CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 21008

MEDICAL REVIEW(S)

Weber

NDA# 21-008
Sandostatin LAR Depot (octreotide acetate for injectable suspension)
Novartis, East Hanover, NJ
Date submitted 5-29-98

Team Leader memo on NDA
Date: 11-23-98

This application proposes marketing of a new depot formulation of octreotide that can be administered once per month instead of three times daily. Pharmacokinetic studies reveal a transient initial peak that declines over the first 3 to 5 days following the IM injection, followed by a slow rise in plasma concentrations over the ensuing 2 to 3 weeks and finally by a prolonged (2-3 week) plateau. The proposed indications for the use of Sandostatin LAR Depot are the same as those for Sandostatin Injection.

Acromegaly
A total of 252 adult male and female patients with acromegaly were studied in three clinical trials (and extensions) with exposures up to 30 months (thus 30 injections). Doses ranged from 10 mg to 40 mg IM monthly, with the majority of patients receiving 20 and 30 mg. All patients had shown clinical response to Sandostatin Injection with GH level < 5 ng/mL. The efficacy analyses included in labeling are based upon the hormonal measurements in patients receiving all the prescribed doses of drug (thus completers). Thus 13 of 101 patients were excluded in the analysis of the pooled efficacy data from the first two trials, and 29 or 151 were excluded in the analysis of the third trial. According to Dr. Temeck, the ITT analyses yield very similar results.

Two important points emerge from the efficacy data: 1) the rates of response to Sandostatin LAR Depot are the same as those to Sandostatin Injection across both pools of patients, and 2) across the two patients pools, the overall response rates differ substantially, clearly a function of differences in the populations studied. The sponsor has proposed to include two efficacy tables in the label. I suggest a complete pooling of the efficacy data for inclusion in the label at some later printing, in order to convey more accurately the expected rates of response to Sandostatin LAR Depot.

Carcinoid syndrome
A total of 67 patients with carcinoid syndrome were treated for up to 24 weeks with Sandostatin LAR Depot at doses of 10- 30 mg monthly. Control of flushing and stool frequency, and the degree of reduction of urinary 5-HIAA levels were similar among Sandostatin LAR patients and the 26 patients who remained on Sandostatin Injection. Because of the progression of tumor and resultant augmentation of symptoms, most patients required increases in the dose of Sandostatin Injection or rescue with Sandostatin Injection (in the Sandostatin LAR group).

VIPoma
No patients with VIPomas were treated in clinical trials with Sandostatin LAR Depot, but the use of the product in these patients is rationalized based on the physiology of secretion of VIP by these tumors.

Safety
With regard to safety, the spectrum of adverse events were similar for Sandostatin LAR Depot and for Sandostatin Injection. Major symptomatic side effects with octreotide are GI in nature, with diarrhea, abdominal discomfort, flatulence and constipation occurring most commonly. Overall 59% of acromegaly patients treated with Sandostatin LAR experienced a GI adverse event, although most were mild in severity, and no patient discontinued due to a GI adverse event.

Gallbladder abnormalities on ultrasound occurred at similar rates among acromegalics and carcinoid patients treated with Sandostatin LAR, with overall rates ranging from This is related to the known effect of somatostatin analogues on gallbladder contractility. The incidence of gallstones was across these patient groups. Approximately 1% of patients treated with octreotide developed symptoms or signs mandating cholecystectomy.

Finally, the other potential adverse effects of octreotide, hypothyroidism due to suppression of TSH and disturbances of glucose metabolism, occurred at similar rates among patients treated with Sandostatin LAR Depot and with Sandostatin Injection. Because of the nature of the underlying diseases in the patients studied and the absence of a non-octreotide control, the assessment of causality for most cases of thyroid and glucose metabolic derangements is not possible.

In summary, the efficacy of Sandostatin LAR is comparable to that of Sandostatin Injection in patients with acromegaly and carcinoid syndrome, and therefore presumably in those with VIPomas. There appears to be no difference in the safety profile between the two formulations (indeed LAR may be associated with fewer GI side effects). Clearly, the availability of a depot form of octreotide will provide a much more convenient means by which to treat these patients.

Recommendation
Sandostatin LAR should be approved.

Recommendation code: AP

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DMEDP/CDER/FDA

/S/
11-23-98

cc:
NDA 21-008 Arch
HFD-510
HFD-510: Temeck/Sobel/Weber

NDA: 21,008
Drug: Sandostatin LAR (Octreotide depot)
Sponsor: Novartis

Date submitted: 5/29/98
Date received: 6/2/98
Date reviewed: 11/18/98

Proposed indication: Acromegaly, Carcinoid Syndrome and VIPoma
Dosage form: long-acting release (depot); Route of administration: IM; Frequency of dosing: q 4 weeks
Acromegaly Controlled Clinical Studies:

1.SMSC 201-E-00: A Double-blind, Dose-finding, Dose-Proportionality Study Assessing the Pharmacokinetics, Pharmacodynamics, Safety and Tolerability of Single Doses (3, 6, 9 and 12 mg) of Sandostatin LAR Given IM to Acromegaly Patients

This was a phase 2 study which was **prematurely terminated after only 14 acromegaly patients were enrolled** (40 patients had been targeted) **due to lack of efficacy** (failure to suppress GH <5 ug/l for at least 4 weeks) with single 3, 6, 9 or 12 mg Sandostatin LAR doses.

Study site: Oslo, Norway

Key inclusion criteria:

Adult patients well-controlled on sq Sandostatin (i.e. GH <5 ug/l and ≥50% reduction relative to the value without treatment).

Protocol schematic:

SQ Sandostatin was administered for at least 4 weeks prior to screening. During the 12 day screening period, suppression of GH to levels <5 ug/l was documented. This was followed by a 2 day wash-out period during which baseline measurements were taken and GH levels were to rise to >5 ug/l. Patients were randomized to single IM Sandostatin LAR injections of 3, 6, 9 or 12 mg. Patients were followed up to 42 days post-injection.

Efficacy parameters:

Primary- mean 12 hour serum GH levels (days -14, 0, 1, 7, 14, 21, 28, 35 and 42) and octreotide levels (days 1, 7, 14, 21, 28, 35 and 42).

Secondary- IGF-1 levels (days -14, 0, 14, 28 and 42) and clinical signs and symptoms of acromegaly (headache, perspiration, paresthesia, fatigue, osteoarthralgia and carpal tunnel syndrome, each rated on a 5 point severity scale with 0= not present and 5= severe and incapacitating)

Efficacy results:

Only 1 patient at each of the 4 LAR doses, or 4 patients, suppressed GH to <5 ug/l for 4 weeks. However, GH was suppressed to <5 ug/l at baseline in all 4 of these patients.

Octreotide levels peaked on day 1 (no dose-dumping) with plateau concentrations reached on days 21-42. Drug levels on LAR were consistently lower than on sq.

All patients reported worsening of the signs/symptoms of acromegaly.

IGF-1: in only 1 patient did IGF-1 levels normalize. This patient received the 12 mg dose (note: GH levels also suppressed to <5 ug/l in this patient).

Safety results:

There were no deaths or other serious AEs .

1 patient prematurely withdrew from the study on day 35 due to treatment failure. After a single 9 mg LAR dose, this patient's GH levels were consistently >15 ug/l and the patient's macroadenoma. had enlarged. This patient had been well-controlled on sq.

The **most common adverse events** were:

At the **injection site-**
- pain: 4/14 (29%) patients,
- rush: 8/14 (57%),
- swelling: 4/14 (29%)

GI AEs- 7/14 (50%)
- nausea: 4/14 (29%)patients,
- diarrhea: 3/14 (21%).
- constipation: 3/14 (21%),
- abdominal pain: 2/14 (14%),
- vomiting: 1/14 (7%),
- flatulence: 1/14 (7%)

These GI events did not appear to be dose-related.
Alopecia- 2 patients (one each at the 6 and 12 mg doses)
Syncope- 2 patients (" " " " " " " ")
Increased SGOT: patient #4007
in 1 patient who received the 12 mg dose.
Asymptomatic biliary duct dilatation on day 42 in 1 patient who received 12 mg.

2. **SMSC 201-E-01: A Double-blind, Dose-finding, Dose-proportionality Study Assessing the Pharmacokinetics, Pharmacodynamics, Safety and Tolerability of Single Doses (20 mg or 30 mg) of Sandostatin LAR Given IM to Acromegaly Patients**

This was a phase 2 study.

Study sites: Italy, Norway and France; Sample size: 20 mg- n= 22 patients, 30 mg- n= 23

Key inclusion criteria, protocol schematic and efficacy parameters were similar to SMSC 201-E-00 except that patients were randomized to either a 20 mg or 30 mg LAR dose and GH levels were also measured on days 2, 3 and 60 after LAR injection. Note: this study comprised patients who completed study SMSC 201-E-00 as well as additional patients.

RESULTS:

Protocol violations:

In the 20 mg dose group, 3 patients failed to suppress GH to < 5 ug/L after wash-out and in 2 patients, the GH was >5 ug/L on sq (8.3 and 11.4 ug/L on sq) but it did decrease by >50% on sq;

In the 30 mg dose group, 9 patients failed to suppress GH to <5 ug/L after wash-out; in 1 patient, GH was >5 ug/L on sq (6.8 ug/L) but it did suppress >50% on sq and 1 patient received a dopamine agonist depot within 2 mos. of screening

EFFICACY RESULTS: Intent-to-Treat (ITT): (Note:1 patient in the 20 mg dose group was withdrawn from the study on day 14 due to repetitive protocol violations. Therefore, there is 1 less patient in efficacy analyses which evaluate hormonal control for ≥ 4 wks.).

A. Growth Hormone Levels

1.a. Comparison of degree of GH control on Sandostatin LAR to Sandostatin sq:

a. In the following analysis, I define the level of GH control using the following cut-offs: GH <1 ug/l, GH ≥1 - <2 ug/l, GH ≥2 - <5 ug/l, GH ≥5 - <10 ug/l and GH ≥ 10 ug/l. I used a 4 week period for the degree of GH control on LAR to be similar to sq because 4 weeks is the dosing interval recommended by the sponsor for LAR.

On 20 mg LAR, 12/21 patients (57%) maintained the same level of GH control for 4 weeks as they demonstrated on sq and in 9 patients (43%), it was worse.

On 30 mg LAR, GH control was similar to sq in 17/23 patients (74%), better in 4 (17%) and worse in 2 (9%).

Conclusion: the 30 mg LAR dose provided more comparable control to sq than the 20 mg dose. On 30 mg LAR, GH control was comparable to or better than sq and was maintained at this level for 4 weeks, in 91% of patients.

b. Mean 12 hour serum GH levels on LAR were very similar to those on sq on day 14 and were maintained until day 28 in the 20 mg dose group and day 42 in the 30 mg dose group:

	Mean 12 hour GH Levels (ug/L):	
	20 mg	30 mg
SQ	2.9	2.3
LAR day 14	3.2	1.9
day 21	2.8	2.1
day 28	3.2	2.3
day 35	4.3	2.5
day 42	5.0	2.6
day 60	7.7	5.5

APPEARS THIS WAY ON ORIGINAL

2. Number (%) of patients who suppressed their mean 12 hour serum GH level to <5, <2 and <1 ug/l by LAR dose and total duration of suppression:

	20 mg LAR N= 22 N (%) of patients			30 mg LAR N= 23 N (%) of patients		
	≤5ug/l	<2ug/l	≤1ug/l	≤5ug/l	<2ug/l	≤1ug/l
0 days	2(9%)	9(41%)	16(73%)	0(0%)	6(26%)	13(57%
1 day-<2 weeks	4(18%)	6(27%)	3(14%)	1(4%)	4(17%)	3(13%)
2 wks-<4 weeks	3(14%)	1(5%)	1(5%)	0(0%)	1(4%)	0(0%)
4 wks-<6 weeks	2(9%)	1(5%)	1(5%)	4(17%)	3(13%)	2(9%)
≥6 wks	11(50%)	5(23%)	1(5%)	18(78%)	9(39%)	5(22%)

Conclusions:

1. all patients suppressed their GH levels to <5 ug/l on the 30 mg LAR dose compared to 9% of patients who did not on 20 mg.
2. the degree and duration of GH suppression was higher on 30 mg than 20 mg
3. the n (%) of patients who suppressed GH for at least 4 weeks:

on 20 mg: GH <5 ug/l 13/21 (62%);
GH <2 ug/l 6/21 (29%);
GH <1 ug/l 2/21 (10%)

on 30 mg: GH <5 ug/l 22/23 (96%);
GH <2 ug/l 12/23 (52%);
GH <1 ug/l 7/23 (30%)

Conclusion:

On 20 mg LAR, the majority of patients: 13/21 (62%) suppressed GH to <5 ug/L for 4 weeks. On 30 mg, almost all patients suppressed GH to <5 ug/L and more than half, to <2 ug/L.

B. IGF-1 Levels:

1. Comparison of Sandostatin LAR to Sandostatin sq:
   a. In the 20 mg LAR dose group, 7 (58%) of the 12 patients with normal IGF-1 levels (i.e. ≤500 ug/L) on sq, continued to maintain normal IGF-1 levels for 4 weeks on LAR. The corresponding data in the 30 mg dose group was 12/14 patients (86%). (Note: there were no patients in either the 20 mg or 30 mg LAR dose groups, in whom IGF-1 was elevated on sq, but normalized on LAR for 4 weeks).
   b. On 30 mg LAR, the mean serum IGF-1 levels were normal and comparable to those on sq (453 ug/L). However, on 20 mg LAR, the mean IGF-1 levels were elevated at all visits although the mean on sq was normal (498 ug/L).

2. Number (%) of patients who normalized serum IGF-1 level (defined as ≤500 ug/L) for at least 4 weeks:

On 20 mg dose: 8/21 (38%) (Note: in 1 of these 8 patients, there no IGF-1 level measured on sq)

On 30 mg dose:12/22 (55%) (Note: IGF-1 levels were not measured in 1 patient)

C. Normalization of Both Growth Hormone and IGF-1 Levels x 4 weeks by LAR dose:

On 20 mg LAR:

In 8/21 (38%) of patients, both GH was <5 ug/L and IGF-1 normalized x 4 weeks
In 4/21 (19%) of patients, both GH was <2 ug/L " " " x " "
In 2/21 (10%) of patients, both GH was <1 ug/L " " " x " "

On 30 mg LAR:

In 13/22 (59%) of patients, both GH was <5 ug/L and IGF-1 normalized x 4 weeks
In 9/22 (41%) of patients, both GH was <2 ug/L " " " x " "
In 6/22 (27%) of patients, both GH was <1 ug/L " " " x " "

Conclusion:

Better hormonal control (defined as % of patients in whom IGF-1 normalized and GH was suppressed below cut-offs of 1, 2 and 5 ug/L) was achieved with the 30 mg dose than with the 20 mg dose. Only on the 30 mg LAR dose, did the majority of patients (59%), suppress GH to <5 ug/L and normalize IGF-1.

Note: When GH was <5 ug/L, IGF-1 normalized in 21/34 or 62% of patients.
When GH was <2 ug/L, IGF-1 normalized in 13/17 or 76% of patients
When GH was <1 ug/L, IGF-1 normalized in 8/8 or 100% of patients.

D. Serum Octreotide Levels:

Mean serum octreotide levels were lower on LAR than on sq and were lower on the 30 mg LAR dose compared to the 20 mg dose. On 20 mg, the mean drug levels peaked on day 14. They were maintained until day 28 on 20 mg and day 42 on 30 mg , corresponding to the period in which mean 12 hr. GH levels on LAR were comparable to those on sq.

Mean Serum Octreotide Levels:

		20 mg (n= 22)	30 mg (n= 23)
Sandostatin sq		2104 ng/ml	1635 ng/ml
Sandostatin LAR	day 14	836 "	938 "
	day 21	721 "	1019 "
	day 28	837 "	1137 "
	day 35	738 "	1166 "
	day 42	685 "	1201 "
	day 60	413 "	836 "

E. Acromegaly Signs and Symptoms

There was a decrease in the # (%) of patients reporting signs/symptoms of acromegaly on days 28 and 42 after 20 or 30 mg LAR compared to wash-out. For most of the signs/symptoms, there was a 50% reduction in the number of patients reporting it on at least one of the 2 days- day 28 and/or day 42 compared to wash-out. The exception was headache where the decrease was less dramatic. There did not appear to be a dose-related effect.

SAFETY RESULTS:

There were no deaths.

1 patient (#5008) was withdrawn from the study on day 14 due to repetitive protocol violations including continued self-administration of Sandostatin sq (patient #5008: in this study, SM-C was increased on LAR).

Adverse events:

Serious Adverse Events:

There were 3 serious adverse events which occurred in 3 patients. All occurred in the 20 mg dose group. They were: intestinal obstruction, depression and, in patient #4007, several episodes of dizziness accompanied by nausea. The dizziness was thought to be possibly related to the Sandostatin LAR. Patient #4007 did not enter the next extension
mean SM-C was normal on LAR).

Overall:

The adverse events did not appear to be dose related. The **most common adverse events** occurred in the following organ systems:

GI: 18/22 (82%) of patients on 20 mg and 16/23 (70%) of patients on 30 mg. These adverse events were:

	20 mg N= 22 n (%)	30 mg N= 23 n (%)	Total N= 45 n (%)
Diarrhea	11(50%)	12(52%)	23(51%)
Flatulence	6(27%)	9(39%)	15(33%)
Abdominal pain	6(27%)	6(26%)	12(27%)
Constipation	2(9%)	4(17%)	6(13%)
Nausea	3(14%)	1(4%)	4(9%)
Steatorrhea	0	2(9%)	2(4%)
Intestinal obstr.	1(5%)	0	1(2%)

In only 3 of these cases, were the GI AEs reported as severe (1 case of intestinal obstruction, 1 severe diarrhea and 1 severe constipation).

Nervous system: 11/22 (50%) of patients on 20 mg and 10/23 (43%) of patients on 30 mg.

	20 mg N=22 n (%)	30 mg N= 23 n (%)	Total N= 45 n (%)
Headache	7(32%)	7(30%)	14(31%)
Dizziness	3(14%)	2(9%)	5(11%)
Paresthesias	0	1	1(2%)

The remaining adverse events were:

-injection site pain: 14/45 patients (31%). Injection site swelling occurred in 2 patients.

-whole body (fatigue, fever, pain, flu-like sx's): 10/45 (22%)

-respiratory (coughing, bronchitis, pneumonia, respiratory disorder, rhinitis): 5 (11%)

-vision disorders (conjunctivitis, photophobia, abnormal lacrimation): 5 (11%)

-anemia: 4/45 patients(9%), most probably secondary to frequent blood sampling

-skin (pruritis, rash, increased sweating): 4 (9%)

-female reproductive (menstrual disorder, lactation, etc): 3/23 (13%)

-the following AEs were each reported in 2 patients: worsening hypertension, abscess/moniliasis, metabolic (1hypoglycemia and 1 edema)

-the following AEs were reported in 1 patient each: **diabetes mellitus- moderate severity and probably related to LAR**, increased SGPT and biliary sludge (#5007), gallstones, arthropathy, angina pectoris, bladder papilloma, depression, UTI and "vein pain". GET MORE INFO ON DIABETES CASE- MODERATE SEVERITY, PROBABLY RELATED

-(Note: there were 2 patients in whom serum bilirubin increased on drug but values were abnormal at baseline: patient #'s 3002 and 3013).

Injection site disorders:

Pain: 14/45 (31%)

Swelling: 2/45 (4%)

Hematology:

Anemia occurred in 16/45 patients (36%) and it was most probably secondary to repeated blood sampling.

Low wbc: 6 (13%) (in the 20 mg dose group only) (clinically notable was patient #3008

Biochemistry:

3 patients developed notable abnormalities:

20 mg: n= 2 patients:

#3002: baseline bilirubin was clinically notable levels

#3013: baseline bilirubin was already notably elevated which

30 mg: n= 1 patient:

#5007: a normal SGPT at baseline became notably elevated on day 42. Sludge had appeared in a previously normal gallbladder.

Gallbladder Echography:

3 patients developed newly occurring abnormalities (note: none were on bile acid dissolution agents):

Stones (+/- also with sediment, sludge, dilitation):	1 (#3003 on 30 mg LAR)
Microlithiasis/sediment (they were not differentiated in this patient): (+/- also with sludge or dilatation)	1 (#3016 on 30 mg)
Sludge (+/- also with dilatation):	1 (#5007 on 30 mg)
Bilary duct dilatation only:	0
Biliary symptoms:	0

3.SMSC 202-E-00: A Double-blind, Dose-finding, Dose-proportionality Study Assessing the Pharmacokinetics, Pharmacodynamics, Safety and Tolerability of Single Doses (10, 20 and 30 mg) of Sandostatin LAR Given IM to Acromegaly Patients

This was a phase 2 study.

Study sites: Denmark, Netherlands, UK and Romania

Sample size: 48 patients

The overall study design was very similar to Study 201-E-01 with the following main differences:

a. 10/48 patients enrolled were partial rather than good responders to Sandostatin sq (partial responder= mean serum GH >5 ug/L on sq despite >50% reduction from levels prior to rx.. In the partial responders, GH on sq

b. the duration of sq Sandostatin treatment could be as short as 2 weeks
c. wash-out period after sq Sandostatin was 3-14 days rather than 2 days
d. the 10 mg dose was studied

Statistical Analysis:

This was done in 2 subgroups:

Intent-to-treat (ITT) n= 48 patients (10 mg n= 16, 20 mg n= 17, 30 mg n= 15)

Efficacy evaluable (EFF), which excluded the partial responders, n= 38 patients (10 mg n= 13, 20 mg n= 14 and 30 mg n= 11)

RESULTS:

GH protocol violations excluding partial responders:

10 mg dose group:

in 1 patient, GH after wash-out was <5 ug/L

in 2 patients, the % reduction in GH levels on sq compared to without rx. was <50%

20 mg dose group:
in 1 patient, GH on sq was >5 ug/L (5.5 ug/L)
in 1 patient, GH reduction on sq was <50%
in 1 patient, the GH after wash-out was <5 ug/L
30 mg dose group:
in 1 patient, GH on sq was >5 ug/L (5.8 ug/L)
in 3 patients, GH after wash-out was <5 ug/L

GH protocol violations in the subgroup of partial responders:

2 patients in each of the 10, 20 and 30 mg dose groups (for a total of 6 patients), failed to reduce GH to >50% on sq compared to prior rx.

Note:1 patient violated the protocol by self-administration of sq Sandostatin from study day 44 because he believed the LAR was ineffective.

EFFICACY RESULTS:

A. Growth Hormone Levels:

1.a. Comparison of the degree of GH control (i.e. GH < 1 ug/L, ≥1 - <2 ug/L, ≥ 2 - <5 ug/L, ≥5 - <10 ug/L or ≥10 ug/L) on LAR to sq:

10 mg LAR: in 6/16 (38%) patients, GH control was comparable to sq for 4 wks.
in 10/16 (63%) patients, it was worse on LAR than on sq
20 mg LAR: in 10/17 (59%) patients, GH control was comparable to sq for 4 wks.
in 7/17 (41%) patients, it was worse on LAR
30 mg LAR: in 11/15 (73%) patients, GH control was comparable to sq for 4 wks.
in 2/15 (13%) patients, GH control was better on LAR
in 2/15 (13%) patients, it was worse on LAR

Conclusion: the 30 mg LAR dose provided more comparable control to sq than either the 10 or 20 mg LAR doses. On 30 mg LAR, GH control was comparable to or better than sq and was maintained at this level for 4 weeks, in 86% of patients compared to 38% of patients on 10 mg and 59% of patients on 20 mg.

b. Mean 12 hour serum GH levels on LAR were similar to those on sq on day 14 and were maintained until day 21 on 10 mg, day 28 on 20 mg and day 42 on 30 mg

2. Number (%) of patients who suppressed their mean 12 hr. serum GH to <5, <2 and <1 ug/L by LAR dose and total duration of suppression:

10 mg

	ITT (n= 16)			EFF (n= 13)		
	<5ug/L	<2ug/L	<1ug/L	<5ug/L	<2ug/L	<1ug/L
0 days	3(19%)	9(56%)	14(88%)	1 (8%)	6 (46%)	11(85%)
1 day-<2 weeks	3(19%)	3(19%)	2(13%)	2 (15%)	3 (23%)	2(15%)
2 wks-<4 weeks	0(0%)	2(13%)	0(0%)	0 (0%)	2 (15%)	0(0%)
4 wks-<6 weeks	1(6%)	2(13%)	0(0%)	1(8%)	2 (15%)	0(0%)
≥6 weeks	9(56%)	0(0%)	0(0%)	9 (69%)	0 (0%)	0(0%)

Conclusion: on the 10 mg LAR dose, the majority of patients (56-69%), suppressed their mean GH to <5 ug/L and did so for at least 6 weeks.

20 mg

	ITT (n= 17)			EFF (n= 14)		
	<5ug/L	<2ug/L	<1ug/L	<5ug/L	<2ug/L	<1ug/L
0 days	3(18%)	8(47%)	15(88%)	0(0%)	5(36%)	12(86%)
1 day-<2 weeks	1(6%)	4(24%)	1(6%)	1(7%)	4(29%)	1(7%)
2 wks-<4 weeks	3(18%)	2(12%)	1(6%)	3(21%)	2(14%)	1(7%)

4 wks-<6 weeks	2(12%)	2(12%)	0(0%)	2(14%)	2(14%)	0(0%)
≥6 weeks	8(47%)	1(6%)	0(0%)	8(57%)	1(7%)	0(0%)

Conclusion: on the 20 mg LAR dose, the majority of patients (59-71%), suppressed their mean GH to <5 ug/L and did so for at least 4 weeks.

30 mg

	ITT (n= 15)			EFF (n= 11)		
	<5ug/L	<2ug/L	<1ug/L	<5ug/L	<2ug/L	<1ug/L
0 days	4(27%)	9(60%)	12(80%)	1(9%)	5(45%)	8(73%)
1 day-<2 weeks	1(7%)	0(0%)	1(7%)	0(0%)	0(0%)	1(9%)
2 wks-<4 weeks	1(7%)	2(13%)	1(7%)	1(9%)	2(18%)	1(9%)
4 wks-<6 weeks	1(7%)	3(20%)	1(7%)	1(9%)	3(27%)	1(9%)
≥6 weeks	8(53%)	1(7%)	0(0%)	8(73%)	1(9%)	0(0%)

Conclusion: on the 30 mg LAR dose, 60-82% of patients, suppressed their mean GH to <5 ug/L and did so for at least 4 weeks.

B. IGF-1 Levels: ITT:

1. Comparison of Sandostatin LAR to Sandostatin sq (normal IGF-1= ≤ 500 ug/L):

a.

	Normal on sq & LAR x 4 wks. N (%) of patients	Abnormal on sq but normal on LAR x 4 wks. N (%) of patients
10 mg	4/7 (57%)	0 (0%)
20 mg	6/6 (100%)	1/11 (9%)
30 mg	3/3 (100%)	1/12 (8%)

2. Number (%) of patients who normalized serum IGF-1 levels for ≥ 4 wks.:
On 10 mg: 4/16 (25%)
On 20 mg: 7/17 (41%)
On 30 mg: 4/15 (27%)
Overall on LAR: 15/48 (31%)

C. Normalization of Both GH and IGF-1 Levels x 4 weeks by LAR dose (ITT):

	GH <5ug/L & IGF-1 normal x 4 weeks N (%) of patients	GH <2ug/L & IGF-1 normal x 4 weeks N (%) of patients	GH <1ug/L & IGF-1 normal x 4 weeks N (%) of patients
10 mg	4/16 (25%)	0/16 (0%)	0/16 (0%)
20 mg	5/17 (29%)	1/17 (6%)	0/17 (0%)
30 mg	3/15 (20%)	1/15 (7%)	1/15 (7%)

Conclusion: the % of patients who suppressed their mean serum GH below given cut-offs of 5, 2 and 1 ug/L and normalized IGF-1, both for ≥4 weeks, appears to be fairly comparable among the three dosing groups.

D. Serum Octreotide Levels:

Mean serum octreotide levels on LAR were comparable to those on sq, only in the 30 mg dose group. Mean drug levels peaked around day 28 in all LAR dosing groups.

E. Acromegaly Signs and Symptoms:

The general tendency was for the # (%) of patients reporting signs/symptoms of acromegaly to decrease in all three dosing groups after administration of LAR. No dose-related effect was observed:

ITT Dose Group	Mean Overall Composite Score For Signs/Symptoms	Mean Overall Composite Score For Signs/Symptoms

	Wash-out	Day 28 After LAR
10 mg (n= 16)	4.3	2.3
20 mg (n= 17)	3.8	1.6
30 mg (n= 15)	5.2	2.4

SAFETY RESULTS:

There were no deaths or serious adverse events.

The most common adverse events occurred in the following organ systems:

GI: 29/48 (60%) of patients

	10 mg N= 16 n (%)	20 mg N= 17 n (%)	30 mg N= 15 n (%)	Total N = 48 n (%)
Abdominal pain*	3(19%)	6(35%)	9(60%)	18(38%)
Diarrhea*	3(19%)	8(47%)	8(53%)	19(40%)
Flatulence	6(38%)	6(35%)	6(40%)	18(38%)
Constipation	4(25%)	3(18%)	4(27%)	11(23%)
Steatorrhea	2(13%)	2(12%)	3(20%)	7(15%)
Dyspepsia	1(6%)	2(12%)	3(20%)	6(13%)
Nausea	2(13%)	1(6%)	2(13%)	5(10%)
Tenesmus	0	2(12%)	3(20%)	5(10%)
Vomiting	0	1 (6%)	2(13%)	3(6%)
Rectal hemorrhage[1]	0	0	1(7%)	1(2%)
Hiccup	0	0	1(7%)	1(2%)

***= Abdominal pain and diarrhea appeared to be dose related.**

1= rectal hemorrhage was actually reported as a "few drops of blood"

The vast majority of GI AEs were mild to moderate in severity.

Nervous system: 18/48 (38%) of patients

	10 mg N= 16 n (%)	20 mg N= 17 n (%)	30 mg N= 15 n (%)	Total N=48 n(%)
Headache	2(13%)	1(6%)	3(20%)	6(13%)
Dizziness	1(6%)	4(24%)	2(13%)	7(15%)
Paresthesias	1(6%)	0	1(7%)	2(4%)
Muscle cramps	2(13%)	3(18%)	1(7%)	6(13%)

Injection site pain: 15/48 (31%): 2 (13%) on 10 mg, 6 (35%) on 20 mg and 7 (47%) on 30 mg. Injection site swelling occurred in 1 patient.

The remaining adverse events occurred in the following organ systems:

-psychiatric (euphoria, insomnia, nervousness): 7/48 (15%)
-"resistance mechanism" (herpes zoster, viral infection, pharyngitis, tonsillitis): 7/48 (15%)
-dermatologic (pruritus, rash, increased sweating): 5/48 (10%)
-respiratory (respiratory disorder, rhinitis): 3/48 (6%)
-musculoskeletal (arthropathy, leg pain): 3/48 (6%)
-whole body (asthenia, flu sx's, malaise, leg edema): 3/48 (6%)
-tachycardia: 2/48 (4%)
-hearing, vestibular (deafness, ear discharge): 2/48 (4%)

- the following AEs occurred in 1 patient each: cholelithiasis, hypoglycemia, dysuria/frequent urination, flushing, transient increase in SGPT, and breast pain (breast pain: 1/22 patients).

Hematologic: Anemia: 16/48 (33%): 5 (31%) on 10 mg, 7 (41%) on 20 mg and 4 (27%) on 30 mg. The anemia was most likely secondary to frequent blood sampling.

Reduced total wbc: 5/48 (10%) of whom 2 were clinically notable (i.e. ≤2.8 x $10^3/mm^3$): #4006 on 10 mg whose baseline wbc was low and on day 42 and #2003 on 20 mg whose baseline wbc was low on day 42.

Biochemistry:

Notable elevation in total bilirubin (i.e. >2 mg/dl): 2/48 (4%) (patient # 5107 in whom baseline bilirubin was high and on LAR. This patient had gallbladder sediment at baseline and developed right hypochondrial pain during the study. The other patients, #4005, had an isolated increase in total bilirubin at baseline which worsened on LAR).

Notable elevation in SGPT (i.e. ≥ 3 x ULN): 1/48 (2%) (patient #5005 in whom SGPT increased on day 42 and became normal on day 60).

Elevations outside the expanded normal limits:

Glucose (≥1.5 x ULN):	3 (none were clinically notable: >250 mg/dl)
SGOT (≥ 1.15 x ULN):	2 (none were clinically notable: ≥ 3x ULN)
SGPT (≥ 1.15 x ULN):	2 (1 was clinically notable: ≥ 3x ULN- see above)
Total bilirubin (≥ 1.15 x ULN):	3 (2 were clinically notable- see above)
Alk phos (≥ 1.15 x ULN):	2 (none were clinically notable: ≥ 3x ULN)
HbA_{1c} (≥ 1.10 x ULN):	2 (none were clinically notable: > 8.5%)

Gallbladder Echography:

Newly occurring abnormalities (note: none were on bile acid dissolution agents):

	10 mg N= 16 n (%)	20 mg N= 17 n (%)	30 mg N= 15 n (%)	Total N= 48 n (%)
Dilatation only	0	1(6%)	0(0%)[1]	1(2%) (# 5104)
Sediment	1(6%)	1(6%)	1(7%)	3(6%) (#'s 5001, 5002, 5003
Sludge	1(6%)	0(0%)	2(13%)[1]	3(6%) (#'s 1009, 5006, 5010
Gallstones(+/- sed/sludge/dil)	1(6%)[1,2]	0	2(13%)[1,2]	3(6%) (#'s 5005, 5105, 5111
Biliary sx's	1(6%)	0	2(13%)	3(6%) (#'s 1009, 5107, 5111

1= with biliary symptoms

2= transient

Note: in 1 patient, #5107, gallbladder sediment and an elevated total bilirubir were present at baseline. The patient developed right hypochondrial pain and the total bilirubin further increased on LAR.

3. **SMSC 303-E-00: A 24 Week, Open-Label, Switch, Multicenter Study to Assess the Tolerability, Safety and Efficacy of Sequential Doses (10, 20 or 30 mg) of Sandostatin (Sandostatin LAR) Given IM to Acromegalic Patients**

This was a phase 3B study which involved 151 adult acromegaly patients (mean age: 49.9 yrs. with range , 77 M & 74 F, 148 Caucasian, 2 Oriental and 1 Black patient) and 40 investigators in 8 countries (Belgium, Denmark, France, Germany, Italy, Netherlands, Sweden and UK).

Key study features:

a. mean 4 hr. serum GH <10 ug/L on Sandostatin sq for ≥ 4 wks.
b. all patients received three 20 mg injections of Sandostatin LAR (days 1, 29 and 57). If the mean 4 hr. serum GH was <1 ug/L on days 29 and 57, the LAR dose was decreased to 10 mg on days 85, 113 and 141 (i.e. injections 4, 5 and 6). If the mean 4 hr. serum GH was >5 ug/L on day 57, the LAR dose was increased to 30 mg.
c. Study assessment:

Efficacy:

Mean 4 hr. GH (1° efficacy) and IGF-1 (2° efficacy) concentrations were measured on days 29, 57, 85, 113, 141 and 169. Clinical signs/symptoms of acromegaly (2° efficacy) were assessed at each of these time points.

Safety:
-hematology and biochemistry profile on days -14 and 169
-special labs: TSH, free T4 and HbA_{1C} on days 1, 85 and 169
-GB ultrasound on days 1, 85 and 169
-assessment for adverse events at each visit

RESULTS:

Only 2 patients prematurely withdrew from the study:
2 patients did not receive LAR injections 5 and 6 due to either treatment failure (n= 1) or an adverse event (n= 1: ischemia of the right foot). Therefore, since the efficacy evaluable population differed from the ITT population by only 2 patients, all analyses were performed on the ITT dataset.

1. In 66% of patients (100/151), the dose of LAR remained 20 mg for the study duration.
   In 19% (29/151), the LAR dose was decreased to 10 mg for the last 3 injections.
   In 15% (22/151), the LAR dose was increased to 30 mg for the last 3 injections.(Note: in 1 of these 22 patients, neither GH or IGF-1 levels were reported on the increased dose).

2. The following analysis compares GH and IGF-1 control on Sandostatin sq to LAR by dose and overall:

		SANDOSTATIN LAR			
	SQ	20/10 mg x 6 mos. N= 29	20/20 mg x 6 mos. N= 100	20/30 mg x 6 mos. N= 20	Overall on LAR N= 149
	n (%)	n (%)	n (%)	n (%)	n (%)
Mean GH <5 ug/L	135/151 (89%)	29/29 (100%)	96/100 (96%)	9/20 (45%)	134/149 (90%)
Mean GH <2.5 ug/L	98/151 (65%)	29/29 (100%)	71/100 (71%)	1/20 (5%)	101/149 (68%)
Mean GH <2 ug/L	83/151 (55%)	29/29 (100%)	53/100 (53%)	1/20 (5%)	83/149 (56%)
Mean GH <1 ug/L	32/151 (21%)	27/29 (93%)	12/100 (12%)	0/20 (0%)	39/149 (26%)
IGF-1 normal	97/151 (64%)	27/29 (93%)	66/100 (66%)	5/20 (25%)	98/149 (66%)
Mean GH <5 & IGF-1 nl.	93/151 (62%)	27/29 (93%)	65/100 (65%)	4/20 (20%)	96/149 (64%)
Mean GH<2.5 & IGF-1 nl	75/151 (50%)	27/29 (93%)	60/100 (60%)	1/20 (5%)	88/149 (59%)
Mean GH <2 & IGF-1 nl.	68/151 (45%)	27/29 (93%)	49/100 (49%)	1/20 (5%)	77/149 (52%)
Mean GH <1 & IGF-1 nl.	29/151 (19%)	26/29 (90%)	11/100 (11%)	0/20 (0%)	37/149 (25%)

Note: the dose groups show all doses a patient used in the extension. It does not show the number of times or the sequence a particular dose was given.

In general, the degree of hormonal control was similar between sq and LAR. Clearly, patients who could be down titrated to 10 mg LAR, were the most responsive to Sandostatin. Overall, after 6 injections of LAR administered over a 6 month period, GH was <5, <2.5, <2 and <1 ug/l and IGF-1 normalized, in 64%, 59%, 52% and 25% of patients, respectively. (Note: although increasing the LAR dose from 20 mg to 30 mg resulted in improved GH control in 7/20 patients (35%), in none of these patients, did the increased dose normalize IGF-1).

The following table demonstrates that, on LAR, mean IGF-1 normalized in 72%, 87%, 93% and 95% of patients who suppressed their mean GH to <5, <2.5, <2 and <1 ug/L, respectively:

(%) of Patients in Whom IGF-1 Normalized when GH was Suppressed Below Cut-offs of 1, 2, 2.5 and 5 ug/L:

		SANDOSTATIN LAR			
	SQ	20/10 mg x 6 mos.	20/20 mg x 6 mos.	20/30 mg x 6 mos.	Overall on LAR
	n (%)	n (%)	n (%)	n (%)	n (%)
Mean GH <5 & IGF-1 nl.	93/135 (69%)	27/29 (93%)	65/96 (68%)	4/9 (44%)	96/134 (72%)
Mean GH<2.5& IGF-1 nl	75/98 (77%)	27/29 (93%)	60/71 (85%)	1/1 (100%)	88/101 (87%)
Mean GH <2 & IGF-1 nl.	68/83 (82%)	27/29 (93%)	49/53 (93%)	1/1 (100%)	77/83 (93%)
Mean GH <1 & IGF-1 nl.	29/32 (91%)	26/27 (96%)	11/12 (92%)	0/0 (0%)	37/39 (95%)

3. Symptoms of acromegaly:

The number of patients overall who reported each of the individual symptoms of acromegaly was reduced by the end of the study. At endpoint, there were statistically significant decreases in the number of patients with headache (p = 0.04), fatigue (p= 0.001), perspiration (p= 0.005), joint pains (p= 0.001) and paresthesias (p= 0.012) compared to baseline. Overall, the total symptom score declined from a mean of 3.7 on sq to 2.5 at the end of the study on LAR, a decrease of 32.4%.

SAFETY RESULTS:

There were no deaths.

1 patient prematurely withdrew from the study due to a serious AE- foot ischemia

Serious AEs were experienced in 11/151 patients (7.3%). The incorrect LAR dose was administered to 2 patients- 30 mg rather than 20 mg and these 2 AEs were labeled "accidental overdose". The serious AEs in the remaining patients, all of which were assessed by the investigators to be either unlikely or not related to LAR, were:

meniscectomy for knee arthritis,

dental clearance,

foot ischemia secondary to partial occlusion of femoral artery,

a visual field defect in a patient with a microadenoma (therefore, defect thought to be possibly due to a "sroke in evolution"),

hypertension in a patient with a hx. of hypertension (patient #3502: baseline BP was 150/100 but was 220/130 on day 85),

cataract surgery,

internal capsule infarct on brain CT in a patient with a hx. of hypertension and NIDDM,
rectal bleeding,
routine admission for f/u MRI s/p resection of adenoma

The most frequent new or worsening AEs (in ≥ 5%) of patients, were (note: in some cases, the relationship to LAR as assessed by the investigator is recorded here):

Body as a Whole: 43/151 (28.5%):

Most frequently reported were:

Pain	8 (5.3%)
Influenza-like symptoms	10 (6.6%)

(note: edema was reported in 4 patients; in all, it was possibly-definitely related to LAR. Malignant hyperpyrexia was reported in 1 patient and was regarded as possibly related to LAR)

Injection site disorders:

Pain	21/151 (14%) (note: reported as an AE in 12/151= 8%)
Erythema	11/151 (7%)
Swelling	9/151 (6%)

GI: 51/151 (34%) of patients-

Diarrhea	24/151 (16%)
Abdominal pain	15/151 (10%)
Flatulence	9/151 (6%)
Constipation	9/151 (6%)
Nausea	5/151 (3%)
Dyspepsia	4/151 (3%)
Colitis	2/151 (1%)
Vomiting	2/151 (1%)
Rectal hemorrhage	2/151 (1%) (unlikely to be related to LAR)
GI hemorrhage	1/151 (1%)
Ulcerative stomatitis	1/151 (1%) (not related to LAR)
Feces discolored	1/151 (1%)

None of these GI AEs appeared to be dose-related

Liver and Biliary System: 20 (13.2%)

Biliary pain	1 (0.7%)
Cholelithiasis	11 (7.3%)
Gallbladder disorder	9 (6.0%)
Hepatocellular damage	1 (0.7%) (probably related to LAR)
Fatty liver	1 (0.7%) (patient #1206) (possibly related to LAR)

Respiratory system: 20 (13.2%)

Cough	4 (2.6%)
Pharyngitis	6 (4.0%)
Sinusitis	3 (2.0%)
URI	4 (2.6%)
Bronchitis	4 (2.6%)

Nervous System: 17 (11.3%)

Headache	8 (5.3%)
Dizziness	3 (2.0%)

Dermatologic: 13 (8.6%)
Pruritis 3 (2.0%) (possibly related to LAR in 2/3 patients)
Rash 4 (2.6%)
(note: alopecia was reported as an AE in 1 patient and was possibly related to LAR)

Cardiovascular: 11 (7.3%)
Hypertension 9 (6%)
Hypertension aggravated 2 (1.3%)
Hypotension 1 (0.7%)

Musculo-skeletal system: 11 (7.3%)
Arthropathy 4 (2.6%)
Pain 3 (2.0%)

Infection: 10 (6.6%)

Note:
Endocrine/Metabolic:
Goiter 1 (0.7%) (patient #4201: FT4 remained normal and TSH, low at baseline, remained low during the study, unlikely to be related to LAR)
Hypothyroidism 1 (0.7%) (patient #1501, not related to LAR)
Hypoglycemia 1 (0.7%) (patient #4202, possibly related to LAR)
CPK increased 1 (0.7%) (possibly related to LAR)

GALLBLADDER ABNORMALITIES:

Newly occurring or worsening abnormalities in patients not on bile acid dissolution agents:
Gallstones/Microlithiasis (+/- also with sediment/sludge/dilatation): 11 patients
(#'s 1001, 1002, 1603, 2004, 31001, 3502, 3503, 4205, 0501, 1106 and 2604)
(note: gallstones/microlithiasis occurred in 1 additional patient, #3103 who was on ursodeoxycholic acid).

Sediment and/or sludge without gallstones/microlithiasis (+/- also with dilatation): 11 patients
(#'s 0301, 0801, 0802, 1204, 1902, 2402, 2601, 3302, 3303, 3703 and 3802)
None of these patients were on bile acid dissolution therapy when sediment/sludge occurred.

Dilatation/gallbladder wall thickening only: 5 patients
(#'s 0202, 1402, 1502, 1607 and 1801)
None were on bile acid dissolution therapy when dilatation/thickening occurred.

Biliary symptoms: 1 patient
(biliary symptoms in patient 2005 were secondary to stones which were present at baseline)

Hematology and Biochemistry Parameters:

1 patient (#2004), with developed a low wbc during the study.

1 patient with IDDM (#2601), had further elevations in serum glucose during the study: which increased at the final visit, with a concomitant rise in HbA_{1c} (see below).

1 patient (#3402) developed a high serum bilirubin and SGOT during the study, which rose on LAR, SGOT was at baseline and rose to on LAR. Gallbladder ultrasound was normal in this patient).

Special Laboratory Parameters:

Thyroid Function:

Although the mean and median serum TSH and FT4 values remained normal throughout the study, in 7 patients (7/127= 5.5%), the serum TSH level decreased from normal at baseline to below normal during the study. This was accompanied by an abnormal rise in FT4 in one patient (#2203: baseline FT4 was which rose at the final visit- normal). Another patient had a low baseline FT4 which worsened during the study, with TSH remaining low normal.

HbA_{1C}:

Although HbA_{1C} decreased from normal to baseline in several patients during this study, hypoglycemia was reported as an adverse event in only 1 patient. In another patient (#2601) who had a hx. of IDDM, a high HbA_{1C} at baseline, worsened during the study

4. SMSC 303-E-01: A 24 Week, Open-label, Extension of the Multicenter Study 303-E-00 to Obtain Additional Information on the Tolerability, Safety and Efficacy of Sequential Doses of Sandostatin LAR Given IM to Acromegaly Patients

This was a phase 3B study which involved 128 acromegaly patients (mean age: 49.9 yrs. with range: 24-81 yrs., 65 M & 63 F, 127 Caucasian and 1 Black) and 39 centers in : Belgium, Denmark, France, Germany, Italy, Netherlands, Sweden and the UK.

Key study features:

1. Patients who completed study 303-E-00 were eligible for this study provided: mean GH on days 113 and/or 141 were not >5 ug/L on 30 mg LAR patients did not have symptomatic cholelithiasis

2. The LAR dose in this extension study was based on the following schema:

Dose in Study 303-E-00	Mean GH	Study Day in 303-E-00	Dose in 303-E-01
10 mg	<1 ug/L	days 113 and 141	10 mg
	≥1 ug/L	day 113 &/or 141	20 mg
20 mg	≤5 ug/L	days 113 and 141	20 mg
	>5 ug/L	day 113 &/or 141	30 mg
30 mg	≤5 ug/L	days 113 and 141	30 mg
	>5 ug/L	day 113 &/or 141	exclude

3. Patients received monthly injections of LAR per the above schema for a total of 6 injections. Mean 4 hr. GH (1° efficacy) and IGF-1 (2° efficacy) concentrations were measured on days 29, 57, 85, 113, 141 and 169. Clinical signs/symptoms of acromegaly (2° efficacy) were assessed at each of these time points.
4. Safety assessment included:
   - -hematology and biochemistry profile on days 1 and 169
   - -special labs: TSH, free T4 and HbA_{1C} on days 1, 85 and 169
   - -GB ultrasound on days 1, 85 and 169
   - -assessment for adverse events at each visit

RESULTS:

6 patients did not participate in this extension study because the mean GH was too high in 303-E-00 (center 9, subject 2; center 15, subjects 2 & 4; center 16, subject 5; center 17, subject 2 and center 34, subject 2).

There were 6 premature withdrawals with only 1 of these due to an AE: hepatitis C. 3 patients withdrew consent, 1 did not return and 1 was scheduled for transphenoidal adenectomy.

Mean GH (ug/L) and IGF-1 (ug/L) Control Over 12 Months on LAR in the 122 Patients Who Completed 303 E-00 and E-01:

	20/10/10mg x 12 mos. N= 17 n (%)	20/10/20mg x 12 mos. N= 7 n (%)	20/20/20mg x 12 mos. N= 78 n (%)	2/20/30mg x 12 mos. N= 5 n (%)	20/30/30mg x 12 mos. N= 15 n (%)	Overall on LAR N= 122 n (%)
Mean GH <5	17(100%)	7(100%)	78(100%)	5(100%)	11(73%)	118(97%)
Mean GH <2.5	17(100%)	7(100%)	55(71%)	0(0%)	1(7%)	80(66%)
Mean GH <2	17(100%)	7(100%)	42(54%)	0 (0%)	1(7%)	67(55%)
Mean GH <1	16(94%)	5(71%)	7(9%)	0 (0%)	0(0%)	28(23%)
IGF-1 normal	17(100%)	6(86%)	54(69%)	1 (20%)	4(27%)	82(67%)
GH<5 & IGF nl.	17/17 (100%)	6/7 (86%)	54/78 (69%)	1/5 (20%)	4/15 (27%)	82/122 (67%)
GH<2.5 &IGF nl	17/17 (100%)	6/7 (86%)	46/78 (59%)	0/5 (0%)	1/15 (7%)	70/122 (57%)
GH<2 & IGF nl.	17/17 (100%)	6/7 (86%)	39/78 (50%)	0/0 (0%)	1/15 (7%)	63/122 (52%)
GH<1 & IGF nl.	16/17 (94%)	4/7 (57%)	7/78 (9%)	0/0 0%	0/0 0%	27/122 (22%)

Note: the dose groups show all doses a patient used in the extension. It does not show the number of times or the sequence a particular dose was given.

Comments:

After the initial 3 month LAR lead-in period, the dose of LAR remained stable in 90% of patients (110/122) with the majority (78/122= 64%), remaining on the 20 mg dose.

Overall, after 12 monthly injections of LAR, mean GH was <5, <2.5, <2 and <1 ug/l and IGF-1 normalized in 67%, 57%, 52% and 22% of patients, respectively.

Note: There were 27 patients in 303 E-00 and E-01, in whom the LAR dose was increased from 20 mg to 30 mg at some time-point in these studies. The increased dose resulted in normalization of IGF-1 in 1/18 patients (6%) in whom IGF-1 was elevated on the 20 mg dose. Mean GH was reduced to <5 ug/L in 8/15 patients (53%) in whom mean GH was >5 ug/L on the 20 mg dose.

The following table demonstrates that, in patients who suppressed their mean GH to <5 ug/L, <2.5, <2 ug/L and <1 ug/L over this 12 month period, mean IGF-1 normalized in 70%, 88%, 94% and 96% of patients, respectively:

(%) of Patients in Whom IGF-1 Normalized when GH was Suppressed Below Cut-offs of 1, 2, 2.5 and 5 ug/L:

	20/10/10mg x 12 mos.	20/10/20mg x 12 mos.	20/20/20mg x 12 mos.	2/20/30mg x 12 mos.	20/30/30mg x 12 mos.	Overall on LAR
GH<5 & IGF nl.	17/17 (100%)	6/7 (86%)	54/78 (69%)	1/5 (20%)	4/11 (36%)	82/118 (70%)
GH<2.5 & IGF nl	17/17 (100%)	6/7 (86%)	46/55 (84%)	0/0 (0%)	1/1 (100%)	70/80 (88%)
GH<2 & IGF nl.	17/17	6/7	39/42	0/0	1/1	63/67

	(100%)	(86%)	(93%)	(0%)	(100%)	(94%)
GH<1 & IGF nl.	16/16 (100%)	4/5 (80%)	7/7 (100%)	0/0 0%	0/0 0%	27/28 (96%)

Symptoms of acromegaly:

Symptoms	SQ N= 151	After 12 months N= 122
Headache	54 (36%)	28 (23%)
Fatigue	79 (52%)	51 (42%)
Perspiration	65 (43%)	22 (18%)
Joint pains	76 (50%)	39 (32%)
Carpal tunnel	25 (17%)	13 (11%)
Paresthesias	39 (26%)	18 (15%)

Total symptom score= sum of the severities of signs and symptoms of acromegaly: at screening- 3.8 and at endpoint- 2.3 on a scale of 0-4, a decrease of 24%.

SAFETY RESULTS:

There were no deaths.

One patient discontinued the study due to an AE- coexisting hepatitis C.

9/128 patients (7%), experienced serious AEs: worsening hypertension; uterine bleeding; hystertectomy/oophorectomy; acute orchitis/orchectomy and thyroid nodule; thyroidectomy; glaucoma surgery; bilateral hip replacement; iliac ishio fracture and herniorrhaphy. All these serious AEs were thought to be unlikely or not related to Sandostatin LAR.

The most frequent new or worsening AEs in $\geq$ 5% of patients were (note: in some cases, the relationship to LAR as assessed by the investigator is recorded here):

Body as a whole: 24 (18.7%)

(most frequently reported were: influenza-likesymptoms and fatigue. Note: edema was reported in 2 patients and was assessed as possibly related to LAR in ½ patients)

GI: 34 (26.5%)

Diarrhea	10 (7.8%)
Flatulence	9 (7.0%)
Abdominal pain	8 (6.2%)
Constipation	6 (4.6%)
Gastritis	4 (3.1%)
Nausea	2 (1.5%)
Steatorrhea	1 (0.7%)
Anorexia	1 (0.7%)
Dysphagia	1 (0.7%)

Note: The majority of GI AEs were mild-moderate in severity. Diarrhea and abdominal pain appeared to be dose-related

Nervous system: 22 (17.1%)

Paresthesias	7 (5.4%)
Headache	6 (5%)

(note: in 1/6 patients, headache was assessed as possibly related to LAR)

Vertigo 5 (4%)

(note: in 3/5 patients, vertigo was assessed as possibly related to LAR)

Cardiovascular disorders: 21 (16.4%)

Hypertension 19 (4.8%)
(note: in 2/19 patients, the hypertension was assessed as possibly related to LAR)
Hypertension, aggravated 2 (1.5%)
ECG abnormal 1 (0.7%)

Musculo-skeletal system: 17 (13.2%)
(most common were arthritis, arthrosis and arthralgia)

Respiratory system: 16 (12.5%)
(most commonly reported were coughing and URI)

Liver and biliary system: 14 (10.9%)
Cholelithiasis 8 (6.2%)
Sludge 6 (4.6%)
Hepatic function abnl. 1 (0.7%) (note: assessed as probably related to LAR)
Fatty liver 1 (0.7%)

Dermatologic: 12 (9.3%)
(most commonly reported was alopecia which was assessed as possibly related to LAR in 1/3 patients. Note: rash was reported in 2 patients and pruritis in 1. These were assessed as possibly-probably related to LAR)

Urinary system: 11 (8.5%)
(most commonly reported were UTI and renal cyst)

Injection site disorders:	9 (7.0%)	
Pain	7 (5.4%)	pain 12/128
local reaction	2 (1.5%)	swelling 3 (2.3%)
mass	1 (0.7%)	erythema 1 (0.8%)

Psychiatric disorders: 8 (6.2%)
(most common were depression and insomnia in 3 patients each or 2%)

Vision disorders: 8 (6.2%)
(most commonly reported was conjunctivitis)

Note: Endocrine: 5 (3.9%)
Goiter 4 (3.1%) (#'s 4103, 3602, 1501, 1603 and 4201)
Hypothyroid 2 (1.5%) (#'s 1501 and ?)
Hypoglycemia 1 (0.7%)- glucose 117 mg/dl at baseline and 27 mg/dl at last visit, ?lab error or problem with blood sample

GALLBLADDER ABNORMALITIES:

Newly occurring or worsening abnormalities in this extension (note: none of the following patients were on bile acid dissolution agents):
Gallstones/Microlithiasis (+/- also with sediment/sludge/dilatation): 2 (#'s 1604 and 2802)
(#'s 1604 and 2802)

Sediment and/or sludge without gallstones/microlithiasis (+/- also with dilatation): 2 (#'s 3401 and 3501)
Dilatation/gallbladder wall thickening only: 0

Biliary symptoms: 1 (#4205)
(biliary sx's in # 4205 were secondary to stones which developed on LAR in 303-E-00)

Overall Gallbladder Abnormalities in Patients Who Were Enrolled in 303-E-00 and 303-E-01:

Newly occurring or worsening gallbladder abnormalities in patients who received up to 12 injections of Sandostatin LAR, i.e. were treated with LAR for up to 1 year and who were not on bile acid dissolution agents:

gallstones/microlithiasis (+/- also with sediment/sludge/dilatation): 13/101 (13%)
sediment and/or sludge without stones (+/- also with dilatation): 13/83 (16%)
dilatation/wall thickening only: 5/66 (8%)
biliary symptoms: 2/101 (2%)

(Explanations for the denominators used to calculate the gallbladder abnormalities: although 149 patients had gallbladder ultrasounds at baseline and after at least 6 months of LAR treatment, the following patients were excluded:

for gallstones and/or microlithiasis, the denominator of 101 results from the exclusion of 48 patients as follows: 14 patients on ursodeoxycholic acid, 29 patients with gallstones/microlithiasis at baseline and 5 patients in whom the abnormalities on baseline ultrasound were not specified;

for sediment and/or sludge without gallstones/microlithiasis, the denominator of 83 results from exclusion of the 48 patients as detailed above for gallstones/microlithiasis plus the 13 patients who developed gallstones and/or microlithiasis post baseline plus 5 patients who had sediment and/or sludge at baseline;

for dilatation/wall thickening only: all the exclusions pertaining to gallstones/microlithiasis (n= 48) and sediment/sludge (n= 18), also pertain here plus the 13 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: 6/35 patients
Sediment/sludge: 5/15
Dilatation/wall thickening: 7/9

Vital Signs:

There were no clinically relevant changes.

Hematology and Biochemistry Parameters:

Mean values remained within the normal range. However, 2 patients developed low wbc on LAR: #2004 with baseline total wbc/neutrophil count of , reached nadir values of respectively at the final study visit; #3601 with baseline wbc of reached a low of at the final study visit. One patient (#3102) had a low platelet count which worsened during the study.

1 patient each had a worsening of: elevated glucose (#2002), high SGOT (#4204) and high direct bilirubin.

Special Laboratory Parameters:

Thyroid function:

Mean and median TSH and FT4 remained normal on LAR. 4 patients had low baseline TSH levels which decreased during the study, but none showed a suppression of FT4 during treatment compared to baseline. Two of these 4 patients were taking concomitant thyroxine during the study. In one patient, a low FT4 worsened during the study (#2101) and, in 2 patients, a high FT4 further increased (#1104 and #1607).

HbA_{1c}:

Mean HbA_{1C} values were within the normal range on day 1 and day 169. 8/128 (6%) of patients had a low HbA_{1C} which further decreased during the study. None of the patients with high HbA_{1C} at day 1, had further increases during the study.

Physical Examination:

Notable new/worsening abnormalities were goiter in 5 patients and hypothyroidism in 1 patient.

Uncontrolled Clinical Studies:

1. SMSC 201-E-02, 03 and 04: Phase 2 Open Extension Studies For An Additional 7, 12 and 9 months, respectively in Patients Who Completed SMSC 201-E-01.

SMSC 201-E-02:

To be eligible for this first extension study (1st extension to 201-E-01), mean 12 hr. serum GH was to have been suppressed to <5 ug/L during SMSC201-E-01 and there was to have been a 50% reduction in mean serum 12 hr. GH relative to wash-out in E-01.

43 patients were enrolled (22M, 21 F, mean age 52.2 yrs., all were Caucasian).

Dosage decision and dosing interval:

Injection 1:

The first dose was that given in E-01: either 20 or 30 mg. The first dose was 30 mg if GH suppression to <5 ug/L had been <28 days in E-01 or GH suppression was not as low as that on sq.

Injections 2-6:

The second injection was administered 60 days later and subsequent injections, q28 days, with doses adjusted between 20-40 mg, to maintain serum GH <5 ug/L. The dose was adjusted downward by 10 mg if serum GH was <1 ug/L and increased by 10 mg if GH was >5 ug/L (with maximum dose of 40 mg).

Efficacy:

Primary efficacy: mean 8 hr. serum GH and octreotide levels

Secondary efficacy: IGF-1 levels, clinical symptoms of acromegaly

Efficacy was assessed on days 28, 42 and 60 after the first injection and on days 1 and 28 after subsequent injections.

Safety:

TFTs (TSH, total and free T3 and T4) were measured 28 days after the first, third and sixth injections,

GB US on the day of the second injection and at the last visit

Physical exam, hematology/chemistry and HbA_{1C} at the last visit.

RESULTS:

In 15 patients, the second LAR injection was given sooner than the protocol specified interval of 60 days: 9 patients received their second injection 28 days after the first and 6 patients rec'd it after 42 days.

Although the 3rd-6th injections were to be administered at 28 day intervals, in reality, this was adhered to in only ~80% of the patients. The actual interval between injection ranged between 23-57 days.

The first dose was:

20 mg in 11 patients

30 mg in 32 patients

Note: the LAR dose was increased from 20 mg in 201-E-01 to 30 mg in 201-E-02 in 9 patients, for the following reasons:

GH not adequately controlled on LAR (i.e. not <5 ug/L for ≥28 days) and degree of GH control better on sq: n= 5

GH<5 ug/L for ≥ 28 days but GH control better on sq: n= 2

GH not adequately controlled on either LAR or SQ: n= 1

Reason unclear: n= 1 GH control adequate on LAR and comparable to sq).

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The LAR Dose At Each Visit and the # of Patients:

Injection 1	Injection 2	Injection 3	Injection 4	Injection 5	Injection 6
20mg: n=11	20mg: n=4 30mg: n=7	20mg: n=4 30mg: n=7	20mg: n= 4 30mg: n=7	20mg: n= 4 30mg: n= 7	20mg: n=4 30mg: n=7
30mg: n=32	20mg: n=10 30mg: n=22	20mg: n= 12 30mg: n= 20	20mg: n=12 30mg: n=20	20mg: n=11 30mg: n=20	20mg:n=10 30mg:n=21
Overall: 20mg: n=11 30mg: n=32	20mg: n=14 30mg: n=29	20mg: n=16 30mg: n=27	20mg: n=16 30mg: n=27	20mg: n=15 30mg: n=27	20mg:n=14 30mg:n=28

Summary of above table:

~2/3's (7/11) of patients receiving 20 mg as the first dose rec'd a dose of 30 mg at the second injection and remained at this dose. ~1/3 of patients (10/32) who received 30 mg as the first dose subsequently rec'd 20 mg and remained on this dose. Overall, ~2/3's of the patients (27-29/43) received the 30 mg dose throughout this study.

Although 43 patients entered into this trial, only 42 completed the study. One patient (#4012) discontinued the study after the fourth injection due to adverse events- severe hair loss and dry skin, attributed to Sandostatin. Mean GH/IGF-1 control in this 1 patient with 4 LAR injections was: mean GH<1 ug/L and IGF-1 normal.

Mean GH and IGF-1 Control With 7 Injections of LAR in 42 Patients Who Completed 201-E-01 and E-02:

Mean GH (ug/L) and IGF-1 (ug/L) With 7 Injections of LAR in the 42 Patients Who Completed 201-E-01 and E-02 vs. SQ:

	SQ N= 42 n (%)	Only 20mg N= 4 n (%)	20/30mg N= 28 n (%)	Only 30mg N= 10 n (%)	Overall on LAR N= 42 n (%)
Mean GH <5	39 (93%)	4 (100%)	23 (82%)	9 (90%)	36 (86%
Mean GH <2.5	25 (60%)	4 (100%)	20 (71%)	2 (20%)	26 (62%
Mean GH <2	18 (43%)	4 (100%)	16 (57%)	2 (20%)	22 (52%
Mean GH <1	6 (14%)	1 (25%)	6 (21%)	1 (10%)	8 (19%)
IGF-1 normal	25 (60%)	3 (75%)	17 (61%)	3 (30%)	23 (55%
GH<5 & IGF nl.	25 (60%)	3 (75%)	17 (61%)	3 (30%)	23 (55%
GH<2.5&IGF nl.	20 (48%)	3 (75%)	16 (57%)	1 (10%)	20 (48%
GH<2 & IGF nl.	15 (36%)	3 (75%)	14 (50%)	1 (10%)	18 (43%
GH<1 & IGF nl.	6 (14%)	1 (25%)	5 (18%)	0 (0%)	6 (14%)

Note: the day 28 post-injection 1 values for GH and IGF-1 were used in the above table.

the dose groups show all doses a patient used in the extension. It does not show the number of times or the sequence a particular dose was given.

Overall, after 7 LAR injections, mean GH was <5, <2.5, <2 and <1 ug/l and IGF-1 normalized in 55%, 48%, 43% and 14% of patients, respectively.

The following table demonstrates that, on LAR, mean IGF-1 normalized in 64%, 77%, 82% and 75% of patients who suppressed their mean GH to <5, <2.5, <2 and <1 ug/L, respectively:

(%) of Patients in Whom IGF-1 Normalized when GH was Suppressed Below Cut-offs of 1, 2, 2.5 and 5 ug/L:

	7 INJECTIONS OF SANDOSTATIN LAR			
	Only 20 mg n (%)	20/30 mg n (%)	Only 30 mg n (%)	Overall n (%)
Mean GH <5 & IGF-1 nl.	3/4(75%)	17/23(74%)	3/9(33%)	23/36(64%)
Mean GH <2.5&IGF-1 nl	¾(75%)	16/20(80%)	½(50%)	20/26(77%)
Mean GH <2 & IGF-1 nl.	3/4(75%)	14/16(88%)	1/2(50%)	18/22(82%)
Mean GH <1 & IGF-1 nl.	1/1(100%)	5/6 (83%)	0/1 (0%)	6/8 (75%)

Serum Octreotide Levels:

There was a progressive increase in octreotide levels until the third injection after which drug levels reached a plateau with the means varying between at the 30 mg dose level and between at the 20 mg dose level.

Symptoms of Acromegaly:

Number of Patients Reporting Symptoms of Acromegaly (day 28 after each injection):

Dose at last injection	20 mg		30 mg	
Injection	Baseline[a]	Injec. 6	Baseline[a]	Injec. 6
Headache	3	4	16	11
Fatigue	6	4	23	14
Perspiration	7	4	18	6
Joint pain	7	3	26	14
Carpal tunnel syndrome	1	0	13	1
Paresthesia	5	2	21	4

a= baseline= day 0 of 201-E-01.

Grouping all 43 patients together, the mean composite score for the above 6 symptoms of acromegaly was reduced from 6.5 at baseline to 2.0 at the last visit.

SAFETY:

There were no deaths.

1 patient prematurely withdrew from the study due to severe alopecia and dry skin which, per the investigator, were probably related to Sandostatin LAR.

There were 7 serious AEs:

1. 60 yr. old F underwent surgery for meningioma. Patient c/o dizziness and hypoacusia prior to LAR administration. Event deemed by investigator as unrelated to LAR.
2. 60 yr. old F was dx'd with papillary thyroid cancer 6 months after the first injection of LAR. The patient subsequently underwent a thyroidectomy. The investigator regarded this event as not related to LAR.

3. 68 yr. old F with a hx. of hemicolectomy for diverticulitis, was hospitalized with intestinal subocclusion several weeks after receiving her first dose of LAR. It resolved with parenteral hydration. Therapy with Sandostatin sq was begun and, after, the second sq injection, the patient re-experienced symptoms which she reported prior to the first episode. She was again hospitalized and the sx's resolved with conservative rx. The patient subsequently entered 201-E-02 and completed the trial. The episode was probably related to Sandostatin.
4. 59 yr. old F on antihypertensive rx., experienced syncope while on LAR. The syncope was felt to be secondary to postural hypotension. The antihypertensive therapy was d/c'd, LAR continued and the patient improved.
5. 38 yr. old F underwent a surgical sterilization procedure- clips on the fallopian tubes.
6. 44 yr. old M was hospitalized for severe depression with heavy alcohol consumption, associated with personal problems. The investigator assessed this event as unrelated to LAR.
7. 70 yr. old M underwent surgical removal of a urinary bladder carcinoma, which the investigator assessed as being unrelated to LAR. This same patient also experienced a severe headache 50 days post the first LAR injection. An MRI revealed extensive penetration of the tumor into the adjacent sinuses. The initial interpretation was partial tumor necrosis. A definitive causality assessment for the severe headache was not provided. The patient cont'd to participate in the study, receiving LAR at reduced intervals of 42 days, with no further relapse of headache.

The AEs in >5% of patients were (note: in some cases, the relationship to LAR as assessed by the investigator is recorded here):

GI : total GI AEs: 32/43 (74%)

Diarrhea	20/43 (only 1 was severe)
Flatulence	18/43 (only 1 was severe)
Constipation	9/43
Feces discolored	5/43
Abdominal pain	4/43
Vomiting	3/43
Nausea	2/43
Dysphagia	1
Enterocolitis	1
GI disorder nos*	1
Esophagitis	1

* nos= not otherwise specified

Note: diarrhea, flatulence and constipation were higher at the 30 mg dose than the 20 mg dose.

Whole body/general: 16/43 (37%)

(most commonly reported were fatigue, fever and influenza-like sx's.
Fatigue was possibly-definitely related to LAR in 3/5 patients)

Hematology (anemia) 15/43 (35%)

Nervous system 15/43 (35%)

(most commonly reported were headache and paresthesia.
Headache was possibly-definitely related to LAR in 6/8 and paresthesia was

definitely related to LAR in ¾ patients)

Musculo-skeletal 12/43 (28%)
(most commonly reported was back pain which was possibly related to LAR in 2/6 patients)

Injection site disorders 12/43 (28%)
(pain: 7/43= 16%, swelling: 4/43= 9%, rash: 1/43= 2%)

Respiratory 7/43 (16%)
(bronchitis, coughing, pharyngitis, respiratory disorder, rhinitis)

Skin and appendages 7/43 (16%)
(alopecia- probably related to LAR in 1/2, pruritis, 1skin dry- probably related, sweating increased- probably related in 1/4)

Liver/biliary 6/43 (14%)
(most commonly reported was cholelithiasis which was possibly-definitely related to LAR in all 4 cases)

Urinary system 6/43 (14%)
(bladder disorder, dysuria, nocturia, renal pain, surgery, UTI)

Psychiatric 5/43 (12%)
(the most commonly reported were anxiety and depression in 2 patients each)

Cardiovascular (hypertension) 4/43 (9%)
(Note: 1 patient, #4002, with a hx. of hypertension, had a hypertensive crisis on LAR)

Endocrine (hypothyroidism: n= 2) 4/43 (9%)
1 mild and 1 moderate severity with 1 of these not related and 1 unlikely

Metabolic and Nutritional 3/43 (7%)
(hypocalacemia, hypovitaminosis, weight increase)

Neoplasms (surgery) 3/43 (7%)

Vision disorders 3/43 (7%)
(eye pain, glaucoma, photophobia)

AEs reported in 1-2 patients (≤5%):
Postural hypotension (#'s 3015 and 3018), prostatic disorder, abscess/pharyngitis, peripheral ischemia, breast pain/menstrual disorder/surgical sterilization (clips on fallopian tubes)

Changes in Vital Signs:
Hypertension: 4/43= 9%, Hypotension: 2/43= 5%
The 4 cases of hypertension occurred in patients (#'s 3006, 4002, 4011 and 6002) who either had a hx. of hypertension or had elevated BP at baseline. It should be noted that a severe hypertensive episode occurred at the last study visit in 1 patient (#4002) who was a known hypertensive . In the investigator's opinion, this was unlikely to have been related to LAR.

Hematology (including HbA_{1C}) and Biochemistry:

Anemia was attributed to frequent blood sampling.

Of the 4 patients with notable abnormalities in this extension, 3 developed these abnormalities in 201-E-01: #'s 3002 and 3013- bilirubin and #5007- SGPT. In only 1 of these 4 patients did the clinically notable abnormality occur in this extension- #3016- glucose: baseline was and rose to (clinical notable glucose: ≥250 mg/dl).

Thyroid function:

No changes deemed to be biologically or clinically relevant.

Gallbladder Ultrasound:

Newly occurring or worsening abnormalities were (note: none of these patients were on bile acid dissolution agents):

Microlithiasis/sediment (they were not distinguished in this patient): 1 (#5003
Sludge only: 1(#4005)
GB or bile duct dilatation only: 2 (#'s 3008 and 4002)
Biliary symptoms: 0
Note: Gallbladder polyps occurred in 2 patients: #4013 and #4006

SMSC 201-E-03:

This was the second extension to study 201-E-01. It was an open-label, multicenter study with 12 injections of LAR in patients who had completed 201-E-01 and 201-E-02. To be eligible, patients must have suppressed GH by >50% from baseline and/or <5 ug/l during 201-E-01 and/or 201-E-02.

1 patient (#4006) did not continue in this extension study due to inadequate suppression of GH (mean GH >5 ug/l and IGF-1 elevated on 30 mg LAR).

41 patients were enrolled in 4 centers (Italy, Norway and France).

12 injections of LAR were administered q4 - 6 weeks, with doses individually titrated between 20-40 mg to maintain a consistent suppression of GH, comparable to that achieved on sq. Consistent clinical efficacy was also required. The dose was to be down titrated by 10 mg in patients whose GH was consistently suppressed <1ug/l during a 3 mo. period.

Efficacy:

Primary efficacy: mean 8 hr. serum GH
Secondary efficacy: serum SMC
clinical signs/symptoms of acromegaly

The primary and secondary efficacy variables and serum octrotide levels were assessed just prior to the next LAR injection- day 28 for a 4 week dosing interval and day 42 for a 6 week dosing interval.

Safety:

Physical exam, hematology/biochemistry, HbA_{1c} and OGGT at 6 and 12 months. Thyroid function (TSH, total and free T3 and T4 in one center and TSH/total T3 at the remaining centers) and GB US at 3, 6, 9 and 12 mos.

Results:

2 patients did not receive all 12 LAR injections:

1 patient (#4002) was prematurely withdrawn from the study due to an AE which occurred after she rec'd 6 injections of LAR which suppressed mean and SMC was normal. This patient was a 57 yr. old F who suffered a cerebral infarction 150 days after starting the study medication. The event was assessed as unlikely to be related to LAR.

One other patient rec'd only 11 injections of LAR because the patient did not receive an injection at visit 5.

The 41 patients comprised 22 M and 19 F, all Caucasian, ranging in age with a mean of 52.1 yrs.

Dose of LAR administered during the 12 months:

7-10% of the patients could be down-titrated to 10 mg, starting with the 7th injection,

~50% rec'd the 30 mg dose throughout the study
~25-30% rec'd the 20 mg dose throughout the study
~10-15% rec'd the 40 mg dose.

Serum Octreotide levels:

10 mg dose: n= 3 patients: mean drug levels ranged from . , 28 days after the 8th and 12th injections.

20 mg dose: n= 11-13 patients: mean drug levels 28 days after the 4th-12th injections (i.e. at steady state) ranged from

30 mg dose: n= 19-24 patients: mean drug levels at steady state:

40 mg dose: n= 1-8 patients: mean drug levels at steady state.

Mean GH (ug/L) and IGF-1 (ug/L) With 19 Injections of LAR in the 40 Patients Who Completed 201-E-01, E-02 and E-03:

	Sandostatin LAR (mg):							
	10/20 n= 2 n (%)	10/20/30 n= 2 n (%)	only 20 n= 1 n (%)	20/30 n= 22 n (%)	20/30/40 n= 3 n (%)	only 30 n= 5 n (%)	30/40 n= 5 n (%)	Total n= 40 n (%)
Mean GH <5	2/2 (100%)	2/2 (100%)	1/1 (100%)	22/22 (100%)	2/3 (67%)	5/5 (100%)	4/5 (80%)	38/40 (95%
Mean GH <2.5	2/2 (100%)	2/2 (100%)	1/1 (100%)	16/22 (73%)	2/3 (67%)	1/5 (20%)	1/5 (20%)	25/40 (63%
Mean GH <2	2/2 (100%)	2/2 (100%)	1/1 (100%)	12/22 (55%)	1/3 (33%)	1/5 (20%)	1/5 (20%)	20/40 (50%
Mean GH <1	1/2 (50%)	1/2 (50%)	0/1 (0%)	6/22 (27%)	0/3 (0%)	0/5 (0%)	0/5 (0%)	8/40 (20%
IGF-1 normal	2/2 (100%)	2/2 (100%)	0/1 (0%)	15/22 (68%)	1/3 (33%)	2/5 (40%)	1/5 (25%)	23/40 (58%
GH<5 & IGF nl.	2/2 (100%)	2/2 (100%)	0/1 (0%)	15/22 (68%)	1/3 (33%)	2/5 (40%)	1/5 (20%)	23/40 (58%
GH<2.5&IGF nl	2/2 (100%)	2/2 (100%)	0/1 (0%)	14/22 (64%)	1/3 (33%)	1/5 (20%)	0/5 (0%)	20/40 (50%
GH<2 & IGF nl.	2/2 (100%)	2/2 (100%)	0/1 (0%)	11/22 (50%)	1/3 (33%)	1/5 (20%)	0/5 (0%)	17/40 (43%
GH<1 & IGF nl.	1/2 (50%)	1/2 (50%)	0/1 (0%)	6/22 (27%)	0/3 (0%)	0/5 (0%)	0/5 (0%)	8/40 (20%

Note: The dose groups show all doses a patient used in the extension. It does not show the number of times or the sequence a particular dose was given.

Overall, after 19 LAR injections, mean GH was <5, <2.5, <2 and <1 ug/l and IGF-1 normalized in 58%, 50%, 43% and 20% of patients, respectively.