallstones/Microlithiasis (+/- also with sediment/sludge/dilatation): (#'s 1109, 4001, 4006 and 5121)	4
Sediment and/or sludge without stones (+/- also with dilatation): (#'s 5119, 5117, 5114 and 1006)	4
Dilatation/wall thickening only:	0
Biliary symptoms:	0

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ON ORIGINAL

Newly occurring or worsening abnormalities in patients with abnormal baseline ultrasound (note: none of these patients were on bile acid dissolution agents):

Gallstones/Microlithiasis (+/- also with sediment/sludge/dilatation) (# 5101)	1
Sediment and/or sludge without stones (+/- also with dilatation): (#5004)	1
Dilatation only:	0
Biliary symptoms:	0

APPEARS THIS WAY
ON ORIGINAL

Overall Gallbladder Abnormalities in Patients Who Were Enrolled in 202-E-00 through 202-E-03:

Newly occurring or worsening gallbladder abnormalities in patients who received up to 28 injections of Sandostatin LAR (note: none of these patients were on bile acid dissolution agents when these abnormalities occurred):

gallstones/microlithiasis (+/- also with sediment/sludge/dilatation):	18/62 (29%)
sediment and/or sludge without stones (+/- also with dilatation):	16/41 (39%)
dilatation/wall thickening only:	4/21 (19%)
biliary symptoms:	3/62 (5%)

(note: biliary symptoms were not present at study end in any of these 3 patients

(Explanations for the denominators used to calculate the gallbladder abnormalities: although 65 patients had gallbladder ultrasounds at baseline and after LAR treatment, the following patients were excluded:

for gallstones and/or microlithiasis, the denominator of 62 results from the exclusion of 3 patients with gallatones at baseline, one of whom was on ursodeoxycholic acid;

for sediment/sludge without gallstones/microlithiasis, the denominator of 41results from exclusion of the 3 patients as detailed above for gallstones/microlithiasis plus the 18 patients who developed gallstones and/or microlithiasis post baseline plus 3 patients who had sediment and/or sludge at baseline;

for dilatation/wall thickening only: all the exclusions pertaining to gallstones/microlithiasis (n= 3) and sediment/sludge (n= 21), also pertain here plus the 16 patients who developed sediment/sludge post baseline plus 4 patients with dilatation/wall thickening at baseline).

(%) of patients with gallbladder abnormalities that were either present at baseline or developed during treatment with LAR, and in whom the last study ultrasound for the patient was normal and the patient was not on bile acid dissolution agents:

Gallstones/microlithiasis: 2/11 patients
Sediment/sludge: 11/17
Dilatation/wall thickening: 6/8

Special Issues With Regard to All the Acromegaly Studies:

1. Of the 25 patients who were partial responders to subcutaneous Sandostatin, only 1 patient (4%) reduced mean GH to <2.5 ug/L and normalized IGF-1.
2. The hormonal response (GH suppression and IGF-1 normalization) was similar between the 24 patients who developed octreotide antibodies compared to those who did not. In 2 patients, the duration of GH suppression following Sandostatin injection was about twice as long as in patients without antibodies. The adverse event profile appeared to be similar between those with antibodies and those without.
3. The hormonal response in studies 201, 202 and 303 in all patients entering these trials was similar to that in patients who completed all extensions in each of these studies:

	Study 201: Total entered	Study 201: Completers only
Mean GH<5 ug/L	44/45 (98%)	31/33 (94%)
Mean GH<2.5	25/45 (56%)	19/33 (58%)
Mean GH<1	8/45 (18%)	6/33 (18%)
IGF-1 normal	26/45 (58%)	20/33 (61%)
Mean GH<5 & IGF-1 nl.	26/45 (58%)	20/33 (61%)
Mean GH<2.5&IGF-1 nl	21/45 (47%)	16/33 (48%)
Mean GH<1 % IGF-1 nl.	8/45 (18%)	6/33 (18%)

	Study 202: Total entered	Study 202: Completers only
Mean GH<5 ug/L	50/63 (79%)	42/55 (76%)
Mean GH<2.5	25/63 (40%)	22/55 (40%)
Mean GH<1	4/63 (6%)	4/55 (7%)
IGF-1 nl.	28/63 (44%)	25/55 (46%)
Mean GH<5 & IGF-1 nl.	28/63 (44%)	25/55 (46%)
Mean GH<2.5&IGF-1 nl.	23/63 (37%)	21/55 (38%)
Mean GH<1 & IGF-1 nl.	4/63 (6%)	4/55 (7%)

	Study 303: Total entered	Study 303: Completers only
Mean GH<5 ug/L	139/151 (92%)	118/122 (97%)
Mean GH<2.5	95/151 (63%)	80/122 (66%)
Mean GH<1	36/151 (24%)	28/122 (23%)
IGF-1 nl.	97/151 (64%)	82/122 (67%)
Mean GH<5 & IGF-1 nl.	97/151 (64%)	82/122 (67%)
Mean GH<2.5&IGF-1 nl.	83/151 (55%)	70/122 (57%)
Mean GH<1 & IGF-1 nl.	33/151 (22%)	27/122 (22%)

Overall Safety of Sandostatin LAR in Acromegaly:

Patients who completed studies 201 and 202, were eligible for entry into another extension trial- study 304 which was of 6 months duration. Patients who completed studies 201, 202 or 303 will also eligible to enter yet another extension study- study 308 which was of 12 months duration. Therefore, we have safety data in acromegaly patients treated with Sandostatin LAR up to 4 years. The major toxicities of Sandostatin are gallbladder abnormalities and GI symptoms.

Across all acromegaly studies, the incidences of newly occurring or worsening GB abnormalities was 22 % for gallstones and/or microlithiasis (43/200), 27% for sediment and/or sludge without stones (41/151) and 16% for dilatation and/or wall thickening only (17/105). Note, there were 2 patients in study 201 in whom microlithiasis and sediment were not distinguished. The overall incidence of GB abnormalities in these acromegaly trials was 103/200= 52%.

The pooled incidences for the following GI abnormalities were:

Diarrhea 36%, abdominal pain 29%, flatulence 26%, constipation 19%, nausea 10% and vomiting 7%.

Since octreotide can suppress secretion of thyroid stimulating hormone, it is important to note the incidence of hypothyroidism. Hypothyroidism was reported as an adverse event in 2% of patients. 2 patients were placed on thyroid hormone suppressive therapy. It is not clear if, in these patients, hypothyroidism was a drug-related effect or due to the patient's underlying disease.

Since octreotide alters the balance between the counterregulatory hormones, insulin, glucagon and GH, hypo or hyperglycemia may ensue. However, acromegaly patients are at increased risk for carbohydratre intolerance. Also, hypoglycemia could be the result of insulin overdoage in an acromegalic with insulin-dependent diabetes mellitus. Therefore, as with hypothyroidism, the relationship of hypo and hyperglycemia to octreotide therapy is not clear. Across all acromegaly studies, the incidence of hypoglycemia was 1.5 %, and hyperglycemia was 15%.

It is important to note that the overall safety profile of Sandostatin LAR is similar to that for Sandostatin sq.

Carcinoid Clinical Study:

SMSE 351: A Randomized Study of the Safety, Tolerability and Efficacy of Multiple Double-Blind Dose Levels of Sandostatin LAR Given at 4 Week Intervals Vs. Open Label SQ Sandostatin in Malignant Carcinoid Syndrome

This was a phase 3 study which involved 9 US centers.

Objectives were:

Primary:

To determine over a 24 week period, the efficacy of 10, 20 and 30 mg of Sandostatin LAR administered at 4 week intervals compared to Sandostatin sq tid in providing continuous symptomatic control in patients with malignant carcinoid syndrome.

Secondary:

To determine the safety and tolerability of Sandostatin LAR in patients with malignant carcinoid syndrome

To assess over a 24 week period, the dose proportionality of serum octreotide concentrations of LAR at doses of 10, 20 and 30 mg administered q 4 weeks

To monitor urinary 5-OHindoleacetic acid (5-HIAA) excretion

Study design:

A 24 week, prospective, multicenter, randomized, parallel-group, switch study; double-blind with respect to LAR dosage and open-label with respect to sq.

Key inclusion criteria:

Males or non-pregnant females, $\geq$ 18 yrs. old, with malignant carcinoid

Patients symptomatically well-controlled on concurrent sq ranging from 0.3-0.9 mg/day, for the 2 weeks prior to study wash-out. Well-controlled symptomatically meant an average stool frequency $\leq$ 3/day with $\leq$ 3 stools on any one day and $\leq$ 2 flushing episodes/day during the 2-week pre-washout period

Stool frequency increase during washout of at least 2/day above pre-washout daily average for 2 consecutive days and/or 3 episodes of flushing/day for 1 day.

Key exclusion criteria:

Patients expected to receive additional therapy during the course of the study which could effect their carcinoid syndrome

Patients with symptomatic abnormalities of the biliary tract.

Patients requiring medications known to affect their urinary output of 5-HIAA.

Details of study design:

After a 2 week screening period during which patients continued their sq tid regimen, there was a washout period of ~ 3 days until the return of symptoms. Patients were then randomly assigned to one of four treatment groups: 10, 20 or 30 mg of LAR q 4 weeks for 24 weeks, or resumption of sq Sandostatin tid, at the same dosage taken during the screening period, for 24 weeks. Due to the delayed onset of achieving therapeutic concentrations of octreotide with LAR, sq therapy was initiated immediately in LAR patients following the first LAR injection on day 1, and was continued through day 11, at which time sq therapy was stopped for LAR patients. LAR patients received 5 additional LAR injections at 4 week intervals. The total duration of the study was 24 weeks.

To assess symptomatic control between visits, patients were required to fill out daily diaries in which they recorded their clinical symptoms, injection site reactions, any adverse events and rescue therapy.

Patients were allowed to receive sq rescue therapy when average daily stool frequency increased by at least 2/day for 2 consecutive days above the screening period average and/or when flushing increased to at least 3 episodes/day for one day. The patient was then allowed to take Sandostatin sq tid until symptoms returned to the screening period frequency, at which point the sq therapy was discontinued. For patients treated with sq alone, rescue was achieved by increasing the dose by 50%. Once symptomatic relief was achieved for 24 hrs., the sq rescue therapy or increased sq dose was discontinued. If symptoms recurred, a second course of sq rescue therapy or increased sq dosage was allowed. If, in any interval between clinic visits, symptomatic relief was not provided by 2 courses of sq rescue medication or increased dosage totalling not more than 5 days of treatment, or if symptoms requiring rescue therapy recurred a third time, the patient was allowed to continue sq rescue therapy tid until the next clinic visit. At that visit, the sq rescue medication was discontinued, and the next dose of LAR was administered or the original dose of sq was resumed.

Efficacy variables:

Primary:

The following definitions were used:

Treatment success:

As defined for patients on LAR= no need for sq rescue medication between weeks 17-20 or weeks 21-24.

As defined for patients on sq= no need for an increased dosage between weeks 17-20 or weeks 21-24.

Partial treatment success:

For patients on LAR: need for sq rescue medication and for patients on sq: need for an increased sq dosage which, in either situation, should be for no more than 2 occasions for a total of $\leq$5 days during the intervals between weeks 17-20 or weeks 21-24.

Treatment failure:

Need for sq rescue medication (LAR patients) or increased doage (sq patients) on $\geq$ 3 occasions or for > 5 days during weeks 17-20 or weeks 21-24.

The primary efficacy analysis was performed as follows:

Treatment Success + Partial Success Vs. Treatment Failure

Endpoint (last non-missing post-baseline evaluation) analyses were used for primary overall assessment of efficacy; however, individual period analyses were made as well.

For intent-to-treat analyses, patients who dropped out of the study for any reason between the first and fourth dosing intervals (weeks 1-16) were considered to be treatment failures.

Secondary efficacy:

-time to first sq rescue Sandostatin after day 11

-proportion of patients experiencing increased stool and/or flushing frequency during a dosing interval

-weekly cumulative proportion of patients experiencing increased stool and/or flushing frequency after day 11

-raw and change from baseline and change from screening in urinary 5-HIAA levels. Note: the 24 hr. urinary 5-HIAA level was deemed invalid and, therefore, excluded from the analysis, if any of the following occurred:

a. if the sample was taken prior to the 2 week screening period
b. if the sample was taken < 48 hrs. after the last sq dose given during the screening period
c. if the baseline octreotide value was > 160 pg/ml
d. if the baseline sample was collected after resumption of sq after the washout period
e. after baseline, if an LAR patient took any sq doses or a sq patient took any increased doses during a 72 hr. period preceeding the sample collection or if the LAR dose was administered prior to the sample collection.

Safety:

Vital signs and 24 hr. urinary 5-HIAA levels at every 4 week visit

Serum hematology and biochemistry: at baseline and weeks 4, 12 and 24

Physical exam, ECG, gallbladder ultrasound and special labs (TFTs: serum TSH, total and free T4; HbA_{1C} and carotene) at baseline and end of study (week 24)

Pharmacokinetics:

Serum octreotide levels were measured at every 4 week visit, prior to the subsequent LAR injection.

Note: the ITT population comprised all patients who had at least 1 efficacy evaluation. The ITT population was used for the primary efficacy analysis. Efficacy evaluable referred to patients who returned for at least the 20 week visit.

RESULTS:

Key demographic data:

93 patients were included in the ITT population (26 on sq and 67 on LAR). 95% were Caucasian and 56% were male. Mean age was 59.7 yrs. with range of

Patient disposition for the ITT population was:

	Sandostatin sq	Sandostatin LAR		
		10 mg	20 mg	30 mg
	n (%)	n (%)	n (%)	n (%)
Randomized	26 (100%)	22 (100%)	20 (100%)	25 (100%)
Completed	25 (96%)	19 (86%)	15 (75%)	21 (84%)
Discontinued	1 (4%)	3[a] (14%)	5[a] (25%)	4 (16%)

a= patients who dropped out of the study after the first through fourth dosing intervals (weeks 1 through 16) for any reason were considered treatment failures in the ITT analyses: 3 patients in the 10 mg dose group, 5 in the 20 mg group and 2 (synopsis says 3) in the 30 mg dose group.

Note: 1 patient on sq and 1 on 30 mg LAR dropped-out prior to the final visit but after the fourth study visit.

Study discontinuations: n= 13 patients:

Adverse event: n= 1 (in 20 mg dose group: #05008: discontinued the study at week 15 because she required a liver lobectomy for progressive metastatic disease)

Deaths: n= 3 (1 in 20 mg dose group and 2 in 30 mg dose group). All had advanced metastatic carcinoid disease at study entry:

Patient #02006, a 63 yr. old F, entered the study with extensive hepatic metastases and repeated episodes of hypoglycemia. After starting the study, the patient had 2 episodes of hypoglycemia. On study day 67, she was found to have progressive hepatic metastases, hepatic insufficiency and progressive myositis. Renal insufficiency developed on day 97 and the disease progressed causing death on study day 102.

Patient #06004, a 75 yr. old M, developed respiratory distress syndrome on day 50 of the study and died on study day 72. The investigator considered the death to be secondary to respiratory failure.

Patient #07001, a 55 yr. old F, entered the study with advanced metastatic carcinoid disease and arterio-venous malformations in the intestine. On study day 66, a Le Veen shunt was placed for ascites unresponsive to medical intervention. Due to malfunction, the shunt was replaced on day 141. On post-op day 2, a pulmonary embolus occurred followed by a superior vena cava syndrome (both due to a thrombogenic state and terminal carcinoid cancer). She developed marked cerebral edema which the investigator attributed to the superior vena cava syndrome. She died on study day 146.

Withdrawal of consent: n= 2 (1 in 10 mg group- #08023 who was discontinued from the study on day 94 due to difficult travel and disease progression and to undergo a hepatic artery embolization: and 1 in 30 mg: #09004 who entered with bone metastases and received only 1 LAR injection)

Treatment failure: n= 2 (1 on sq: #03001 who was discontinued from the study on day 168 with abdominal pain and disease progression and 1 in the 10 mg LAR group: #09006 who was discontinued from the study at week 8 with disease progression)

Failure to return: n= 4

(10 mg: n=1: patient #02011 was as well controlled at study discontinuation on day 96 as during screening;
20 mg: n=2: #02012 with bipolar disorder requiring psychiatric evaluation, discontinued the study at week 8 and #05022 who was lost to f/u, having failed to return for his day 141 visit.

Both patients were well controlled prior to study d/c;
30 mg: n= 1: #02014 with enlargement of liver metastases but well controlled clinically until study d/c on day 152)

Other: n= 1 (in the 20 mg dose group: #08024: required hepatic artery embolization for progression of liver metastases)

NOTE: The incidence of premature withdrawal due to disease progression or complications of underlying carcinoid disease or lack of symptomatic control by dose group was:

SQ:	1/26 (4%) (#3001)
10 mg LAR:	2/22 (9%) (#'s 08023 & 09006)
20 mg LAR:	3/20 (15%) (#'s 08024, 05005 & 02006)
30 mg LAR:	3/25 (12%) (#'s 02014, 07001 & 06004)

In addition, although #07004 completed this study, she was not entered into the subsequent carcinoid trial (SMSE 451) due to progressive disease and uncontrollable diarrhea. Rather, the patient was treated with chemotherapy.

Octreotide serum levels:

The 20 mg and 30 mg groups reached steady state trough levels by day 57, whereas the 10 mg group did not reach steady-state until day 85. Mean (median) and range of serum octreotide levels (pg/ml) at steady state were:

20 mg: n= 17: 2311 (1750)
30 mg: n= 21: 4429 (3560)
10 mg: n= 18: 1231 (894)

Steady-state octreotide mean and median values were higher for females and for patients ≥60 yrs.

EFFICACY:

Primary Efficacy:

Treatment success was assessed at study weeks 20 (day 141: after the 5th injection) and 24 (day 169: after the 6th), i.e. after serum octreotide levels had reached steady-state.

ITT Population: Treatment success at weeks 20 and 24 and at Endpoint (last not missed post-baseline evaluation):

ITT: % Treatment Success at Week 20

Outcome	Sandostatin sq n= 26	10 mg LAR n= 19	20 mg LAR n= 16	30 mg LAR n= 23
Complete success	62%	63%	63%	61%
Partial success	4%	11%	6%	-
Complete+Partial Success	65%	74%	69%	61%

ITT: % Treatment Success at Week 24

Outcome	Sandostatin sq n= 26	10 mg LAR n= 19	20 mg LAR n= 15	30 mg LAR n= 21
Complete success	54%	63%	60%	62%
Partial success	4%	-	7%	5%
Complete+Partial Success	58%	63%	67%	67%

ITT: % Treatment Success at Endpoint

Outcome	Sandostatin sq n= 26	10 mg LAR n= 22	20 mg LAR n= 20	30 mg LAR n= 25
Complete success	54%	55%	45%	52%
Partial success	4%	-	5%	4%
Complete+Partial Success	58%	55%	50%[a]	56%

a= the lower success rate in the 20 mg dose group was due to the high incidence of early discontinuations in this group. Although 3/5 patients randomized to the 20 mg dose group (#'s 2012, 5005 and 5022) who discontinued the study did not use sq rescue medication and were symptomatically well controlled prior to the discontinuation, they were rated as failures, as were all early discontinuations in this study.

Note: Results were similar in the efficacy evaluable population compared to ITT.

No statistically significant differences between LAR treatment groups were observed at weeks 20 and 24 in either the ITT or efficacy evaluable populations in the combined success rate.

Across treatment groups, there did not appear to be any correlation between octreotide levels and treatment outcome in either age or gender.

Secondary efficacy:

a. Time to First SQ Rescue Medication After Day 11 in Patients Receiving LAR or Time to First Increased SQ Dose in Patients Receiving SQ:

	Sandostatin sq	10 mg LAR	20 mg LAR	30 mg LAR
Mean (Median) days	54 (46)	20 (15)	25 (15)	22 (13)
Range (days)				

Comment: time to first rescue medication was shorter in the LAR groups because optimally effective blood levels are not attained with the first LAR injection.

% of Patients Using Rescue Medication by Treatment Group and LAR Dose at Weeks 20 and 24 and at Endpoint (i.e. once steady-state serum octreotide levels have been reached):

Week 20				Week 24				Endpoint			
SQ	10mg	20mg	30mg	SQ	10mg	20mg	30mg	SQ	10mg	20mg	30mg

39% 37% 33% 39% 50% 37% 40% 41% 50% 77% 70% 52%

Comment: at the final study visit, week 24, the percentage of patients using rescue medication in the LAR groups was similar to or less than the percentage using rescue in the sq group.

No rescue medication was used throughout the study by:
5/22 patients (23%) in the 10 mg dose group
6/20 patients (30%) on 20 mg
12/25 patients (48%) on 30 mg
13/26 patients (50%) on sq

Comment: the smallest percentage of patients taking rescue medication was in the sq group and the highest was in the 10 mg LAR group.

b. Stool Frequency:

Mean (Range) Daily Total Number of Bowel Movements and Consistency (Watery Stools) at Screening, Baseline and Endpoint for the ITT Population:

	Sandostatin sq n= 26		10 mg LAR n= 22		20 mg LAR n= 20		30 mg LAR n= 25	
	Total	Watery	Total	Watery	Total	Watery	Total	Watery
Screening	2.4 (0.6-6.1)	0.6 (0.0-6.1)	2.2 (1.0-4.0)	0.2 (0.0-1.6)	2.1 (1.1-4.4)	0.2 (0.0-2.2)	2.5 (1.3-5.0)	0.5 (0.0-2.4)
Baseline	3.7 (0.8-7.8)	2.0 (0.0-6.3)	4.6 (1.2-9.7)	3.1 (0.0-8.3)	4.0 (2.0-10.0)	2.1 (0.0-8.0)	4.9 (0.7-11.8)	3.1 (0.0-11.8)
Endpoint	2.6 (0.7-5.9)	0.7 (0.0-5.9)	2.8 (0.9-6.2)	0.9 (0.0-4.3)	2.1 (1.0-4.7)	0.3 (0.0-2.6)	2.8 (0.8-11.8)	1.0 (0.0-9.5)

Comment: the efficacy of Sandostatin LAR and sq in controlling the # of daily stools and stool consistency was similar.

The average # of daily stools per 4 week interval were similar for each time point across all treatment groups.

There were statistically significant decreases from baseline in the average # of daily stools in all treatment groups at all visits.

The cumulative # and % of patients experiencing increased stool frequency from weeks 12-24 (after steady-state had been reached - last study visit):

Sandostatin sq	10 mg LAR	20 mg LAR	30 mg LAR
n= 26	n= 22	n= 20	n= 25

No statistically significant differences were observed between LAR treatment groups and sq for the # (%) of patients experiencing increased stool frequency.

c. Flushing frequency:

ITT: Mean (Range) Daily Flushing Episodes at Screening, Baseline and Endpoint:

	Sandostatin sq n= 26	10 mg LAR n= 22	20 mg LAR n= 20	30 mg LAR n= 24
Screening	0.3	0.5	0.3	0.4
Baseline	3.0	3.0	5.9	6.1

Endpoint	0.5	0.9	0.6	1.0

Comment: mean daily flushing episodes were similar at all doses of Sandostatin LAR and on sq. The 20 and 30 mg dose groups had the greatest mean baseline to endpoint decrease in daily flushing episodes.

The average # of flushing episodes per 4 week interval were similar for each time point across all treatment groups.

There were statistically significant decreases from baseline in the average # of flushing episodes in all treatment groups at all visits.

The cumulative # and % of patients experiencing increased flushing episodes from weeks 12-24 (after steady-state had been reached - last study visit):

Sandostatin sq	10 mg LAR	20 mg LAR	30 mg LAR
n= 26	n= 22	n= 20	n= 25
	73%		

The only statistically significant difference was between the 10 mg LAR treatment group and sq at the 12 week time point. At week 12, the cumulative % of patients experiencing increased flushing episodes was significantly higher ($p < 0.05$) for the 10 mg LAR group than for the sq group (73% vs. 42%, respectively). However, it should be noted that steady-state octreotide levels were not reached until week 12 in the 10 mg LAR group.

Comparison Between Treatment Groups Regarding the Cumulative Number (%) of Patients Experiencing Increased Stool Frequency and/or Increased Flushing Episodes From Weeks 12-24 (after steady-state had been reached – last study visit):

Sandostatin sq	10 mg LAR	20 mg LAR	30 mg LAR
n= 26	n= 22	n= 20	n= 25
	86%		

The cumulative % of patients experiencing increased stool frequency and/or increased flushing was significantly higher ($p < 0.05$) in the 10 mg group at weeks 12 and 16, 86%, than in the 20 mg dose group, 55%. No other pairwise comparisons were statistically significantly different.

d. 24 hr. Urinary 5-HIAA Excretion:

The most frequent reason for invalidity was if an LAR patient took any sq doses or if a sq patient took any increased dose during a 72 hr. time period preceding the sample collection.

ITT: Mean (Median with Range) and % Change for the Mean and Median from Baseline to Study Endpoint for 24 hr. Urinary 5-HIAA (Note: + change= increase from baseline, - change= decrease from baseline) :

	Sandostatin sq n= 22	10 mg LAR n= 16	20 mg LAR n= 15	30 mg LAR n= 15
Baseline: Mean (median) mg:	57 (42)mg	214 (121)mg	122 (69)mg	96 (84)mg
Range (mg):				
Endpoint: Mean (median) mg:	49 (27)mg	128 (72)mg	62 (27)mg	126 (77)mg
Range (mg)				
Mean (median) % change:	-7% (-26%)	-22%[a] (-38%)	-39%[b](-50%)	+85% (-39%)

a= significant decrease ($p<0.05$) in mean 24 hr. urinary 5-HIAA levels from baseline to endpoint in the 10 mg LAR dose group.

b= significant decrease ($p <0.01$) in mean 24 hr. urinary 5-HIAA levels from baseline to endpoint in the 20 mg dose group.

Note the higher mean and median baseline 24 hr. urinary 5-HIAA levels in the LAR groups compared to the sq group. Very high 5-HIAA levels, above 150 mg/24 hrs., were recorded in 9/17 (53%), 5/16 (31%) and 2/15 (13%) of patients in the 10, 20 and 30 mg LAR groups, respectively. This contrast with only 1/23 (4%) of patients in the sq group who had urinary 5-HIAA level >150 mg/24 hrs.

Comment: as can be seen above, there is a wide range of 5-HIAA levels; therefore, median values and change in median values are more representative than the means for this analysis. There were no statistically significant differences in urinary 5-HIAA levels from baseline to endpoint among the LAR groups, although control was best in the 20 mg group.

Control was best in the 20 mg group with regard to 5-HIAA levels as compared to not only the other LAR groups but to sq as well; control was worst in the 30 mg group where the mean 5-HIAA levels actually increased from baseline to endpoint.

There was no significant correlation between the 24 hr. urinary 5-HIAA (mg) and octreotide levels (pg/ml) or incidence of flushing. There was a weak correlation between urinary 5-HIAA and the number of bowel movements.

SAFETY:

There were 3 deaths- see above for narratives under Patient Disposition, Study Discontinuations.

Premature discontinuations:

See above under Patient Disposition, Study Discontinuations.

In addition, 2 patients had serious AEs during wash-out:

#08005 who experienced severe abdominal pain and multiple episodes of flushing due to stopping Sandostatin sq. The patient was subsequently randomized to 10 mg LAR;

#03999 who experienced vomiting and diarrhea with subsequent dehydration and metabolic acidosis when Sandostatin sq was withdrawn. Hypercalcemia was also noted. The patient was not randomized.

Serious Adverse Events: all were considered to be not related or unlikely to be related to study drug:

Deaths: 3 patients (#'s 02006, 06004 and 07001- see above)

Non-fatal serious AES: n= 14 (sq: n= 4, 10 mg LAR: n= 3, 20 mg LAR: n= 4 and 30 mg LAR: n= 3):

SQ: n= 4:

#02010: small bowel obstruction on study day 57, regarded as secondary to adhesions from the patient's underlying disease. The patient also had chronic cholecystitis for which he received a cholecystectomy.

#03004: abdominal mass diagnosed 2 mos. prior to the study. The patient underwent a total hysterectomy and pathology report revealed metastatic carcinoid tumors of both ovaries.

#05003: abdominal distension, pedal edema and possible bowel obstruction on study day 140.

#05012: partial small bowel obstruction on study day 71, in a patient with a history of hemicolectomy and abdominal adhesions. The investigator regarded this serious adverse event as was most likely secondary to adhesions from previous surgery.

10 mg LAR: n= 3:

#05006: proteinuria on study day 63 in a patient with a history of diabetes mellitus, CAD and hypertension. The investigator stated the event was due to coexistent disease.

#06002: repiratory distress for which he was hospitalized on study day 26. The repiratory distress was considered by the investigator to be secondary to COPD which, in this patient, was caused by asbestosis.

#08023: dehydration for which the patient was hospitalized on study day 91. The patient had multiple episodes of breakthrough diarrhea and had carcinoid heart disease.

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20 mg LAR: n= 4:

#02012: decreased mobility, weakness and right flank pain for which the patient was hospitalized on study day 48. Brain CT was negative for metastases. Hypokalemia was noted and subsequently resolved. The investigator stated this event was due to her coexistent disease.

#02013: severe abdominal cramping, small bowel ileus and clostridial enterocolitis for which the patient was hospitalized on study day 41.

#07004: progressive carcinoid disease with uncontrollable diarrhea. CT on study day 144, revealed an increase in the size of the patient's hepatic lesion and in the number of bony metastases. Although the patient completed this study, the investigator did not enroll her into the follow-up study (SMSE 451) but decided to treat her with chemotherapy.

#08004: hypertension, tachycardia and chest pain for which he was hospitalized on day 116. The investigator stated the event was related to coexisting carcinoid heart disease and coronary heart disease.

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30 mg LAR: n= 3:

#02014: severe RUQ abdominal pain, fever and nausea for which he was hospitalized on study day 102. The patient had a history of small bowel resection. An inferior venacavogram showed high grade stenosis in the intrahepatic portion associated with occlusion. Four days later, the patient had an inferior venacavogram with wall stent placement. CT scan showed massive enlargement of the liver due to expansion of the tumor.

#05008: symptomatic hypoglycemia (weak, dizzy, then patient became unresponsive; serum glucose was 20 mg/dl) in a patient with a history of carcinoid syndrome, hypertension and type II diabetes (for which he received insulin). The patient was hospitalized on study day 86 and started on a 2,000 calorie ADA diet and a sliding scale insulin regimen. While in hospital, the patient was found to have a LLL pneumonia. Also, he was placed on hydrochlorthiazide for hypertension. He became hypokalemic and was started on daily potassium supplementation. He was discharged with his glucose and hypertension controlled. Although the investigator attributed the hypoglycemia to coexistent disease, it is possible that LAR inhibited his glucagon response which could have precipitated hypoglycemia.

#08003: small bowel obstruction and right heart failure. The patient had a history of small bowel obstruction secondary to carcinoid and a history of CAD and carcinoid heart disease. The patient was hospitalized with small bowel obstruction on study days 63 and 134. He was hospitalized for worsening carcinoid syndrome associated with right heart failure secondary to carcinoid heart disease on day 177. Per the investigator, the events were related to coexistent disease.

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Adverse Events:

Adverse Events by Treatment Group and Body System

Occurring in ≥ 5 % of Subjects (Note: in some cases, the relationship to LAR as assessed by the investigator, is recorded here):

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Body System	SQ n= 26	10mgLAR n= 22	20mgLAR n= 20	30mgLAR n= 25
GI*	18 (69%)	16 (73%)	11 (55%)	13 (52%)
Nausea	8 (31%)	9 (41%)	6 (30%)	6 (24%)
Abdominal pain	8 (31%)	8 (36%)	2 (10%)	5 (20%)

Flatulence	3 (12%)	2 (9%)	2 (10%)	4 (16%)
Vomiting	3 (12%)	0 (0%)	0 (0%)	4 (16%)
Diarrhea	3 (12%)	0 (0%)	0 (0%)	1 (4%)
Constipation	3 (12%)	0 (0%)	2 (10%)	1 (4%)
Musculo-skeletal[b]	13 (50%)	11 (50%)	6 (30%)	4 (16%)
Back pain	7 (27%)	6 (27%)	2 (10%)	2 (8%)
Arthropathy	5 (19%)	2 (9%)	3 (15%)	2 (8%)
Myalgia	0 (0%)	4 (18%)	1 (5%)	1 (4%)
Pain	4 (15%)	0 (0%)	1 (5%)	0 (0%)
Central/peripheral NS[c]	11 (42%)	8 (36%)	11 (55%)	10 (40%)
Dizziness	4 (15%)	4 (18%)	4 (20%)	5 (20%)
Headache	5 (19%)	4 (18%)	6 (30%)	4 (16%)
Respiratory system[d]	13 (50%)	7 (32%)	5 (25%)	9 (36%)
URI	6 (23%)	4 (18%)	2 (10%)	3 (12%)
Sinusitis	4 (15%)	0 (0%)	1 (5%)	3 (12%)
Coughing	0 (0%)	3 (14%)	0 (0%)	1 (4%)
Dyspnea	3 (12%)	3 (14%)	0 (0%)	3 (12%)
Body as a whole[e]	9 (35%)	11 (50%)	8 (40%)	7 (28%)
Fatigue	3 (12%)	7 (32%)	2 (10%)	2 (8%)
Pain	4 (15%)	2 (9%)	3 (15%)	1 (4%)
Asthenia	0 (0%)	3 (14%)	2 (10%)	3 (12%)
Chest pain	0 (0%)	3 (14%)	1 (5%)	0 (0%)
Skin and Appendages[f]	3 (12%)	6 (27%)	3 (15%)	3 (12%)
Pruritis	0 (0%)	4 (18%)	0 (0%)	0 (0%)
Rash	1 (4%)	0 (0%)	3 (15%)	0 (0%)
Psychiatric[g]	3 (12%)	3 (14%)	3 (15%)	5 (20%)
Insomnia	3 (12%)	0 (0%)	0 (0%)	2 (8%)
Cardiovascular[h]	2 (8%)	9 (41%)	2 (10%)	5 (20%)
Edema	1 (4%)	5 (23%)	1 (5%)	4 (16%)
Vision disorders	3 (12%)	4 (18%)	0 (0%)	0 (0%)
Conjunctivitis	2 (8%)	3 (14%)	0 (0%)	0 (0%)
Resistance mechanism[i]	3 (12%)	3 (14%)	3 (15%)	2 (8%)

a= anorexia, dyspepsia, hemorrhoids and intestinal obstruction each occurred in 0-2 patients in each treatment group. Eructation and enlarged abdomen each occurred in 0-1 patient in each treatment group. The majority of GI adverse events were mild-moderate in severity and there were no relevant differences between treatment groups..

b= arthralgia, stiffness and leg pain each occurred in 0-2 patients in each treatment group.

c= paresthesia, tremor and vertigo each occurred in 0-2 patients in each treatment group. Convulsions, abnormal gait and hypertonia each occurred in 0-1 patient in each treatment group.

d= pharyngitis occurred in 0-2 patients per treatment group; laryngitis, rhinitis and bronchitis each occurred in 0-1 patient in each treatment group.

e= fever, influenza-like symptoms and accidental trauma each occurred in 0-2 patients in each treatment group; abdominal pain occurred in 1 patient and death in 1 patient in the 20 mg dose group.
f= skin cyst occurred in 1 patient in the 20 mg dose group.
g= anxiety and somnolence each occurred in 0-2 patients in each treatment group and depression in 1 patient each in the 20 mg and 30 mg LAR groups.
h= chest pain in 2 patients in the 10 mg LAR dose group; hypertension in 1 patient each in the 10 mg and 20 mg LAR dose groups.
i= otitis media in 0-2 patients in each treatment group; infection and fungal infection in 0-1 patients in each treatment group.

Note: 1-3 patients in each treatment group reported adverse events in the following organ systems with the most commonly reported AEs listed for that organ system:

Liver and biliary system (cholelithiasis),

Metabolic and nutritional disorders (hypoglycemia: 1 patient in each treatment group; hypokalemia: 1 patient in each of the 20 mg and 30 mg LAR groups)

Urinary system disorders (cystitis, micturition disorder, UTI)

Up to 2 patients/treatment group (i.e. $\leq$ 10%) reported AEs in the following organ systems:

Special senses (taste perversion: 2 patients (9%) in the 10 mg LAR group)

Male reproductive (impotence: 1 patient each in the 20 mg and 30 mg LAR groups)

Neoplasm: 2 patients (10%) in the 20 mg group and 1 patient in the 30 mg group (4%)

Heart rate and rhythm disorders (palpitation: 2 patients (10%) in the 10 mg group, 1 at 20 mg (5%) and 1 at 30 mg (4%); tachycardia: 1 patient (5%) at 20 mg)

Hearing and vestibular disorders (earache: 1 patient (4%) on sq and 2 patients (10%) on 20 mg)

Autonomic nervous system (increased sweating: 1 patient each in the sq and 10 mg groups and 2 patients in the 30 mg group)

Endocrine (Hypothyroidism: 1 patient (5%) in the 20 mg dose group)

Application site disorders (injection site disorder)

In general, similar percentages of adverse events were reported in all four treatment groups. The GI system had the highest rates of adverse events in all four treatment groups. The most commonly reported GI adverse events were abdominal pain and nausea. Very few adverse events were classified as severe. Very few AEs were considered related to Sandostatin, either sq or LAR, by the investigators. There did not appear to be any clinically meaningful differences between genders in rates of adverse events.

The following AEs in the following organ systems were considered study drug (i.e. Sandostatin) related:

GI:

Abdominal pain: 1 patient on sq
Flatulence: 1 patient each on sq and 30 mg LAR
Nausea: 1 patient each on sq, 10 mg and 20 mg LAR
Anorexia: 1 patient on 30 mg LAR
Steatorrhea: 1 patient on 30 mg LAR

Liver and biliary system:

Cholelithiasis: 2 patients on sq & 1 patient on each of the 3 LAR doses

Application site disorders: injection site inflammation/reaction:

1 patient in each of the sq, 20 mg and 30 mg groups

Body as a whole:

Asthenia: 1 patient in the 10 mg LAR group
Fever: 1 patient in the 10 mg LAR group

Skin and appendages:

Rash: 2 patients on 20 mg LAR

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Endocrine:

Hypothyroidism: 1 patient in the 20 mg LAR group

Special senses:

Taste perversion: 1 patient on 10 mg LAR

Urinary system:

Renal calculus: 1 patient on 30 mg LAR

Injection site evaluations: % of patients in each treatment group with injection site pain, erythema, swelling and "other" (e.g. bruise, itching, bump, etc.) reactions:

	SQ	LAR 10mg	LAR 20mg	LAR 30mg
	%	%	%	%
Pain	67%	32%	53%	56%
Erythema	54%	18%	35%	18%
Swelling	38%	14%	15%	22%
Other	38%	16%	20%	23%

The injection site reactions were generally mild-moderate in severity and were noted immediately after injection. Overall, LAR patients experienced fewer events than did sq patients. The best tolerated dosage was 10 mg.

Vital Signs:

Vital signs remained stable throughout the study except for a slight increase in diastolic BP from median values of 80 to 86 mm Hg on day 169 in the 20 mg group.

Physical exam:

No clinically meaningful differences between treatment groups occurred during therapy.

Hematology abnormalities:

No clinically relevant changes were recorded and all mean values across all visits were well within the normal range for each of the hematology parameters. However, clinically notable hematology abnormalities (Hgb/Hct: male: $\leq$11.5/$\leq$37%; female: $\leq$9.5/$\leq$32%; wbc: $\leq$2.8 k/mm^3, $\geq$16 k/mm^3) occurred in isolated patients (note: M= male and F= female):

SQ:

Notably low Hgb/Hct: n= 1 patient

(#05003M: Hgb/Hct decreased from baseline values of at week 24. Due to progression of his carcinoid disease, the patient was receiving Interferon which can result in myelopsuppression. The investigator attributed this change to the patient's current medical condition).

Notably low wbc: n= 1 patient

(#05003: baseline wbc was at week 24. Hgb/Hct also significantly decreased in this patient- see above. He was on Interferon which can result in myelosuppression. The investigator attributed this change to the patient's underlying medical condition).

Notably high wbc: n= 1 patient

(#07003: baseline wbc was ^{3} at week 12 but was wnl at week 24. The cause was unknown).

10 mg LAR:

Notably low Hgb/Hct: n= 3 patients

(#02003F: baseline Hct was week 24. The investigator attributed this change to the patient's current medical condition;

#08005M: baseline Hct was which decreased to at week 24. The investigator felt this change was not clinically significant and not related to study medication;
#08013M: baseline Hgb/Hct was , which decreased to at week 12. The patient was diagnosed at this time with an ulcer. He subsequently received a blood transfusion. Hgb/Hct increased at week 24).

20 mg LAR: notable hematology changes: n= 0
30 mg LAR:
Notably low Hgb/Hct: n= 5 patients
(#02004M: baseline Hct was , which decreased at week 24. The investigator felt the decrease was not related to study medication;
#02009M: baseline Hgb/Hct was which decrerased , at week 24. The investigator felt the decrease was not clinically significant and not related to study med.;
#02014M: Hgb decreased from at week 12. The investigator felt the decrease was not clinically significant and not related to study medication;
#03002M: decrease in Hct at week 12 at week 24. This decrease followed radiation therapy for prostate cancer;
#07001F: decrease in Hgb/Hct , to at week 12. The investigator felt this was due to her current medical condition and not related to LAR).

Biochemistry abnormalities;
No clinically relevant or statistically significant differences between the sq group and the LAR groups were observed. In the 10 mg group, 2 patients had worsening of an elevated baseline glucose. Isolated patients in the sq or LAR groups had worsening in the high concentrations of SGPT, SGOT and total bilirubin or had a shift from normal to high expanded ranges for the above biochemistry parameters. No clinically relevant shifts were observed. No significant differences between treatment groups were observed.
Isolated patients had clinically notable changes from baseline in the following biochmistry parameters:

Glucose:
Decreased glucose (clinically notable: <45 mg/dl): n= 2 patients
(#08021 on 10 mg LAR: decrease from at week 4, unassociated with hypoglycemic symptoms. Subsequent values were . The investigator felt this was not related to study medication;
#05008 on 30 mg LAR: patient had a hx. of type II diabetes and was on insulin. Patient developed symptoms of hypoglycemia on day 86. Serum glucose was The investigator felt this was related to his current medical condition)

Increased glucose
n= 2 patients
(# 09006 on 10 mg LAR: patient had a hx. of insulin-dependent diabetes mellitus. Her baseline glucose increased at week 4 and was at study d/c;
#05019 on 30 mg LAR: the patient had
at week 24. Relationship to study medication cannot be excluded). Note: mean change in serum glucose from baseline to study endpoint, approached statistical significance (p= 0.052) in the 30 mg LAR dose group- baseline glucose was and, at endpoint, was However, the majority of patients had not fasted.

Bilirubin:
Increased bilirubin (clinically notable: ≥2 mg/dl): n= 6 patients
(on sq: n= 3: #02010- at week 4 and was at week 24. The investigator felt this change was due to the patient's current medical condition; #08018- elevated bilirubin during the study with baseline of 2.4

mg/dl) in a patient with a hx. of elevated bilirubin probably secondary to Gilbert's syndrome; #09001 at week 24;
on 10 mg LAR: n= 2: #05007- which peaked at week 12 and #09006- bilirubin increased from at week 8 when the patient was d/c'd from the study;
on 20 mg LAR: n= 1: #05005- bilirubin of at week 15 when she was d/c'd from the study due to disease progression. The investigator felt this event was due to her current medical condition and not related to LAR;
on 30 mg LAR: n= 0

Uric acid: (clinically notable: for female- ≥9 mg/dl):
N= 1 patient (#09006- uric acid increased from at week 8 when the patient was d/c'd from the study. This patient also had clinically notable elevations in serum glucose, bilirubin and alkaline phosphatase, attributed to end stage disease by the investigator).

Alkaline phosphatase (clinically notable:≥ 3 x ULN):
n= 1 patient (#09006- baseline alk phos was and rose to at week 8 when the patient was d/c'd from the study. This patient also had clinically notable elevations in serum glucose, bilirubin and uric acid- see above, attributed, by the investigator, to end stage disease).

Urinalysis:
No statistically significant differences between treatment groups were observed. In 2 patients (#05023 on sq and #05013 on 30 mg LAR), urine glucose was negative at baseline but became positive during the study. In patient #05023, serum glucose at baseline (non-fasting) was and rose to at week 12. It is probable this patient was an undiagnosed diabetic or this was related to the study medication. In patient #05013 developed unexplainable glucosuria at week 4. Concomitant serum glucose and there was no hx. of diabetes. Urine glucose was negative in this patient at week 24.

Special Labs:
Thyroid function tests, carotene and HbA_{1C}:
In the comparison of the sq to the LAR groups, no statistically significant differences were observed for T4, serum carotene or HbA_{1C}. No evidence of TSH suppression was observed. Analysis of carotene levels revealed no evidence of malabsorption.

ECG:
No clinically relevant or statistically significant differences between treatment groups were observed. New or worsening EKG abnormalities occurred in 16/54 patients (30%) on Sandostatin LAR (10 mg LAR: 3/19: 16%, 20 mg LAR: 5/15= 33% and 30 mg LAR: 8/20= 40%). The corresponding incidence on Sandostatin sq was 26% (6/23). These abnormalities included sinus bradycardia, heart block, PVCs, prolonged QT interval, repolarization abnormalities and non-specific ST-T wave changes. In only 1 patient, #08003 in the 30 mg LAR group, was a post-baseline change considered to be clinically significant. This patient had a clinically significant worsening of left axis deviation vs. baseline.

Gallbladder ultrasound:
Newly Occurring or Worsening Gallbladder Abnormalities:

Gallstones:
SQ: 1/12= 8% (patient # 1-04)
LAR: 4/27= 15% (2 patients in each of the 10 mg and 30 mg LAR groups- patient #'s 2-09, 6-02, 8-08 and 8-15)
Sludge:
SQ: 0/9= 0%

Sludge: LAR: 2/20 (10%) (both in the 10 mg LAR group- patient #'s 5-16 and 6-06).
Dilatation: SQ: 0/8= 0%
LAR: 3/18= 17% (patient #'s 2-04, 4-03 and 9-05).

No patient required a cholecystectomy.

Patients who completed carcinoid study 351, were eligible for entry into a 12 month extension trial- study 451. This was an open label Sandostatin LAR trial. See Dr. Parks' review for a summary of this trial.

Across both carcinoid trials, newly occurring or worsening GB abnormalities on (stones, sluge, dilatation) occurred in 62% of patients on Sandostatin LAR. The incidence of gallstones was 24%.

Hypothyroidism is a concern because octreotide may suppress TSH secretion. Hypothyroidism was reported as an adverse event in only 1 patient who received Sandostatin LAR and no patient who received Sandostatin sq.

Octreotide may alter the balance between the counterregulatory hormones, insulin, glucagon, and growth hormone. In study 351, 16% of patients (4/25) shifted from normal to high glucose on Sandostatin sq and 13% of patients (8/64) did so on LAR. In study 451, 28% of patients shifted from normal to high values. However, the majority of specimens were non-fasting.

Literature submitted: No new safety information emerged from review of the submitted literature.

Evaluation and Regulatory Action:

Both the efficacy and safety profile of Sandostatin LAR Depot are similar to subcutaneous Sandostatin Injection for both acromegaly and malignant carcinoid syndrome patients.

The long-term efficacy of Sandostatin LAR Depot to suppress GH and IGF-1 levels in patients with acromegaly has been demonstrated with up to 30 months of therapy in 88 patients who received doses of 10-40 mg IM every 4 weeks. 42% (37/88) of these patients maintained suppression of mean GH to <2.5 ug/L and normalization of mean IGF-1 levels over 30 months of Sandostatin LAR therapy. The majority of patients received doses of 20-30 mg LAR.

Since efficacy is similar between the depot and short-acting Sandostatin formulations, failure to achieve an adequate GH (<2.5 ug/L) and IGF-1 (normalization) response to sq, is likely to result in an inadequate hormonal response with the depot preparation.

Some patients developed antibodies to octeotide but this does not appear to effect the efficacy of the drug.

The efficacy of Sandostatin Depot is similar to sq Sandostatin with regard to control of the flushing and stool frequency in patients with carcinoid syndrome. Likewise, median 24 hr.urinary 5-HIAA levels were reduced to at least a comparable degree with LAR depot. However, across the two carcinoid studies, there was high premature withdrawal rate due to either disease progression or failure to achieve symptomatic control with octreotide therapy- 27% (25/93, with 8 of these 25 being deaths). Of those patients who completed the study, the majority required either an increase in their sq Sandostatin dose or sq rescue therapy.

Safety data has been collected for up to 4 years in patients with acromegaly and up to 18 months in carcinoid patients receiving Sandostatin LAR therapy.

Gallbladder abnormalities and GI adverse events are the main toxicities of octreotide. The overall incidence of gallbladder abnormalities on Sandostatin LAR Depot was 52% in acromegaly patients and 62% in carcinoid patients. The corresponding incidence of gallstones was 22% and 24%. The majority of patients did not have biliary symptoms.

Although GI adverse events were common in acromegaly patients- overall incidence of 59% (153/261), the majority were mild-moderate in severity. In addition, no acromegaly patient receiving Sandostatin LAR Depot, discontinued therapy for a GI event.

Octreotide may suppress TSH secretion and result in hypothyroidism. Hypothyroidism was reported as an adverse event in 2% of acromegaly patients across all studies; with only two

patients requiring thyroid hormone replacement therapy. Hypothyroidism was reported as an adverse event in isolated patients with carcinoid syndrome.

Since octreotide may alter the balance between the counterregulatory hormones, insulin, glucagon and GH, hypoglycemia or hyperglycemia may occur. However, due to the nature of the underlying disease in these patients, causality to octreotide therapy is difficult to assess. In acromegaly patients, the incidence of hypoglycemia was 1.5% and, of hyperglycemia, 15%. Although the incidence of hyperglycemia was also high in carcinoid patients, 13% in study 351 and 28% in study 451, the majority of the patients were not fasting.

Regulatory Action:

Sandostatin LAR Depot therapy is approved for long-term maintenance therapy in patients with acromegaly who can respond to and tolerate subcutaneous Sandostatin. It is also approved for long-term treatment of the diarrhea and flushing episodes associated with malignant carcinoid tumors in patients who can respond to and tolerate subcutaneous Sandostatin.

Revisions of the PI for Sandostatin Injection and Sandostatin LAR Depot, as per an internal meeting of the Division on 11/16, were faxed to the sponsor on Wednesday, 11/18. A copy of these revisions is appended.

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/S/
Jean Temeck, M.D.

cc. NDA Arch 21008
HFD-510 Division file
HFD-510: Dr. Sobel, Dr. Orloff, Dr. Parks and Ms. Weber

/S/
11-23-98

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Novartis SMSC 304-E-00

An open-labelled, multicenter, extension study on the tolerability and safety of the long-term treatment with Sandostatin LAR in patients who completed one of the phase 2 studies, SMSC 201 or 202.

Number of subjects: 49 male or female acromegalic patients 18 years or older. 5 patients came from SMSC 201 and 43 came from SMSC 202. Both of these studies were of 30 months average duration.

Inclusion criteria: subjects 18 years or older from studies SMSC 201 or 202 who acceptably tolerated the long-term treatment with Sandostatin LAR in those previous studies and who showed a clinical and biological improvement of their disease and who had received the same dose of Sandostatin LAR at least during the last 3 administrations in the previous studies. Excluded were patients with symptomatic cholelithiasis and females who were pregnant or lactating.

Drug dosing: Each subject received the dose of Sandostatin LAR that was administered for the last 3 injections in the previous studies. These doses were:

- 10 mg (n=4)
- 20 mg (n=11)
- 30 mg (n=33)
- 40 mg (n=1)

administered as intramuscular injection in the hospital at 4 week intervals

Study duration: 169 days (approximately 6 months); total duration exposed to Sandostatin from previous studies was approximately 34 months

Efficacy parameters: mean 8 hour GH serum concentrations, total IGF-1 serum concentrations, and symptoms and signs of acromegaly

Safety parameters: adverse events (every visit), local tolerability at the injection site (every visit), laboratory safety assessments (visits 1, 7, and 8 if required), echographic examination of the biliary region (visits 1 and 7), physical examination (visits 1 and 7), and vital signs (every visit)

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Adverse Events Reported (All events reported in extension period only)

Adverse Event	(n=49) overall n (%)	Dose of last injection	Duration (days) mean	Onset (days) mean
Injection site pain	4 (8.2)	30 mg (n=3) 40 mg (n=1)	3.7 3.0	48 29
Body as whole (general disorder)	6 (12.2)	10 mg (n=1) 20 mg (n=1) 30 mg (n=3) 40 mg (n=1)	1.0 14.0 39.3	167.0 166.0 79.7 35.0
• accidental trauma	• 1 (2.0)	• 10 mg	• 1.0	• 167.0
• back pain	• 1 (2.0)	• 40 mg		• 35.0
• fatigue	• 3 (6.1)	• 30 mg	• 54.5	• 79.7
• hot flushes	• 1 (2.0)	• 30 mg		• 118.0
• influenza-like symptoms	• 2 (4.1)	• 20 mg 30 mg	• 14.0 9.0	• 166.0 132.0
• edema	• 1 (2.0)	• 30 mg		• 168.0
Hypertension	1 (2.0)	30 mg	82.0	116
CNS and PNS disorders	6 (12.2)	30 mg (n=5), 40 mg (n=1)	50.3, 58.0	61.2,1.0
• dizziness	• 1 (2.0)	• 30 mg		• 107
• headache	• 4 (8.2)	• 30 mg (n=3), 40 mg (n=1)	• 38.0	• 44.3,1.0
• paresthesias	• 2 (4.1)		• 21.2	• 66.0
• vertigo	• 1 (2.0)	• 30 mg • 30 mg		• 97.0
GI disorders	3 (6.1)	20 mg (n=1), 30 mg (n=2)	14.0, 29.0	150.0,71.5
• diarrhea	1 (2.0)	30 mg	4.0	46.0
• nausea	2 (4.1)	20 mg (n=1), 30 mg (n=1)	14.0, 54.0	150.0,97.0
Ear disorder	1 (2.0)	30 mg	5.0	4.0
Cholelithiasis	1 (2.0)	30 mg		4.0
Hypercalcemia	1 (2.0)	30 mg	168.0	170.0
Arthralgia	1 (2.0)	30 mg	11.0	79.0
Purpura	1 (2.0)	40 mg	40.0	130.0
Respiratory system disorder	4 (8.2)	10 mg (n=1), 30 mg (n=3)	8.0,13.5	19.0,123.3
• respiratory disorder	• 1 (2.0)	• 30 mg		• 107.0
• rhinitis	• 2 (4.1)	• 30 mg	• 13.5	• 131.5
• sinusitis	• 1 (2.0)	• 10 mg	• 8.0	• 19.0
Hyperhydrosis	1 (2.0)	30 mg	8.0	61.0
Vision disorders	2 (4.1)	30 mg	5.0	82.5
conjunctivitis	1 (2.0)	30 mg	5.0	84.0
eye pain	1 (2.0)	30 mg		81.0
Total patients of all system organ classes	13 (26.5)	10 mg (n=2) 20 mg (n=2) 30 mg (n=8) 40 mg (n=1)	4.5 14.0 72.9 58.0	93.0 158.0 63.5 1.0

Conclusion: 13/49 (26.5%) patients had reported AEs after the first injection of Sandostatin LAR in this extension study with 77% of these being mild to moderate in severity. Four events were reported as severe: 2 headaches, 1 influenza-like symptom, and 1 hearing disorder. The most common AEs were injection site pain (8.2%), fatigue (6.1%), and headache (8.2%). The dose at which the most reported AEs occurred was 30 mg. No adverse events were reported for thyroid function.

Adverse Events of the Gallbladder and/or Biliary System

18/49 with abnormal gallbladder +/or biliary system evaluated by echography (36.7% of patients enrolled in extension study 304)

- 9 gallstones/microlithiasis (18.4%)
- 7 sludge/sediment (14.3%)
- 2 biliary dilatation (4.1%)

Excluding patients who had abnormalities in specific categories at baseline and those on bile acid therapy resulted in the following findings of newly occurring gallbladder abnormalities for those patients treated with Sandostatin LAR for an average of 36 months (i.e. extension of 201 and 202 studies which averaged 30 months into the 304 study which averaged 6 months):

- **1/39 (3%) cases of gallstones or microlithiasis** reported for patients treated with Sandostatin LAR for an average of 36 months
- **2/35 (6%) cases of sediment or sludge** reported for patients treated with Sandostatin LAR for an average of 36 months
- **1/33 (3%) cases of dilatation/wall thickening** reported for patients treated with Sandostatin LAR for an average of 36 months

Novartis SMSC 308-E-00

An open-labelled study to extend the available information on the tolerability and safety of the long-term treatment with Sandostatin LAR in acromegalic patients who completed one of the phase 2 or phase 3 studies with Sandostatin LAR.

Number of subjects: 69 male or female acromegalic subjects, 8 patients were from SMSC 201, 28 were from SMSC 202, and 33 were from SMSC 303. 28 of these patients had also been enrolled in the 304 extension study.

Inclusion criteria: male or female subjects, 18 years or older with acromegaly who acceptably tolerated Sandostatin LAR treatment in previous studies (201-E-04, 202-E-03, 303-E-01, 304-E-00). Excluded were patients with symptomatic cholelithiasis or who had not previously been treated with Sandostatin sc.

Drug dosing: Sandostatin LAR was administered as depot injections q 4 weeks in the following doses:

10 mg (n=3)
20 mg (n=35)
30 mg (n=31)

Each subject received the dose of Sandostatin LAR that was administered in the previous study from which they were recruited.

Study duration: approximately 510 days (11-15 months) and total Sandostatin exposure for patients was dependent upon their previous study enrollment (23-50+ months).

Efficacy parameters: mean 4 hr serum GH concentrations, total IGF-1 serum concentrations, and signs and symptoms of acromegaly.

Safety parameters: adverse events (all visits), local tolerability at the injection site (all visits), laboratory safety assessments (visits 7, 13, and 16), echographic examination of

the biliary region (visit 7, 13, and 16), physical examination (visit 16), vital signs (visit 16), thyroid function tests (visit 16)and ECG examination.

Adverse Events

The most commonly reported adverse events were: injection site pain and gastrointestinal complaints with nausea, abdominal pain, diarrhea, and constipation being reported.

Deaths: there was 1 death from a myocardial infarction in a 64 year-old female who was on Sandostatin LAR 20 mg dose

Serious Adverse Events (SAEs): defined as events which were fatal or considered life-threatening or which required or prolonged hospitalization, caused permanent disability, cancer, congenital anomaly, or overdose. There were a total of 16 SAEs occurring in a total of 9 subjects. These are listed below and are categorized according to relationship to study drug:

SAEs	not related	unlikely	possibly	drug dose (mg)
bladder calculus	x			20
surgery for prostate ca	x			30
hemorrhoids	x			30
tenesmus	x			30
cerebrovascular disorder		x		20
cerebrovascular disorder		x		20
death (MI)		x		20
GH overproduction	x			30
surgery for hemorrhoids	x			30
possible tumor of liver hilius		x		30
anemia			x	30
leucopenia			x	30
surgery for perineal laceration	x			20
herpes zoster	x			30
neuropathy	x			20
hospitalization for insulin adjustment	x			

Abnormalities of the Gallbladder and/or Biliary System (as evaluated by echography)
There were a total of 32/69 (46.4%) reported abnormal ultrasounds of the gallbladder and biliary system. These were characterized as the following:

- 20 gallstones/microlithiasis
- 7 sludge/sediment
- 5 biliary duct dilatation or wall thickening

Excluding patients with baseline abnormalities for each of these categories and who were on bile acid therapy the incidence of newly occurring abnormalities were classified as follows:

- **5/43 (12%) who developed gallstones or microlithiasis** while on Sandostatin LAR for 40-45+ months.
- **3/33 (9%) who developed sludge/sediment** while on Sandostatin LAR for 40-45+ months
- **4/31 (13%) who developed dilatation or wall thickening** while on Sandostatin LAR for 40-45+ months.

There were a total of ~~6 p~~atients who were taking bile acid therapy at time of enrollment into SMSC308. Two developed gallstones (33%) and none had sediment/sludge or dilations/wall thickening.

Abnormalities of Thyroid Function
There were 2 cases of goiter reported during this study.

Conclusions on Safety Review of Extension Studies 304 and 308

- The most common adverse events reported were injection site pain and gastrointestinal complaints. Adverse events reported in extension period were typical of those seen in initial studies including abnormalities of thyroid function and carbohydrate metabolism.
- Only 1 death was reported in a 64 year-old woman with underlying heart disease.
- Comparing the incidence of gallbladder abnormalities in the different studies the following conclusions can be made:
  1. The combined incidence of abnormalities for all acromegaly studies (201, 202, 303, 304, and 308) results in the following:
     - 43/200 (21.5%) gallstones/microlithiasis
     - 41/151 (27%) sediment/sludge
     - 17/105 (16.2%) dilatation/wall thickening

  2. The incidence of abnormalities for those subjects receiving Sandostatin LAR for an extended period of time (Studies 304 and 308) did not exceed those of earlier studies. They were for gallstones/microlithiasis, sediment/sludge, and for biliary dilatation/wall thickening.
  3. The use of bile acid therapy did not appear to confer a consistent protective effect against the development of gallbladder abnormalities while on Sandostatin LAR. However, the number of patients on bile acid therapy were small and difficult to interpret across all the studies.

/S/ /S/ 11-18-98

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Medical reviewer

/S/S/ 11-18-98

cc: Division File NDA 21,008
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Novartis SMSE 451

An open label study to assess the long-term safety and efficacy of Sandostatin LAR injected at 4 week intervals for 52 weeks in patients with malignant carcinoid syndrome who have completed Sandostatin LAR Study SMSE 351.

Number of subjects: 78 male or female patients with malignant carcinoid syndrome

Drug dosing: Each subject received the dose of Sandostatin LAR intramuscularly at 4 week intervals with 20 mg given for doses 1 to 4 and 30 mg for the remaining doses (5-13).

Study duration: 56 weeks (approximately 1 year)

Efficacy parameters: number and duration of rescue medication episodes, suppression of carcinoid symptoms such as frequency of flushing episodes and/or stool frequency per day, and suppression of 24 hr urinary 5-HIAA levels.

Safety parameters: evaluation of injection site, vital signs, ECG, hematology, blood chemistry and urinalysis, serum thyroid stimulating hormone (TSH), free and total T4, serum carotene and HbA1c, ultrasonography of the gallbladder and biliary system, adverse events and physical examinations.

Study completion rate and discontinuations: 56 subjects completed the study by week 52 (71.8%) and 54 completed the study by week 56 (69.2%). The most common reasons for discontinuing the study were adverse events (7/23), death (4/23), and treatment failure (4/23).

Adverse Events

The most common reported AEs were gastrointestinal disorders (25/78 or 32.1%) which included abdominal pain, flatulence, constipation, nausea, diarrhea, and vomiting. Cholelithiasis was reported in 11/78 subjects (14.1%) with a lower incidence by ultrasound evaluation (9/78; 11.5%). One patient developed acute cholecystitis and 2 patients had cholecystectomies (Patients 01 004 and 02 005). Other frequently reported AEs included application site disorders in 7/78 (9%), malaise and fatigue.

Newly occurring gallbladder abnormalities in Study 451 were:

- 9/39 (23%) gallstones
- 7/28 (25%) sludge
- 4/20 (20%) biliary dilatation

Sandostatin is known to inhibit TSH secretion. Only 1 case of hypothyroidism was reported in SMSE 451 and this occurred in the 20 mg treatment group.

Mean HbA1c levels increased from baseline to week 52 across all dose groups with no mean values exceeding 7.0. In 20/71 patients, non-fasting plasma glucose levels shifted from normal to high values.

Other atypical reported adverse events included:

- 3 cases of renal calculi were noted in 3 different patients treated with Sandostatin LAR
- reports of needle clogging in 36 episodes involving 28 patients. The sponsor further investigated the different study centers reporting this problem and noted that vehicle may have been added too quickly and once the suspension was made there was a

delay in patient administration. Emphasis on adding the vehicle gently and allowing adequate time for the wetting of the Sandostatin LAR microspheres was made to study centers. Furthermore, the recommendation that Sandostatin LAR be administered immediately after suspension was completed appeared to decrease the number needle clogging reports.

Discontinuations

23/78 patients discontinued for the following reasons:

- disease progression or treatment failure – 5
- abdominal pain – 2
- prostate cancer – 1
- withdrew consent – 2
- other (including changing of study site) – 7
- renal failure after hepatic artery embolization – 1
- death – 5 (all deaths were reported as related to disease progression and study narratives are supportive of this claim)

Conclusions on Safety Update of Extension Study 451 in Carcinoid Patients

- The most common reported adverse event was gastrointestinal. The incidence of carbohydrate intolerance was comparable to Study 351 and there was only one report of hypothyroidism.
- An atypical finding of renal and ureteral calculi were noted in 3 subjects (of note, 1 patient with bladder calculus was reported in Study 308)
- The incidence of gallbladder abnormalities in this extension study was higher than those reported in Study 351: gallstones (23% vs 13%), sludge (25% vs 7%), and biliary dilatation (20% vs. 14.3%). There were 2 cases of cholecystectomy resulting from acute cholecystitis or abdominal pain.
- Needle clogging was a reported complication possibly due to improper technique used in preparation of Sandostatin LAR suspension and timing of injection.
- Unlike the acromegalic extension studies, there was a high incidence of discontinuation (29.5%) in Study 451 with 22% due to treatment failure or disease progression and 22% due to deaths. All deaths were reported as progression of malignant carcinoid syndrome.

/S/ 11-18-98

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