The following table demonstrates that, on LAR, mean IGF-1 normalized in 61%, 80%, 85% and 100% 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:

19 INJECTIONS OF SANDOSTATIN LAR

Sandostatin LAR (mg):

	10/20 n (%)	10/20/30 n (%)	only 20 n (%)	20/30 n (%)	20/30/40 n (%)	only 30 n (%)	30/40 n (%)	Total n (%)
Mean GH <5 & IGF-1 normal	2/2 (100%)	2/2 (100%)	0/1 (0%)	15/22 (68%)	1/2 (50%)	2/5 (40%)	1/4 (25%)	23/38 (61%
Mean GH<2.5 &	2/2 (100%)	2/2 (100%)	0/1 (0%)	14/16 (88%)	½ (50%)	1/1 (100%)	0/1 (0%)	20/25 (80%
Mean GH <2 & IGF-1 normal	2/2 (100%)	2/2 (100%)	0/1 (0%)	11/12 (92%)	1/1 (100%)	1/1 (100%)	0/1 (0%)	17/20 (85%
Mean GH <1 & IGF-1 normal	1/1 (100%)	1/1 (100%)	0/0 (0%)	6/6 (100%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	8/8 (100%

Symptoms of acromegaly:

Number of Patients Reporting Symptoms of Acromegaly on Day 28 After the 1st and 12th Injections Administered in Study SMSC201-E-03:

Dose at last injection	10mg		20mg		30mg		40mg	
Injection	1	12	1	12	1	12	1	12
N=	0	3	13	11	25	25	3	1
Headache	0	0	2	1	8	4	0	0
Fatigue	0	2	9	2	13	10	3	0
Perspiration	0	0	3	2	8	3	0	0
Joint pain	0	2	7	8	17	15	0	0
Carpal tunnel syndrome	0	0	0	0	3	1	0	0
Paresthesias	0	1	2	1	7	6	0	0

The total symptom score was computed as the sum of the severity of signs and symptoms of acromegaly.The overall mean scores declined during the study. Mean values at baseline after wash-out in 201-E-01 and visits 1, 4, 8 and 12 in 201-E-03 were: 6.4, 2.9, 2.1, 1.8 and 2.3, suggesting good and consistent control of signs and symptoms during the 12 mos. of rx. in this study.

SAFETY:

There were no deaths.

There was 1 premature withdrawal (patient #4002). After receiving 6 LAR injections in this study, a 57 yr. old F suffered a cerebral infarction which the investigator assessed as unlikely to be related to LAR. The patient had a hx. of hypertension for which she was on treatment. BP rose in this study to . In this patient (#4002), mean GH was and SM-C was normal on LAR.

9 patients (22%) experienced serious AEs:

1 patient experienced a cerebral infarct *see above) which was thought to be unlikely related to LAR by the investigator.

A 64 yr. old M experienced atrial fibrillation and gastritis with diarrhea ~10 months after starting LAR. This event was regarded by the investigator to be remotely related to LAR.

A 60 yr. old F with a hx. of hypertension experienced a hypertensive crisis 28 days after starting LAR in this extension study. The investigator assessed this event as not related to LAR (see below).

The remaining serious AEs were as follows and were all assessed as not related to LAR: malaise, precordial pain (single episode with pre-existing hx.), hospitalization for arthroscopy, hip arthroplasty, partial colectomy for polyps, prostatic adenoma/pollakiuria/dysuria/ endoscopic prostatic resection.

Adverse Events (note: in some cases, the relationship to LAR as assessed by the investigator, is recorded here):

All patients experienced one or more adverse events.

These AEs are listed in decreasing order of severity:

Whole body/general 29 (71%)

(most commonly reported was fatigue which was possibly related to LAR in 2/8 cases)

GI total 28 (68%)

Diarrhea	14 (1 severe)
Flatulence	14
Abdominal pain	11 (1 severe)
Constipation	7
Feces discolored	3
Tooth disorder	2 (1 severe)
Nausea	2
Vomiting	3
GI disorder nos*	1
Gastroeneriitis	1
GE reflux	1
Mouth dry	1

nos= not otherwise specified

Note: only diarrhea appeared to be dose-related, occurring more frequently in those on 30 mg than in those on 20 mg.

Central and peripheral Nervous system: 14 (34%)

(most commonly reported were headache and dizziness)

Hematology (anemia) 14 (34%)

Respiratory 10 (24%)

(bronchospasm, cough, dyspnea, emphysema, pharyngitis, rhinitis, sinusitis, URI)

Liver and biliary 10 (24%)

(cholelithiasis, GB disorder, SGOT increased: n= 1)

Musculo-skeletal 9 (22%)

(arthralgia, arthropathy, myalgia, surgery)

Endocrine 7 (17%)

(Note:hyperthyroidism: n= 1, hypothyroidism: n= 1, both were regarded as either not related or unlikely to be related to LAR by the investigator)

Skin and Appendages

(alopecia, furunculosis, hypertrichosis, pruritis, sweating increased) 7 (17%)

Metabolic and Nutritional 6 (15%)

(diabetes mellitus: n= 1, probably related to LAR; glucose tolerance abnormal: n= 1, probably related to LAR; hyperglycemia: n= 1, probably related to LAR; hypoglycemia: n= 1, not related to LAR)

Psychiatric (most commonly reported was anxiety)	6 (15%)
Cardiovascular disorders (hypertension)	5 (12%)
Vascular (CV disorder, peripheral ischemia and phlebitis)	4 (10%)
Urinary (cystitis, hematuria, micturition frequency, renal pain and surgery)	4 (10%)
Vision (conjunctivitis, eye abnormality)	3 (7%)

In addition, 2 patients each reported epistaxis and vaginitis, and 1 patient each: atrial fibrillation and viral infection.

Injection site disorders:

Pain	9 (22%)
Swelling	3 (7%)
Rash	1 (2%)

Vital signs:

Mean values remained within the normal ranges.

Hypertension:

Hypertension was reported as an AE in 5 patients. In actuality, it was worsening hypertension as all 5 patients either had a hx. of hypertension (n= 4) or an elevated BP at baseline (n= 1). The hypertension was considered possibly due to LAR in 1 patient, unlikely in 2 and not related in 2.

Physical examination:

Worsening of hemiparesis which was present at baseline in 1 patient.

Hematology and biochemistry abnormalities:

Newly occurring hematologic abnormalities were:

low white blood cell counts in 3 patients (#'s 3013, 4003 and 5005)

low Hct in 1 patient (#3016)

worsening of high glucose in 3 patients (7%)

high HbA1C in 1 diabetic patient (#4011).

Newly occurring biochemical abnormalities:

2 patients: high alk phos

2 patients (Ctr. 30, subj 8 and Ctr. 40, subj 10): high SGOT

1 patient: high SGPT (Ctr. 30, subject 10)

1 patient: high cholesterol

1 patient: high triglycerides

OGTT:

OGGT was performed at study mid-point (28/42 days after injection 6) and at the final visit. Out of 36 patients assessed, 29 (81%) had normal OGTT. The abnormalities were as follows: high fasting glucose levels in 1 patient, a known diabetic, who also had high glucose levels 2 hrs. after ingestion of glucose. The latter abnormality also occurred in 6 other patients.

At the time of the second OGTT (injection 12, day 28), 17/39 patients tested had GH <2 ug/L and 10/39 (26%) had GH <1 ug/L.

Thyroid function tests:

Mean values for TFTs remained within normal limits. 4 patients with normal baseline TSH, developed low TSH values during the study (#'s 4004, 4011, 5003 and 5005). There were no clinically relevant changes in TFTs during this study.

Gallbladder abnormalities:

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

Gallstones/Microlithiasis (+/- also with sediment, sludge or dilatation):	4 (#'s 3001, 3005, 4011 and 5002)
Sediment without stones (+/- also with sludge or dilatation):	0
Sludge without stones or sediment (+/- also with dilatation):	1 (#4016)
GB or bile duct dilatation only:	2 (#'s 3004 and 3015)
Biliary symptoms:	0

Note: gallbladder polyps developed in 1 patient: #4016

SMSC 201-E-04:

This was the third open-label extension to study 201-E-01. It was a muticenter, open-dose-titration phase 2 study with 9 injections of LAR administered to patients completing 201-E-01, -02 and -03. Patients need to demonstrate good clinical and biological improvement of acromegaly during these previous studies. 36 patients entered from 4 centers in Italy, Norway and France.

Patients were administered 9 injections of LAR at 4 week intervals at individually titrated doses (10, 20, 30 or 40 mg) necessary to maintain a consistent suppression of GH and at least to the same extent as on sq. Consistent clinical efficacy was also required.

Efficacy:

Primary: mean 8 hr. serum GH profile on day 28 after injections 3, 6 and 9

Secondary: Serum SM-C levels (measured at same times as GH)

Clinical signs/symptoms of acromegaly evaluated on day 28 after each injection

Note: serum octreotide concentrations were measured at the same time as GH and SM-C

Safety:

Physical exam on days 28 after injections 6 and 9
Vital signs at the last study visit
Biochemistry & hematology: day 28 after injections 6 and 9.
OGTT: day 28 after injection 6
HbA_{1C}: day 28 after injections 6 and 9
TFTs (TSH, total and free T3 and T4) on day 28 after injection 6

GB US on day 28 after injections 6 and 9

Results:

36 patients entered this study. Mean age at entry was 53.6 yrs. (range 32-80 yrs.). All were Caucasian, 53% were male and 47% were female.

4 patients who completed study 201-E-03 did not enter this study for the following reasons:

#4008: patient felt her symptoms were better controlled on sq (note: in the last study, on LAR.)

#5006: personal reasons (note: in the last study, on LAR. Patient had a serious AE in the last study: partial colectomy for polyps, not related to LAR)

#5007: personal reasons (note: in the last study, Biliary duct dilatation occurred in the last study).

#6002: sponsor requested that patient enter another Sandostatin study (note: in the last study, In the last study, this patient had a serious AE: prostatic adenoma and resection, not related to LAR. Patient also became anemic in the last study Patient has a hx. of hypertension and is on treatment.

5 patients who completed 201-E-03 preferred surgical treatment and 2 patients withdrew prematurely from this study for transsphenoidal adenectomy. Patient #4016 withdrew after the 6th injection Patient #4013 withdrew after the 8th injection . An additional patient prematurely withdrew after the 8th injection to undergo an operation for an abdominal aortic aneurysm. (Note: another patient missed 1 LAR injection: injection #8).

Dose administered:

10 mg: 5 patients (14%), injections 4-9
20 mg: 9-10 patients (25-28%), injections 4-9
30 mg: 17-18 patients (47-50%), injections 4-9
40 mg: 2-3 patients (6-8%), injections 1-9

Mean serum octreotide levels 28 days after injections 3, 6 and 9:

10 mg (n= 2-5 patients):
20 mg (n= 9-11 patients)
30 mg (n= 16-18 patients):
40 mg (n= 1-3 patients):

Mean GH (ug/L) and IGF-1 (ug/L) With 28 Injections of LAR in the 33 Patients Who Completed 201-E-01, E-02, E-03 and E-04:

	Sandostatin LAR (mg):						
	10/20	10/20/30	20/30	20/30/40	only 30	30/40	Total
	n= 2	n= 4	n= 18	n= 3	n= 4	n= 2	n= 33
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Mean GH <5	2/2 (100%)	4/4 (100%)	18/18 (100%)	2/3 (67%)	4/4 (100%)	1/2 (50%)	31/33 (94%)
Mean GH<2.5	2/2 (100%)	4/4 (100%)	11/18 (61%)	2/3 (67%)	0/4 (0%)	0/2 (0%)	19/33 (58%)
Mean GH <2	2/2 (100%)	4/4 (100%)	8/18 (44%)	1/3 (33%)	0/4 (0%)	0/2 (0%)	15/33 (46%)
Mean GH <1	0/2	3/4	3/18	0/3	0/4	0/2	6/33

	(0%)	(75%)	(17%)	(0%)	(0%)	(0%)	(18%)
IGF-1 normal	1/2 (50%)	4/4 (100%)	12/18 (67%)	1/3 (33%)	2/4 (50%)	0/2 (0%)	20/33 (61%)
GH<5 & IGF nl.	1/2 (50%)	4/4 (100%)	12/18 (67%)	1/3 (33%)	2/4 (50%)	0/2 (0%)	20/33 (61%)
GH<2.5&IGF nl.	1/2 (50%)	4/4 (100%)	10/18 (56%)	1/3 (33%)	0/4 (0%)	0/2 (0%)	16/33 (48%)
GH<2 & IGF nl.	1/2 (50%)	4/4 (100%)	8/18 (44%)	1/3 (33%)	0/4 (0%)	0/2 (0%)	14/33 (42%)
GH<1 & IGF nl.	0/2 (0%)	3/4 (75%)	3/18 (17%)	0/3 (0%)	0/4 (0%)	0/2 (0%)	6/33 (18%)

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.

Patients up-titrated to the 40 mg dose, did not show better suppression of mean GH and their SM-C levels remained elevated.

Overall, after 28 LAR injections, mean GH was <5, <2.5, <2 and <1 ug/l and IGF-1 normalized in 61%, 48%, 42% and 18% of patients, respectively.

The following table demonstrates that, on LAR, mean IGF-1 normalized in 65%, 84%, 93% and 100% 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:

28 INJECTIONS OF SANDOSTATIN LAR

	Sandostatin LAR (mg):						
	10/20 n (%)	10/20/30 n (%)	20/30 n (%)	20/30/40 n (%)	only 30 n (%)	30/40 n (%)	Total n (%)
Mean GH <5 & IGF-1 normal	1/2 (50%)	4/4 (100%)	12/18 (67%)	1/2 (50%)	2/4 (50%)	0/1 (0%)	20/31 (65%)
Mean GH<2.5 &	1/2 (50%)	4/4 (100%)	10/11 (91%)	1/2 (50%)	0/0 (0%)	0/0 (0%)	16/19 (84%)
Mean GH <2 & IGF-1 normal	1/2 (50%)	4/4 (100%)	8/8 (100%)	1/1 (100%)	0/0 (0%)	0/0 (0%)	14/15 (93%)
Mean GH <1 & IGF-1 normal	0/0 (0%)	3/3 (100%)	3/3 (100%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	6/6 (100%)

45 patients had entered SMSC 201-E-01 but only 33 patients completed SMSC 201-E-04. The following list provides the degree of hormonal control in these 12 patients for the # of LAR injections the patient rec'd , any adverse events experienced by the patient and the reason, when available, for study discontinuation (note: wd= withdrew) (note: for the following patients, the # of LAR injections stated below may, in some cases, be less than the total # of LAR injection the patient actually received. Only those injection for which GH/SM-C data was available 28 days later, is tallied below):

Patient #	# LAR injections	Mean GH (ug/l)	Mean SM-C (ug/l)	Adverse Event(s)	Reason for study discontinuation

#4007	1	normal	dizziness	dizziness
#5008	1	elevated		repetitive protocol violations (wd day 14)
#4006	7	elevated	GB polyps	
#4012	5	normal		severe alopecia and dry skin
#4002	12	normal	cerebral infarction	cerebral infarction
#4008	19	elevated		patient felt symptoms were better controlled on sq
#5006	19	normal	partial colectomy for polyps	personal reasons
#5007	19	normal	biliary duct dilatation	personal reasons
#6002	19	elevated	worsening hypertension & prostatic adenoma resection	sponsor requested patient enter another study
#4009	26	normal		surgery for aortic aneurysm
#4013	24	elevated		transsphenoidal adenectomy
#4016	24	elevated		transsphenoidal adenectomy

Symptoms of acromegaly:

Overall, the number of patients reporting individual signs/symptoms of acromegaly, declined from the first to the last injections in this study. The number of patients reporting signs/symptoms of acromegaly on day 28 after the first vs. the last injections in this study, by dose at the last injection, were:

	10 mg		20 mg		30 mg		40 mg	
Injection	1	9	1	9	1	9	1	9
N=	1	5	12	9	21	17	2	2
Headache	0	1	1	1	3	3	0	0
Fatigue	0	1	4	2	8	6	0	0
Perspiration	0	1	2	2	5	3	0	0
Joint pain	1	3	8	4	11	9	0	1
Carpal tunnel syndrome	0	0	0	0	0	0	0	0
Paresthesias	1	1	0	0	4	4	0	0

SAFETY:

No patients died during the study.

5 patients experienced serious adverse events:

#3015: 70 yr. old F was hospitalized for cholangiopancreatography and surgery 179 days after starting LAR in this study. The investigator assessed this event as not related to LAR but to coexisting disease.

#4009: 70 yr. old M was hospitalized for surgery for an abdominal aortic aneurysm. The investigator assessed this event as unlikely to be related to LAR.

#4013: 53 yr. old M was withdrawn from the study after the 8th LAR injection in this study to undergo a transsphenoidal adenectomy.

#4016: a 55 yr. old M withdrew after the 6th injection in this study to undergo a transsphenoidal adenectomy. The patient did not have an optimal hormonal response to LAR ug/l after 24 injections of LAR

#6001: 46 yr. old M attempted suicide 222 days after starting LAR. The investigator assessed the event as not related to LAR.

There were 3 premature discontinuations- 2 patients for transsphenoidal adenectomy and 1 patient for surgery for an abdominal aortic aneurysm.

Adverse Events (note: in some cases, the relationship to LAR as assessed by the investigator, is recorded here):

GI: 24 (67%)

Diarrhea	11
Constipation	10
Flatulence	10
Abdominal pain	7
Vomiting	2

1 each of the following: dyspepsia, feces discolored, gingivitis, hemorrhoids, nausea, steatorrhea and tooth disorder.

(Note: none of these GI AEs were severe or appeared to be dose-related)

Whole body/general: 22 (61%)
(trauma, asthenia, back pain, fatigue, influenza-like symptoms, pain, surgery, cholesterol-rich polyps in 2 patients: #'s 3001 and 3004 and the polyps were assessed as probably related to LAR)
CHECK ON CHOLESTEROL POLYPS

Respiratory: 12 (33%)
(bronchitis, bronchospasm, coughing, pharyngitis, pneumonia, rhinitis, sinusitis, URI)

Liver and biliary: 9 (25%)
(cholelithiasis, GB disorder)

Red blood cells: 8 (22%)
(anemia)

Dermatologic: 8 (22%)
(alopecia, eczema, pruritis, folliculitis, furunculosis, sweating increased)

Nervous system: 7 (19%)
(cramps, dizziness, headache)

Psychiatric: 3 (8%)
(most commonly reported was anxiety)

Urinary: 3 (8%)
(dysuria, frequency, nocturia, polyuria, UTI)

1-2 patients experienced the following AEs: alkaline phosphatase increased, arthropathy, aneurysm and herpes simplex)

Injection site disorders: 9 (25%)
Pain 8
Swelling 1

Vital signs:

Mean values remained within the normal range. No patient had hypertension reported as an AE.

Physical exam:

There were no newly-occurring or worsening abnormalities.

Hematology and Biochemistry:

In 1 patient (#4011), baseline wbc was normal became clinically notable at the end of this extension

In 1 diabetic patient (#3016), HbA_{1c} rose from baseline during this extension.

Following is a list of the # of patients with newly occurring or worsening abnormalities outside the expanded normal limits (expanded normal limits for glucose was $\geq$1.3 x ULN; and for total bilirubin, SGOT and total cholesterol: $\geq$1.15 x ULN):

Increased glucose: 4 patients
(note: an already high blood glucose worsened during the study in these 4 patients. For example, patient #3016, a known diabetic, had a baseline glucose of which notably increased week 24 but declined at the end of this study)

Increased total bilirubin: 4 patients
(note: patient #3008 had a normal baseline total bilirubin which rose at week 24 but returned to normal at the end of this study. Jaundice was not reported; therefore, the elevated total bilirubin was probably a data entry error).

Increased SGOT: 1 patient (#4003 with normal baseline SGOT: which rose which is , after 6 LAR injections and returned to normal at the end of the study).

Increased total cholesterol: 2 patients

Of these patients, only 2 had newly occurring biochemical abnormalities outside the expanded normal limits in this extension study:

#4003: high SGOT (see above)
#3006: high total cholesterol

OGGT:

Of 21 patients assessed, 8 (38%) appeared to have some abnormalities in glucose tolerance. 1 patient, a known diabetic, had high fasting glucose levels and 8 patients had high glucose levels (>140 mg/dl) 2 hr. after ingestion of 75 g glucose.

By the end of the study, 5/21 patients (24%) had mean serum GH concentrations <2 ug/l but <1 ug/l and 6/21 (29%) of those assessed had mean serum GH levels $\leq$ 1 ug/l.

Thyroid function tests:

Mean serum TSH, FT4 and TT3 remained within normal limits during this extension.

9/35 patients (26%) had low serum TSH levels in this study. Of these 9 patients, 7 had low TSH levels at entry into this study and 2 patients (#'s 3006 and 5003), had newly occurring low

TSH levels. 4 of these 9 patients were on levothyroxine. The low TSH levels in these patients were not accompanied by abnormalities in either FT4 or TT3.

Gallbladder ultrasound:

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

Gallstones/Microlithiasis (+/- also with sediment, sludge or dilatation): 2 (#'s 3002 and 4011)
Sediment without stones (+/- also with sludge or dilatation): 0
Sludge without stones or sediment (+/- also with dilatation): 4 (#'s 3004, 4014, 5001 and 5005)
GB/biliary duct dilatation only: 0
Biliary symptoms: 0

Overall Gallbladder Abnormalities in Patients Who Were Enrolled in 201-E-00 through 201-E-04:

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 (+/- sediment, sludge, dilatation): 6/37 (16%)
Note: in an additional 2 patients, either microlithiasis and/or sediment occurred (these events were not distinguished from each other in these 2 patients: #'s 3016 and 5003)
Sludge without stones or sediment (+/- also with dilatation): 7/28 (25%)
Dilatation only: 3/19 (16%)
Note: in 3 patients (#'s 4006, 4013 and 4016), gallbladder polyps occurred.
Biliary symptoms: 0 (0%)

(Explanations for the denominators used to calculate the gallbladder abnormalities: although 44 patients had gallbladder ultrasounds at baseline and after LAR treatment, the following patients were excluded:

for gallstones and/or microlithiasis, the denominator of 37 results from the exclusion of 7 patients as follows: 5 patients on ursodeoxycholic acid and 2 patients with gallstones/microlithiasis at baseline;

for sludge without gallstones/microlithiasis, the denominator of 28 results from exclusion of the 7 patients as detailed above for gallstones/microlithiasis plus the 6 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= 7) and sediment/sludge (n= 9), also pertain here plus the 7 patients who developed sediment/sludge post baseline plus 2 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 ultrasound for the patient was normal and the patient was not on bile acid dissolution agents:

Gallstones/Microlithiasis: 0
Sediment: 0
Sludge: 2/6 patients
Dilatation: 2/5

SMSC 202-E-01, 02 and 03: Phase 2 Open Extension Studies For An Additional 6, 12 and 9 Months, Respectively, in Patients Who Completed SMSC 202-E-00.

SMSC 202-E-01:

To be eligible for this first extension study, patients had to be either good responders or partial responders or partial responders to Sandostatin sq which was to be administered from 2-4 weeks. A good responder was a patient in whom mean 12-hr. serum GH was suppressed to <5 ug/L and there was a 50% reduction in mean serum 12 hr. GH levels relative to wash-out.

A partial responder reduced their GH to >50% relative to untreated levels but GH was not suppressed below 5 ug/L.

58 patients (37 F and 21 M with mean age of 46 years and range of 14-72 yrs.) were enrolled from 5 centers in Denmark, Romania, Holland and the U.K. (Note: 46 of 48 patients enrolled in SMSC 202-E-00, were enrolled in this first extension).

Dosage decision and dosing interval:

First LAR injection:

For centers 1-4, the first dose was identical to that administered in 202-E-00 (10, 20 or 30 mg) provided mean GH had been suppressed to <5 ug/L for at least 4 weeks. Otherwise, patients were to receive 30 mg.

For center 5, the initial dose was 30 mg for all patients.

The first dose was to be administered 60 days after the first dose in 202-E-00.

2nd-6th LAR injections:

The second injection was to have been administered 60 days after the first injection in this study; all subsequent injections were administered at 28 day intervals. The dose administered was to be 20, 30 or 40 mg (in violation of the protocol, 2 patients rec'd doses of 60 mg), the aim being to maintain mean 8 hr. GH levels at <5 ug/L. The dose was to be increased if mean GH was >5 ug/L or reduced (minimum dose was 20 mg) if the mean GH levels were consistently <1 ug/L.

Efficacy:

Primary: mean 8 hr. serum GH and octreotide levels

Secondary: IGF-1 levels, clinical symptoms of acromegaly (headache, fatigue, perspiration, joint pains, carpal tunnel syndrome and paresthesia scored on a scale ranging from 0= absent to 4= severe and incapacitating)

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

Safety:

Physical exam, vital signs, hematology, biochemistry profile and Hb A_{1C} at the last visit.

Gallbladder ultrasound on the day prior to the first injection and on day 28 after the second or third, fourth or fifth, and sixth LAR injections.

TFTs (serum TSH, total and free T3 and T4): prior to injection 1 and on days 28 after injections 2 or 3, 4 or 5 and 6

Results:

2 patients did not enter this extension study from 202-E-00: patient #2008 whose mean GH control on sq was better than on LAR and patient #3004 whose mean GH control on LAR was similar to that on sq but the patient had not been compliant with all study visits and there had been difficulty with venipuncture.

46 patients who participated in 202-E-00 also participated in this study: 34 good responders to sq Sandostatin and 12 partial responders. An additional 12 patients were recruited for this study: 8 good reponders to sq Sandostatin and 4 partial responders. Therefore, 58 patients total entered this extension of whom 42 were good responders to Sandostatin sq and 16 were partial responders.

1 patient (#5110) prematurely withdrew from the study after receiving the fifth injection to undergo a transsphenoidal adenectomy. She did, however, receive the sixth LAR injection one month after her surgery.

Dose of LAR administered: injections 3-6:

20 mg: 18-19 patients (31-33%)

30 mg: 29-32 patients (50-55%)

40 mg: 5- 9 patients (9-16%)
60 mg: 2 patients (3%)

Mean Serum Octreotide Levels:
Increased up to the 4th injection and depending on the dose with no evidence of drug accumulation.

thereafter plateaued at levels between

Mean GH (ug/L) and IGF-1 (ug/L) with 6-7 injections of LAR in the Patients Who Completed 202-E-00 and/or 202-E-01 (6 LAR injections: n= 12; 7 LAR injections: n= 46):

Sandostatin LAR (mg):

	SQ n= 58 n (%)	10/20 n=1 n (%)	10/20/30 n= 3 n (%)	10/30 n= 9 n (%)	10/30/40 n= 3 n (%)	only 20 n= 1 n (%)	20/30 n=23 n (%)	20/30/40 n= 2 n (%)
Mean GH<5	42/58 (72%)	1/1 (100%)	3/3 (100%)	6/9 (67%)	2/3 (67%)	1/1 (100%)	23/23 (100%)	0/2 (0%)
Mean GH<2.5	26/58 (45%)	1/1 (100%)	2/3 (67%)	3/9 (33%)	0/3 (0%)	1/1 (100%)	16/23 (70%)	0/2 (0%)
Mean GH<2	23/58 (40%)	1/1 (100%)	2/3 (67%)	3/9 (33%)	0/3 (0%)	1/1 (100%)	12/23 (52%)	0/2 (0%)
Mean GH<1	5/58 (9%)	0/1 (0%)	1/3 (33%)	1/9 (11%)	0/3 (0%)	0/1 (0%)	4/23 (17%)	0/2 (0%)
IGF-1 nl.	18/58 (31%)	0/1 (0%)	2/3 (67%)	4/9 (44%)	1/3 (33%)	1/1 (100%)	14/23 (61%)	0/2 (0%)
Mean GH<5 & IGF-1 nl.	18/58 (31%)	0/1 (0%)	2/3 (67%)	4/9 (44%)	1/3 (33%)	1/1 (100%)	14/23 (61%)	0/2 (0%)
Mean GH<2.5 & IGF-1 nl.	16/58 (28%)	0/1 (0%)	2/3 (67%)	3/9 (33%)	0/3 (0%)	1/1 (100%)	13/23 (57%)	0/2 (0%)
Mean GH<2 & IGF-1 nl.	14/58 (24%)	0/1 (0%)	2/3 (67%)	3/9 (33%)	0/3 (0%)	1/1 (100%)	10/23 (43%)	0/2 (0%)
Mean GH<1 & IGF-1 nl.	4/58 (7%)	0/1 (0%)	1/3 (33%)	1/9 (11%)	0/3 (0%)	0/1 (0%)	4/23 (17%)	0/2 (0%)

	20/30/40/60 n= 1 n (%)	Only 30 n= 10 n (%)	30/40 n= 4 n (%)	30/40/60 n= 1 n (%)	Total on LAR n= 58 n (%)
Mean GH<5	0/1 (0%)	7/10 (70%)	1/4 (25%)	0/1 (0%)	44/58 (76%)
Mean GH<2.5	0/1 (0%)	3/10 (30%)	0/4 (0%)	0/1 (0%)	26/58 (45%)
Mean GH<2	0/1 (0%)	3/10 (30%)	0/4 (0%)	0/1 (0%)	22/58 (38%)

Mean GH<1	0/1 (0%)	1/10 (10%)	0/4 (0%)	0/1 (0%)	7/58 (12%)
IGF-1 nl.	0/1 (0%)	4/10 (40%)	0/4 (0%)	0/1 (0%)	26/58 (45%)
Mean GH<5 & IGF-1 nl.	0/1 (0%)	4/10 (40%)	0/4 (0%)	0/1 (0%)	26/58 (45%)
Mean GH<2.5 & IGF-1 nl.	0/1 (0%)	3/10 (30%)	0/4 (0%)	0/1 (0%)	22/58 (38%)
Mean GH<2 & IGF-1 nl.	0/1 (0%)	3/10 (30%)	0/4 (0%)	0/1 (0%)	19/58 (33%)
Mean GH<1 & IGF-1 nl.	0/1 (0%)	1/10 (10%)	0/4 (0%)	0/1 (0%)	7/58 (12%)

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.

Comment on above table:

Overall, after 6-7 LAR injections, mean GH was <5, <2.5, <2 and <1 ug/l and IGF-1 normal in 45%, 38%, 33% and 12% of patients, respectively.

The following table demonstrates that, on LAR, mean IGF-1 normalized in 59%, 85%, 86% and 100% 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:

6-7 Injections of Sandostatin LAR

Sandostatin LAR (mg):

	10/20 n (%)	10/20/30 n (%)	10/30 n (%)	10/30/40 n (%)	only 20 n (%)	20/30 n (%)	20/30/40 n (%)	20/30/40/60 n (%)
Mean GH<5 & IGF-1 nl.	0/1 (0%)	2/3 (67%)	4/6 (67%)	1/2 (50%)	1/1 (100%)	14/23 (61%)	0/0 (0%)	0/0 (0%)
Mean GH<2.5 & IGF-1 nl.	0/1 (0%)	2/2 (100%)	3/3 (100%)	0/0 (0%)	1/1 (100%)	13/16 (81%)	0/0 (0%)	0/0 (0%)
Mean GH<2 & IGF-1 nl.	0/1 (0%)	2/2 (100%)	3/3 (100%)	0/0 (0%)	1/1 (100%)	10/12 (83%)	0/0 (0%)	0/0 (0%)
Mean GH<1 & IGF-1 nl.	0/0 (0%)	1/1 (100%)	1/1 (100%)	0/0 (0%)	0/0 (0%)	4/4 (100%)	0/0 (0%)	0/0 (0%)

	Only 30 n (%)	30/40 n (%)	30/40/60 n (%)	Total n (%)
Mean GH<5 & IGF-1 nl.	4/7 (57%)	0/1 (0%)	0/0 (0%)	26/44 (59%)
Mean GH<2.5 IGF-1 nl.	3/3 (100%)	0/0 (0%)	0/0 (0%)	22/26 (85%)
Mean GH<2 & IGF-1 nl.	3/3 (100%)	0/0 (0%)	0/0 (0%)	19/22 (86%)

Mean GH<1 & IGF-1 nl.	1/1 (100%)	0/0 (0%)	0/0 (0%)	7/7 (100%)

None of the 16 patients who were partial responders to Sandostatin sq (mean GH >5 ug/l but ≥50% reduction in mean GH compared to wash-out and, in all these patients, IGF-1 was increased), suppressed their mean GH to < 5ug/l and normalized IGF-1 after receiving 6-7 injections of LAR. However, in 4/16 (25%), mean GH was suppressed below 5 ug/l on LAR.

In 8 patients, the dose of LAR was increased to 40 mg for at least 3 consecutive doses to allow for adequate assessment of the increased dose on the degree of hormonal control. Mean IGF-1 normalized in 1 of these patients and mean GH, which had been >5 ug/L, suppressed to <5 ug/L in 2 additional patients. Increasing the LAR dose to 60 mg in 2 patients, failed to affect mean GH or IGF-1 levels.

Symptoms of acromegaly:

Overall, the # of patients reporting individual signs/symptoms of acromegaly decreased from injection1 to injection 6, the final injection:

# of Patients Reporting Signs/Symptoms of Acromegaly, day 28 After Injection 1 and Day 28 After Injection 6:

	Injection 1	Injection 6
Headache	11/28	8/28
Fatigue	18/32	16/32
Perspiration	16/24	12/24
Joint pain	14/25	12/25
Carpal tunnel syndrome	9/19	6/19
Paresthesia	8/16	4/16

The mean composite score for signs/symptoms of acromegaly decreased from 4.2 at baseline to 1.2, 28 days after the last injection in this study.

SAFETY:

There were no deaths.

There was 1 premature discontinuation, patient #5110, who withdrew after the fifth LAR injection, for a transsphenoidal adenectomy. However, she received the sixth LAR study injection 1 month after her surgery.

There were 2 patients who had serious adverse events:

Patient #5110: see above

Patient #1002: hemicolectomy secondary to intestinal obstruction from a cecal volvulus. The event occurred after administration of the second LAR injection and was assessed by the investigator as not related to LAR.

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

Any event:		40 (69%)
GI:		34 (59%)
	Abdominal pain: 23	
	Diarrhea 24	
	Flatulence 15	
	Nausea 8	
	Dyspepsia 5	
	Constipation 4	
	Vomiting 2	

1 each: tenesmus , eructation, discolored feces, gastritis, gastroenteritis, ulcerative stomatitis, gingivitis and mouth dry.

Note: none appeared to be dose-dependent and the vast majority were mild-moderate in severity and they tended to decrease in prevalence as the study progressed.

Nervous system: 17 (29%)

(most commonly reported were cramps and headache. Cramps were possibly-probably related to LAR in 8/8 patients. Note: dizziness was possibly related to LAR in ½ patients)

Skin and appendages: 9 (16%)

(most commonly reported were alopecia and sweating increased. Alopecia was probably related to LAR in 6/6 patients. Note: pruritis was possibly related to LAR in ½ patients)

Musculo-skeletal system: 8 (14%)

(most commonly reported was myalgia which was possibly related to LAR in ¼ patients)

Psychiatric: 8 (14%)

(most commonly reported was somnolence and nervousness. Somnolence was probably related to LAR in ¼ patients and nervousness in 2/2. Note: anxiety and insomnia were possibly related to LAR in 1/1 and ½ patients, respectively)

Body as a whole: 6 (10%)

(most commonly reported were fatigue and influenza-like symptoms)

Female reproductive 3 (5%)

(lactation, leukorrhea and menorrhagia)

Resistance mechanism: 3 (5%)

(viral infection)

Tachycardia: 2 (3%)

Anemia: 2 (3%)

1 each: Hypoglycemia (probably related to LAR), dyspnea (probably related to LAR), cystitis, flushing, abnormal lacrimation and lymphadenopathy.

Injection site disorders:

Pain at the injection site was reported in 19 (33%) of patients.
Mild rash and moderate swelling was reported by 1 patient.

Vital signs:

There were no clinically relevant changes.

Physical exam:

None were of clinical significance.

Hematology and biochemistry:

Reduced hematocrit was reported in 13 patients (22%), due to frequent blood sampling.

Clinically notable decrease in wbc (to levels ≤ 2.8) occurred in 1 patient, #4006. Baseline wbc was low which decreased at the end of study 202-E-00 and at the end of this extension.

There were 5 patients in whom serum glucose levels were above the expanded limits of normal (i.e. >138 mg/dl) but was clinically notable (> 250 mg/dl) in only 1 (#1002). Of these 5 patients, baseline glucose was normal in only 1 patient: #5102. In this patient, baseline glucose was . and reached at the end of this study. CHECK IF #5102 WAS A DIABETIC

In 2 patients, there was an isolated elevation in SGPT: #'s 5006 in whom baseline SGPT was and reached . at the end of the study and #5110 with normal baseline which increased to on LAR. No explanation was available.

In 3 patients, there was an increase in total bilirubin above the expanded normal limit of 1.15 mg/dl and it was clinically notable (i.e. ≥2 mg/dl) in 1 of these patients. In 2 of the patients (#'s 5009 and 5012), the baseline bilirubin was normal but increased on LAR. In the third patient (#5107), baseline bilirubin was high but increased further on LAR and was associated with gallbladder sediment and hypochondrial pain.

Elevations in HbA_{1C} above normal was observed in 6 patients (#'s 1001, 1002, 1004, 1005, 1007 and 2003). In 2 of these patients (#'s 1002 and 1005- both diabetics), the elevation was above the expanded normal limit (i.e. >6.6%) and was clinically notable in 1 (>8.5%). Baseline HbA_{1C} was elevated in all these patients except one, #2003, who had no baseline value.

Thyroid function tests:

No consistent trends of change were noted in any patient, nor were there any clinically notable changes.

Gallbladder Ultrasound (note: none of the following patients were on ursodeoxycholic acid at the time these abnormalities occurred):

Newly occurring or worsening abnormalities in patients with normal baseline:

a) in patients with normal baseline:

Gallstones/microlithiasis (+/- also with sediment, sludge, dilatation): 1 patient (#3001)
Sediment without stones (+/- also with dilatation): 2 patients (#'s 5113 and 5123)
Sludge without stones or sediment (+/- also with dilatation): 2 patients (#'s 1002 and 4001)
Dilatation only: 1 patient (# 5120)
Symptoms: 0

Newly occurring or worsening abnormalities in patients with abnormal baseline:

Gallstones/microlithiasis (+/- also with sediment, sludge, dilatation): 3 (# 5002, 5006, 5011)
Sediment without stones (+/- also with dilatation): 4 (#'s 5009, 5103, 5109 and 5118)
Sludge without stones or sediment (+/- also with dilatation): 0
Dilatation only: 0
Biliary symptoms: 0

Total of newly occurring or worsening gallbladder abnormalities in patients not on bile acid dissolution agents for study 202-E-01:

Stones/microlithiasis (+/- also with sediment, sludge, dilatation): 4/58 (7%)
(#'s 3001, 5002, 5006, 5011)
Sediment/sludge without stones (+/- also with dilatation): 8/58 (14%)
(#'s 5113, 5123, 1002, 4001, 5009, 5103, 5109 and 5118)
Dilatation only: 1 (2%)
(#5120)
Biliary symptoms: 0/58 (0%)

SMSC 202-E-02:

A phase 2, second open extension of 202-E-00 and of 12 months duration. This extension was conducted in 5 centers in Denmark, Romania, Holland and the U.K.

57 of the 58 patients who completed 202-E-01 participated in this second extension (the one patient who did not was patient #3003 in whom mean GH was and IGF-1 was normal on sq and, on LAR in 201-E-01, mean GH was 1.01 ug/L and IGF-1 was normal). An additional 5 patients were recruited into this second extension (#'s 1010, 1011, 1012, 1013 and 1015). Mean GH on Sandostatin sq was <5 ug/L in these 5 patients.

Dose and dosing interval:

First LAR injection:

The first dose was to be administered 28 days after the last dose in 202-E-01. The first dose in the second extension was to be the same as the final dose administered in 202-E-01.

2nd-12th LAR injections:

The dose was to be titrated between 10-40 mg with the goal of maintaining mean GH <5 ug/L. The dose was to be increased by 10 mg if mean GH was >5 ug/L. The dose was to be reduced in 10 mg steps if serum mean GH was consistently <1 ug/L during a 3 month period. The dosing interval was generally 28 days, or. exceptionally, 42 days.

Efficacy:

Primary: mean 8-hr. serum GH

Secondary: mean IGF-1 levels and signs/symptoms of acromegaly (which were rated on a 5- point scale ranging from 0= absent to 4= severe and incapacitating).

Each efficacy parameter was assessed at the end of the dosing interval after each LAR injection.

Safety:

Physical exam, vital signs, hematology and biochemistry screen and OGTT were performed at 6 month intervals;

HbA_{1c} (centers 1-3 only) was measured at 6 month intervals;

GB ultrasound and TFTs (serum TSH, total and free T3 and T4) at ~3 month intervals.

RESULTS:

Of the 62 patients who participated, a total of 45 patients had participated in 202-E-00 and a total of 57 patients had participated in 202-E-01. An additional 5 patients were recruited into this extension. Of these 62 patients, 46 were good responders (mean GH <5 ug/L) to sq and 16 were partial responders.

Key demographics: 38 F and 24 M with mean age of 47 yrs.

Dose of LAR administered at any injection over the time course of the study:

:

The majority of patients received doses of 20 or 30 mg LAR at each injection. Although only doses between 10-40 mg were to be administered, in 7 patients, doses of 50-60 mg LAR were given. However, in 2 of these 7 patients, only the first dose administered exceeded that specified in the protocol, i.e. 40 mg.

15 patients (24%) received doses between 40-60 mg at any time point in the study. In 4 of these 15 patients, only the first dose was 40 mg, thereafter, 30 mg was maintained to the end of the study. Therefore, in only 11 patients (18%), were doses of 40-60 mg employed to achieve hormonal control.

Mean serum octreotide levels:

After doses of 20 or 30 mg LAR, mean and median levels of serum octreotide remained stable throughout the duration of the study (the mean serum octreotide levels after LAR injections 1-12 ranged from, by dose,:

On 20 mg (n= 19)
On 30 mg (n= 31)
On 40 mg (n= 8).
On 60 mg (n= 2)

Mean GH (ug/L) and IGF-1 (ug/L) with 18-19 injections of LAR in Patients who Participated in 202-E-00 and/or 2020-E-01 and/or 202- E-02 (18 LAR injections: n= 12, 19 LAR injections: n= 45):

Sandostatin LAR (mg):

	10/20 n=1 n (%)	10/20/30 n= 9 n (%)	10/30 n= 2 n (%)	10/30/40 n= 3 n (%)	10/30/40/50/60 n= 1 n (%)	only 20 n= 1 n (%)	20/30 n= 25 n (%)
Mean GH<5	1/1 (100%)	8/9 (89%)	1 / 2 (50%)	1/3 (33%)	1/1 (100%)	1/1 (100%)	25/25 (100%
Mean GH< 2.5	1/1 (100%)	5/9 (56%)	0/2 (0%)	0/3 (0%)	0/1 (0%)	1/1 (100%)	15/25 (60%
Mean GH<2	1/1 (100%)	4/9 (44%)	0/2 (0%)	0/3 (0%)	0/1 (0%)	1/1 (100%)	12/25 (48%)
Mean GH<1	0/1 (0%)	1/9 (11%)	0/2 (0%)	0/3 (0%)	0/1 (0%)	0/1 (0%)	4/25 (16%
IGF-1 normal	1/1 (100%)	5/9 (56%)	1/2 (50%)	0/3 (0%)	1/1 (100%)	1/1 (100%)	15/25 (60%
Mean GH<5 & IGF-1 nl.	1/1 (100%)	5/9 (56%)	1/2 (50%)	0/3 (0%)	1/1 (100%)	1/1 (100%)	15/25 (60%
Mean GH<2.5 & IGF-1 nl.	1/1 (100%)	5/9 (56%)	0/2 (0%)	0/3 (0%)	0/1 (0%)	1/1 (100%)	13/25 (52%
Mean GH<2 & IGF-1 nl.	1/1 (100%)	4/9 (44%)	0/2 (0%)	0/3 (0%)	0/1 (0%)	1/1 (100%)	10/25 (40%
Mean GH<1 & IGF-1 nl.	0/1 (0%)	1/9 (11%)	0/2 (0%)	0/3 (0%)	0/1 (0%)	0/1 (0%)	4/25 (16%

	20/30/40 n= 3 n (%)	20/30/40/60 n= 1 n (%)	only 30 n= 6 n (%)	30/40 n= 2 n (%)	30/40/60 n= 3 n (%)	Total on LAR n= 57 n (%)
Mean GH<5	1/3 (33%)	0/1 (0%)	3/6 (50%)	1 /2 (50%)	1/3 (33%)	44/57 (77%)
Mean GH<2.5	1/3 (33%)	0/1 (0%)	1/6 (17%)	0/2 (0%)	0/3 (0%)	24/57 (42%)
Mean GH<2	0/3 (0%)	0/1 (0%)	1/6 (17%)	0/2 (0%)	0/3 (0%)	19/57 (33%)

Mean GH<1	0/3 (0%)	0/1 (0%)	0/6 (0%)	0/2 (0%)	0/3 (0%)	5/57 (9%)
IGF-1 normal	1/3 (33%)	0/1 (0%)	1/6 (17%)	0/2 (0%)	0/3 (0%)	26/57 (46%)
Mean GH<5 & IGF-1 nl.	1/3 (33%)	0/1 (0%)	1/6 (17%)	0/2 (0%)	0/3 (0%)	26/57 (46%)
Mean GH<2.5 & IGF-1 nl.	1/3 (33%)	0/1 (0%)	1/6 (17%)	0/2 (0%)	0/3 (0%)	22/57 (39%)
Mean GH<2 & IGF-1 nl.	0/3 (0%)	0/1 (0%)	1/6 (17%)	0/2 (0%)	0/3 (0%)	17/57 (30%)
Mean GH<1 & IGF-1 nl.	0/3 (0%)	0/1 (0%)	0/6 (0%)	0/2 (0%)	0/3 (0%)	5/57 (9%)

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.

Comment on above table:

Overall, after 18-19 injections of LAR, mean GH was <5, <2.5, <2 and <1 ug/l and IGF-1 normal in 46%, 39%, 30% and 9% of patients, respectively.

The following table demonstrates that, on LAR, mean IGF-1 normalized in 59%, 92%, 90% and 100% 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:

18-19 Injections of Sandostatin LAR:

Sandostatin LAR (mg):

	10/20 n (%)	10/20/30 n (%)	10/30 n (%)	10/30/40 n (%)	10/30/40/50/60 n (%)	only 20 n (%)	20/30 n (%)
Mean GH<5 & IGF-1 nl.	1/1 (100%)	5/8 (63%)	1/1 (100%)	0/1 (0%)	1/1 (100%)	1/1 (100%)	15/25 (60%)
Mean GH<2.5 & IGF-1 nl.	1/1 (100%)	5/5 (100%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (100%)	13/15 (87%)
Mean GH<2 & IGF-1 nl.	1/1 (100%)	4/4 (100%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (100%)	10/12 (83%)
Mean GH<1 & IGF-1 nl.	0/0 (0%)	1/1 (100%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	4/4 (100%)

	20/30/40 n (%)	20/30/40/60 n (%)	only 30 n (%)	30/40 n (%)	30/40/60 n (%)	Total n (%)
Mean GH<5 & IGF-1 nl.	1/1 (100%)	0/0 (0%)	1/3 (33%)	0/1 (0%)	0/1 (0%)	26/44 (59%)
Mean GH<2.5 & IGF-1 nl.	1/1 (100%)	0/0 (0%)	1/1 (100%)	0/0 (0%)	0/0 (0%)	22/24 (92%)
Mean GH<2 &	0/0	0/0	1/1	0/0	0/0	17/19

IGF-1 nl.	(0%)	(0%)	(100%)	(0%)	(0%)	(90%)
Mean GH<1 & IGF-1 nl.	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	5/5 (100%)

In only 6 patients in this extension was the LAR dose increased to 40-60 mg for at least 3 consecutive dosing administrations to allow an assessment for the affect of the increased dose on the patient's degree of hormonal control (#'s 1001, 1004, 1005, 1006, 1010 and 1011). In only 1 of these 6 patients, was an effect seen: mean IGF-1 normalized on 60 mg in #1004.

In another 6 patients (#'s 3001, 3002, 4001, 4003, 4005 and 4006), LAR was administered at q 42 day intervals for the entire study in 5 and for the first half of the study in 1. Using a 42 day dosing interval, mean GH was <5 ug/L in 6/6 patients, <2.5 ug/L in 4/6, <2 ug/L in 4/6 and <1 ug/L in 0/6. Mean IGF-1 was normalized in 5 of these 6 patients.

Of the 16 patients who were partial responders to Sandostatin sq, only 1 suppressed their mean GH and IGF-1 on LAR during the 12 months of the study. In this patient (#5110),

. In 4 additional patients, although mean GH suppressed to <5 ug/L on LAR, (on LAR, mean GH <5 ug/l in 4; mean GH <2.5 ug/l in 1: 2.45 ug/L), IGF-1 remained elevated.

Symptoms of acromegaly:

Number of Patients Reporting Symptomsof Acromegaly: Day 28 After Injection 1 vs. Injection 12:

Symptom	Injection 1	Injection 12
Headache	6/30	6/30
Fatigue	22/37	15/37
Perspiration	15/28	7/28
Joint pain	11/25	11/25
Carpal tunnel syndrome	9/22	7/22
Paresthesia	5/18	6/18

The mean composite score for signs/symptoms of acromegaly decreased from 4.2 at baseline to 1.1, 28 days after the last injection in this study.

SAFETY:

There were no deaths.

There were no premature discontinuations.

There were 6 serious adverse events. None were assessed by the investigators as related to LAR:

Patient #2101: seizures, vomiting and Addisonian crisis with hypotension 11 days after the 9th injection in a 45 yr. old M with panhypopituitarism and a history of seizures.

Patient #4003: gash on the head after being knocked over by a cyclist.

Patient #4006:after the 5th injection, mild intermenstrual bleeding for which this 51 yr. old F received dilatation and curretage.

Patient #5101: hysterectomy on the day of the 4th injection in a 40 yr. old F with a hx. of metorrhagia due to fibroids.

Patient #5110: acute hepatitis B one month after the first injection in a 14 yr. old F.

Patient #5121: CSF rhinorrhea two days after the sixth injection in a 44 yr. old F.

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: 46 (74%)

GI: 30 (48%)

Abdominal pain: 16
Diarrhea: 15
Flatulence: 6
Nausea: 3
Vomiting: 3
Feces discolored: 3
Dyspepsia: 3

1 each of the following: anus disorder, gastroenteritis, GE reflux, rectal hemorrhage, gingivitis, and salivary duct obstruction.

These GI AEs did not appear to be dose dependent and the majority were mild to moderate in severity.

Body as a whole: 17 (27%)
(most commonly reported were influenza-like symptoms and fatigue; peripheral edema in 2/3 patients was reported as probably related to LAR)

Skin and appendages: 15 (24%)
(most commonly reported was alopecia in 12 patients: probably related to LAR in 11; note: erythematous rash was reported in 1 patient and was probably related to LAR)

Central and peripheral nervous system: 12 (19%)
(most commonly reported was headache: possibly or probably related to LAR in 2/7; cramps: possibly related in 4/4 and dizziness in ½ patients)

Liver and biliary systems disorders: 9 (15%)
(cholelithiasis: 5; GB disorder: 4)

Musculo-skeletal system: 5 (8%)
(arthralgia: possibly related to LAR in 1/3, arthropathy, myalgia: probably related to LAR in ½ patients)

Red blood cell disorders: 8 (13%)
(anemia in 8 patients)

Injection site disorders: 8 (13%)
(injection site pain or reaction)

Psychiatric: 7 (11%)
(most common was somnolence: probably related to LAR in 1/4 patients)

Resistance mechanism: 6 (10%)
(most common was infection)

Respiratory system disorders: 6 (10%)
(most common was URI)

CV disorders: 4 (6%)
(per investigators, all of these were unlikely to be related to LAR:
circulatory failure: 1; hypotension: 1; angina pectoris: 2)

Urinary system disorders: 3 (5%)
(cystitis in 2 patients and polyuria in 1)

2 patients for the following:
Hearing and vestibular disorders (deafness in 1and ear discharge in 1- not related to LAR in either case)

1 patient each for the following adverse events:
pituitary insufficiency, palpitation, hyperglycemia (possibly related to LAR), uterine fibroid, epistaxis, intermenstrual bleeding, menopause, orchitis, conjunctivitis and leukopenia)possibly related to LAR.

Injection site disorders:

Pain:	n= 10	
Swelling:	n= 8	
Rash:	n= 1	

Vital signs:
No clinically relevant changes were observed.

Physical exam:
None of the new or worsening abnormalites were considered to be related to LAR.

Hematology and biochemistry:
Anemia was reported as an AE in 8 patients and was attributed to frequent blood sampling.

Reduced leukocytes: 2 patients. In only 1 of these patients, #4006, was the decrease in wbc clinically notable This latter patient, #4006, had a history of long-standing neutropenia for which she attended hematology clinic. Baseline wbc was low and reached a nadir of at study endpoint.

Elevated fasting glucose: 9 patients. In 3 of these 9 patients, baseline glucose was normal. None were clinically notable (i.e. >250 mg/dl or >13.9 mmol/l).

Elevated SGOT: 3 patients. None were clinically notable (i.e. $\geq$ 3 x ULN).

Elevated SGPT: 6 patients. None were clinically notable (i.e. $\geq$ 3 x ULN).

Elevated total bilirubin: 8 patients. In 3 of these 8 patients, the elevation in total bilirubin was clinically notable (i.e. $\geq$2.0 mg/dl or $\geq$: 34.2 umol/l):

Patient #5012 with normal baseline bilirubin , which increased to GB ultrasound was normal as were liver transaminase levels;

Patient #5107 with elevated baseline bilirubin , which had peaked at in study 2020-E-00 and had been associated with gallbladder sediment and mild right hypochondrial pain. In 202-E-00, the GB ultrasound was normal and the total bilirubin which was at the sixth month time point, had normalized by the end of this study.

Patient #4005 with an elevated baseline . Total bilirubin levels were in this study. The patient was asymptomatic and the gallbladder ultrasounds were normal.

Elevated HbA_{1C}: 6 patients (note: HbA_{1C} was measured in 18 patients total). The elevation was clinically notable (>8.5%) in 2:

Patient # 1002 had a history of diabetes mellitus and was on insulin. Baseline was 7.6% which increased to 10.6%.

Patient #3002 had a history of type II diabetes and had been on glibenclamide for the preceeding 12 years. At the end of this study, the HbA_{1C} was notably increased at

OGTT:

21 (34%) of patients had impaired glucose tolerance. 2 of these patients had known diabetes mellitus.

In 19 (45%) of the patients, serum GH levels remained below 2 ng/ml or were suppressed to below 2 ng/ml during the OGTT.

Thyroid function tests:

28 (45%) of the patients were receiving concomitant thyroid hormone therapy. A total of 50 patients were followed for 12 mos. Although fluctuating abnormalities of TFTs were found throughout the study, no consistent or progressive pattern of new or worsening abnormalities was apparent during the 12 month study period.

Gallbladder ultrasound (GB US):

Abnormalities in patients with normal baseline US:

Gallstones/microlithisis (+/- sediment/sludge/dilatation):	3 (#'s 5102, 5115 and 5123)
Sediment and/or sludge (+/- dilatation):	2 (#'s 1010 and 1015)
Dilatation/wall thickening only:	2 (#'s 1005 and 4008)
Biliary symptoms:	0

New or worsening abnormalities in patients with abnormal baseline US:

Gallstones/microlithiasis (+/- sediment/sludge/dilatation):	3 (#5118, 5009 and 5112)
Sediment and/or sludge (+/- dilatation):	3 (#'s 1011, 5007 and 5101)
Dilatation/wall thickening only:	0
Biliary symptoms:	0

Per vol. 45, page 52, 15 pts. with octreotide antibodies.

SMSC202-E-03:

A phase 2, third open extension of 202-E-00 and of 9 months duration. This extension was conducted in 5 centers in Denmark, Romania, Holland and the U.K.

61 of the 62 patients who completed 202-E-02 were enrolled in this trial. Patient #1011, who participated in 202-E-02, did not enter this study because it was decided to treat the microadenoma surgically. In this patient, the mean GH was >2.5 but <5 ug/l and the mean IGF-1 remained elevated after 12 injections of LAR, administered at doses of 30-60 mg, in the previous study.

Dose and dosing interval:

The first dose in this extension was generally administered 28 days, exceptionally, 42 days, after the final injection in 202-E-02. The dose administered ranged from 10-40 mg, and, exceptionally 60 mg, with the goal of maintaining mean GH <5 ug/l. The LAR dose was to be increased by 10 mg if mean GH was >5 ug/l and decreased by 10 mg if mean GH at 3 consecutive visits was <1 ug/l. However, in some cases, the LAR dose was adjusted although no change was required by the protocol. Dosing interval throughout the study was generally q 28 days, and was, exceptionally, q 42 days. (Note: for a 40 mg dose, the suspensions for two 20 mg doses were drawn into the syringe).

Efficacy:

Primary: mean 8 hr. serum GH was measured either 28 days or 42 days, depending on the dosing interval, after the third, sixth and ninth injections.

Secondary: mean IGF-1 (same time points as for GH) and signs/symptoms of acromegaly (after each injection).

PK: serum octreotide levels after the third, sixth and ninth injections.

Safety:

Physical exam, vital signs, hematology and biochemistry screen, HbA_{1c}, OGGT, TFTs (serum TSH, total and free T3 and T4) and GB ultrasound at visits 6 and 9 (the final visit).

RESULTS:

Of the 61 patients who participated, 38 were F and 23 were M, with a mean age of 48 yrs. A total of 45 patients had participated in 202-E-00, a total of 57 had participated in 202-E-01 and a total of 61 patients had participated in 202-E-02. Of these 61 patients, 45 were good responders to Sandostatin sq (mean GH < 5 ug/l) and 16 were partial responders (mean GH on sq not < 5 ug/l but was reduced by 50% compared to wash-out).

Dose of LAR administered at any injection over the time course of the study:

10 mg: n= 4 patients
20-30 mg: n= 52 patients (85%)
40 mg: n= 4 patients
60 mg: n= 2 patients

The majority of the patients remained on the same dose throughout the study.

Mean serum octreotide levels:

10 mg
20 mg
30 mg
40 mg
60 mg

Mean GH (ug/l) and IGF-1 (ug/l) in 55 patients who received 27-28 injections of LAR (12 patients received 27 injections and 43 patients received 28 injections):

Sandostatin LAR (mg):

	10/20 n=1 n (%)	10/20/30 n= 9 n (%)	10/30 n= 2 n (%)	10/30/40 n= 3 n (%)	10/30/40/50/60 n= 1 n (%)	only 20 n= 1 n (%)	20/30 n= 23 n (%)
Mean GH<5	1/1 (100%)	8/9 (89%)	1 / 2 (50%)	1/3 (33%)	1/1 (100%)	1/1 (100%)	23/23 (100%
Mean GH< 2.5	1/1 (100%)	5/9 (56%)	0/2 (0%)	0/3 (0%)	0/1 (0%)	1/1 (100%)	13/23 (57%)
Mean GH<2	1/1 (100%)	5/9 (56%)	0/2 (0%)	0/3 (0%)	0/1 (0%)	1/1 (100%)	10/23 (44%)
Mean GH<1	0/1 (0%)	2/9 (22%)	0/2 (0%)	0/3 (0%)	0/1 (0%)	0/1 (0%)	2/23 (9%)
IGF-1 normal	1/1 (100%)	5/9 (56%)	1 /2 (50%)	0/3 (0%)	1/1 (100%)	1/1 (100%)	14/23 (61%
Mean GH<5 & IGF-1 nl.	1/1 (100%)	5/9 (56%)	1/2 (50%)	0/3 (0%)	1/1 (100%)	1/1 (100%)	14/23 (61%
Mean GH<2.5 & IGF-1 nl.	1/1 (100%)	5/9 (56%)	0/2 (0%)	0/3 (0%)	0/1 (0%)	1/1 (100%)	12/23 (52%
Mean GH<2 & IGF-1 nl.	1/1 (100%)	5/9 (56%)	0/2 (0%)	0/3 (0%)	0/1 (0%)	1/1 (100%)	9/23 (39%
Mean GH<1 & IGF-1 nl.	0/1 (0%)	2/9 (22%)	0/2 (0%)	0/3 (0%)	0/1 (0%)	0/1 (0%)	2/23 (9%

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	20/30/40 n= 3 n (%)	20/30/40/60 n= 1 n (%)	only 30 n= 6 n (%)	30/40 n= 2 n (%)	30/40/60 n= 3 n (%)	Total on LAR n= 55 n (%)
Mean GH<5	1/3 (33%)	0/1 (0%)	3/6 (50%)	1 /2 (50%)	1/3 (33%)	42/55 (76%)
Mean GH<2.5	1/3 (33%)	0/1 (0%)	1/6 (17%)	0/2 (0%)	0/3 (0%)	22/55 (40%)
Mean GH<2	0/3 (0%)	0/1 (0%)	1/6 (17%)	0/2 (0%)	0/3 (0%)	18/55 (33%)
Mean GH<1	0/3 (0%)	0/1 (0%)	0/6 (0%)	0/2 (0%)	0/3 (0%)	4/55 (7%)
IGF-1 normal	1/3 (33%)	0/1 (0%)	1/6 (17%)	0/2 (0%)	0/3 (0%)	25/55 (46%)
Mean GH<5 & IGF-1 nl.	1/3 (33%)	0/1 (0%)	1/6 (17%)	0/2 (0%)	0/3 (0%)	25/55 (46%)
Mean GH<2.5 & IGF-1 nl.	1/3 (33%)	0/1 (0%)	1/6 (17%)	0/2 (0%)	0/3 (0%)	21/55 (38%)
Mean GH<2 & IGF-1 nl.	0/3 (0%)	0/1 (0%)	1/6 (17%)	0/2 (0%)	0/3 (0%)	17/55 (31%)
Mean GH<1 & IGF-1 nl.	0/3 (0%)	0/1 (0%)	0/6 (0%)	0/2 (0%)	0/3 (0%)	4/55 (7%)

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.

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Comment on above table:

Overall, after 27-28 injections of LAR, mean GH was <5, <2.5, <2 and <1 ug/l and IGF-1 normal in 46%, 38%, 31% and 7% of patients, respectively.

The following table demonstrates that, on LAR, mean IGF-1 normalized in 60%, 95%, 94% and 100% 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:

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27-28 Injections of Sandostatin LAR:

Sandostatin LAR (mg):

	10/20 n (%)	10/20/30 n (%)	10/30 n (%)	10/30/40 n (%)	10/30/40/50/60 n (%)	only 20 n (%)	20/30 n (%)
Mean GH<5 & IGF-1 nl.	1/1 (100%)	5/8 (63%)	1/1 (100%)	0/1 (0%)	1/1 (100%)	1/1 (100%)	14/23 (61%)
Mean GH<2.5 & IGF-1 nl.	1/1 (100%)	5/5 (100%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (100%)	12/13 (92%)
Mean GH<2 &	1/1	5/5	0/0	0/0	0/0	1/1	9/10

IGF-1 nl.	(100%)	(100%)	(0%)	(0%)	(0%)	(100%)	(90%)
Mean GH<1 & IGF-1 nl.	0/0 (0%)	2/2 (100%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	2/2 (100%)

	20/30/40 n (%)	20/30/40/60 n (%)	only 30 n (%)	30/40 n (%)	30/40/60 n (%)	Total n (%)
Mean GH<5 & IGF-1 nl.	1/1 (100%)	0/0 (0%)	1/3 (33%)	0/1 (0%)	0/1 (0%)	25/42 (60%)
Mean GH<2.5 & IGF-1 nl.	1/1 (100%)	0/0 (0%)	1/1 (100%)	0/0 (0%)	0/0 (0%)	21/22 (95%)
Mean GH<2 & IGF-1 nl.	0/0 (0%)	0/0 (0%)	1/1 (100%)	0/0 (0%)	0/0 (0%)	17/18 (94%)
Mean GH<1 & IGF-1 nl.	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	4/4 (100%)

There were 6 patients who participated in this study but they are not included in the above table because they received <27 LAR injections (note: 2 of these 6 patients received 26 injections and 4 received 21 injections of LAR). The mean GH and IGF-1 control in these 6 patients was:

Mean GH: < 5 ug/l: n= 6, <2.5: n= 4, <2: n= 3, <1: n= 1

IGF-1 nl: n= 3

Mean GH<5 ug/l & IGF-1 nl: n= 3, GH<2.5 & IGF-1 nl.: n= 3, GH<2 & IGF-1 nl.: n= 2. GH <1 & IGF-1 nl.: n= 1

In only 4 patients was the dose of LAR 40-60 mg for at least 3 consecutive dosing administrations to allow an assessment for the affect of the increased dose on the patient's degree of hormonal control (#'s 1001, 1004, 1005, 1006). In only 1 of these 4 patients, was an effect seen: mean IGF-1 normalized on 60 mg in #1001.

In another 5 patients (#'s 3001, 3002, 4001, 4003 and 4006), LAR was administered at q 42 day intervals for the entire duration of time the patient was enrolled in the study: 2 patients received 6 injections and 3, 9 injections. Mean GH was <2 ug/L in all; <1 ug/L in 2. Mean IGF-1 was normalized in all.

Of the 16 patients who were partial responders to Sandostatin sq, only 2 suppressed their mean GH to <5 ug/L and normalized IGF-1 on LAR during the 9 months of the study. In one patient (#5110)

In the other patient, #2003

. In 6 additional patients, although mean GH suppressed to <5 ug/L on LAR, (on LAR, mean GH >5 ug/L in 6, <2.5 ug/l in 2 and <2 ug/l in none), IGF-1 remained elevated.

Symptoms of acromegaly:

The mean composite score for signs/symptoms of acromegaly decreased from 4.2 at baseline to 1.5, 28 days after the last study injection.

SAFETY:

There were no deaths.

There were no premature discontinuations due to adverse events.

5 patients experienced serious adverse events: