CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 21008

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY & BIOPHARMACEUTICS REVIEW

NDA 21-008/N-000	**SUBMISSION DATES: 29-MAY-98, 16-JUL-98, 31-JUL-98, 09-SEP-98, 19-OCT-98**
BRAND NAME:	**Sandostatin LAR® 10, 20, 30 mg**
GENERIC NAME:	**Octreotide acetate for IM injection**
REVIEWER:	**Robert M. Shore, Pharm.D.** **Xiaoxiong Wei, Ph.D.** **Raymond Miller, Ph.D. (Consultant)**
SPONSOR:	**Novartis,** **E. Hanover, NJ**
TYPE OF SUBMISSION:	**Modified formulation Code: 3P**

TERMS AND ABBREVIATIONS:

90%CI . ..... 90% confidence interval
AUCa-b ..... area under the plasma-concentration-time curve from time a to time b
BA .... bioavailability
Cmax... ..... maximum concentration
CV .... coefficient of variation
DMEDP ..... Division of Metabolic and Endocrine Drug Products
DPE-2.. ..... Division of Pharmaceutical Evaluation 2
GH, hGH ..... growth hormone
GnRH .. .. gonadotropin releasing hormone
IGF-1 ... . insulin-like growth factor-1
IM .... intramuscular
IV..... ..... intravenous
IVIVC... ..... in vitro-in vivo correlation
LAR .... long acting release
LH..... ..... leutinizing hormone
OCPB.. ..... Office of Clinical Pharmacology and Biopharmaceutics
PK/PD . ..... pharmacokinetic/pharmacodynamic

SC .... subcutaneous
SLS .... sodium lauryl sulfate

SYNOPSIS:

Octreotide (Sandostatin®) is currently approved in the US for SC and IV use. The sponsor seeks approval for a new IM formulation (LAR); therefore, the underlying question for this new product is one of equivalence to the currently marketed SC formulation. A PK/PD model was developed to compare the effect of SC and LAR administration on GH response over 27 months. The model used was found to be acceptable and demonstrated that GH suppression in Acromegalic patients is similar for the SC and LAR formulation. The LAR formulation was also found to have a durable effect on GH over 27 months with no signs of tolerance.

Sandostatin LAR® is proposed for intragluteal IM administration at four-week intervals. The proposed labeling indicates that patients must first receive Sandostatin® SC for at least 2 weeks before switching to a starting dose of 20 mg of the LAR product. After initiating LAR therapy, the dose will be titrated, if needed, to 10 mg or 30 mg, depending on clinical measures.

The results from an *in vivo* bioequivalence study comparing these two products indicated that they were similar in their release characteristics.

The dissolution specification originally proposed by the sponsor was deemed unacceptable. OCPB has decided that a 'tighter' interim specification can be accepted at this time; however, investigation into dissolution methods by the sponsor is ongoing and the interim specification will only be acceptable for 1 year from the date of NDA approval.

APPEARS THIS WAY
ON ORIGINAL

RECOMMENDATION:

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (OCPB/DPE-2) has reviewed NDA 21-008/N-000 submitted 29-MAY-98, 16-JUL-98, 31-JUL-98, 09-SEP-98, and 19-OCT-98. The overall Human Pharmacokinetic Section is acceptable to OCPB providing the sponsor accepts a Phase 4

This recommendation, comments (p. 25), and labeling comments (p. 25) should be sent to the sponsor as appropriate.

APPEARS THIS WAY
ON ORIGINAL

Table of Contents **Page**

Appendix 2. Study summaries 52

(Appendices and/or Attachments available from DPE-2 upon request, if not included)

BACKGROUND:

Octreotide is a cyclic octapeptide which exerts pharmacologic actions similar to the natural hormone somatostatin – it inhibits GH, glucagon, insulin, LH response to GnRH, serotonin, gastrin, vasoactive intestinal peptide, secretin, motilin, and pancreatic polypeptide. Octreotide is currently marketed in the US as the acetate salt (Sandostatin®) for SC or IV injection. It was approved in 1994 for the treatment of Acromegaly, excessive GH secretion. Sandostatin® was also approved in 1988 for the symptomatic treatment of carcinoid tumors and vasoactive intestinal peptide tumors (VIPomas), conditions characterized by excess secretion of bioactive substances which result in severe diarrhea, flushing and wheezing. Octreotide has a half-life of about 2 hours and requires dosing a day since it's activity is closely related to serum concentrations.

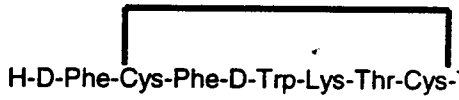
Sandostatin LAR® is a depot injection of octreotide acetate to be administered IM once a month – octreotide is slowly released continually as the in which the drug is hydrolyzes in the muscle. The LAR product is approved for use in a number of European countries to treat Acromegaly. As the LAR product represents a major benefit in patient convenience and compliance, this NDA was granted priority review status (3P) by DMEDP. The sponsor is seeking approval of LAR for the same three indications as Sandostatin® SC.

DRUG FORMULATION:

APPEARS THIS WAY

The chemical structure of octreotide is shown in Figure 1.

Figure 1: Chemical structure of octreotide, the active principle of Sandostatin LAR®



Molecular formula: $C_{49}H_{66}N_{10}O_{10}S_2 \bullet x\ C_2H_4O_2$ x = 1.4 to 2.5

APPEARS THIS WAY
ON ORIGINAL

Molecular weight: 1019.3 (free peptide)

Octreotide acetate is highly water soluble at acidic and physiological pH. The compound shows pK values of 7.02 and 10.15.

The LAR product will incorporate octreotide into a polymer matrix (poly(DL-lactide-co-glycolide); the slowly hydrolyzes *in vivo* releasing octreotide into the body at a constant rate.

The finished product Sandostatin LAR® consists of one vial of microspheres, two ampoules of vehicle, and an injection set consisting of syringe, two needles, and two swabs, assembled in a cardboard box. One ampoule of vehicle is intended for use with the microsphere product, which requires 2 mL , the other ampoule serves as reserve in case of breakage etc.

The composition of the finished drug product is shown in Table 1. The vehicle for reconstituting the microspheres prior to injection is manufactured as a liquid product. It consists of carboxymethyl cellulose, , mannitol, and water,

APPEARS THIS WAY

Table 1: Composition of Sandostatin LAR®

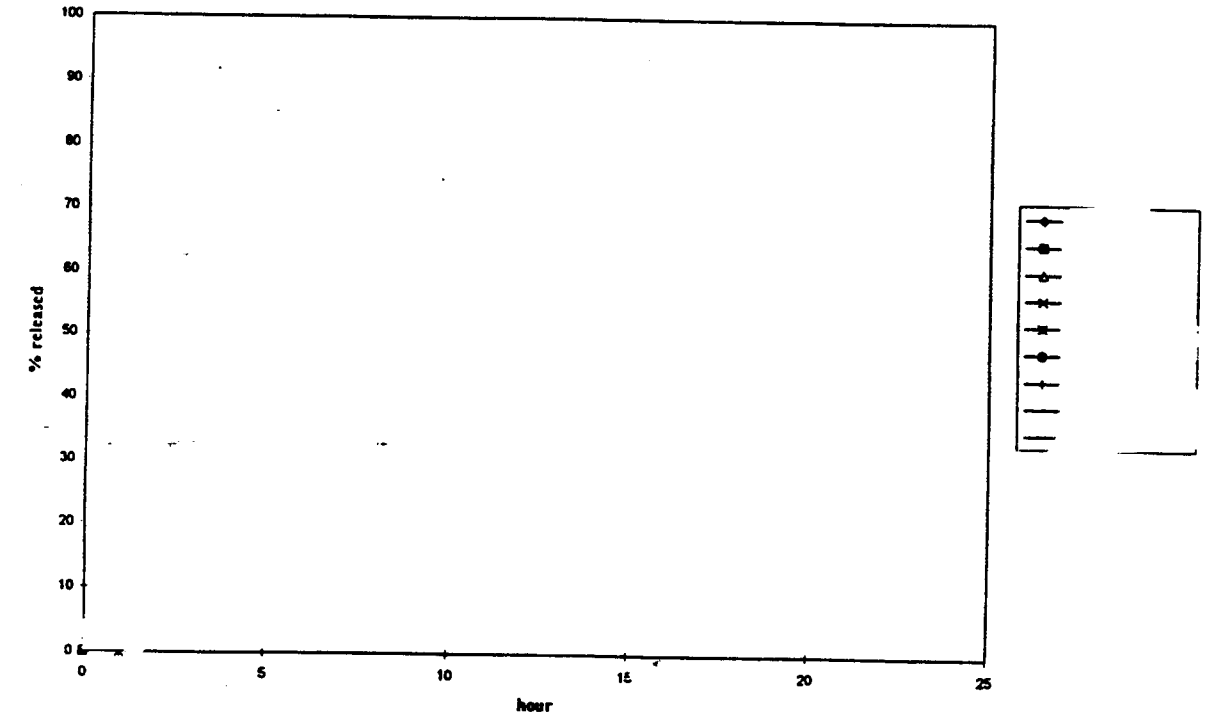
Ingredients	Sandostatin LAR®		
	10 mg	20 mg	30 mg
(% of total)			
Mannitol	41 mg	82 mg	123 mg
(% of total)			
Octreotide acetate	11.2 mg	22.4 mg	33.6 mg
(% of total)			
(% of total)			
Total fill weight (theoretical)			
Overage			
Actual fill weight			

The drug product for marketing is

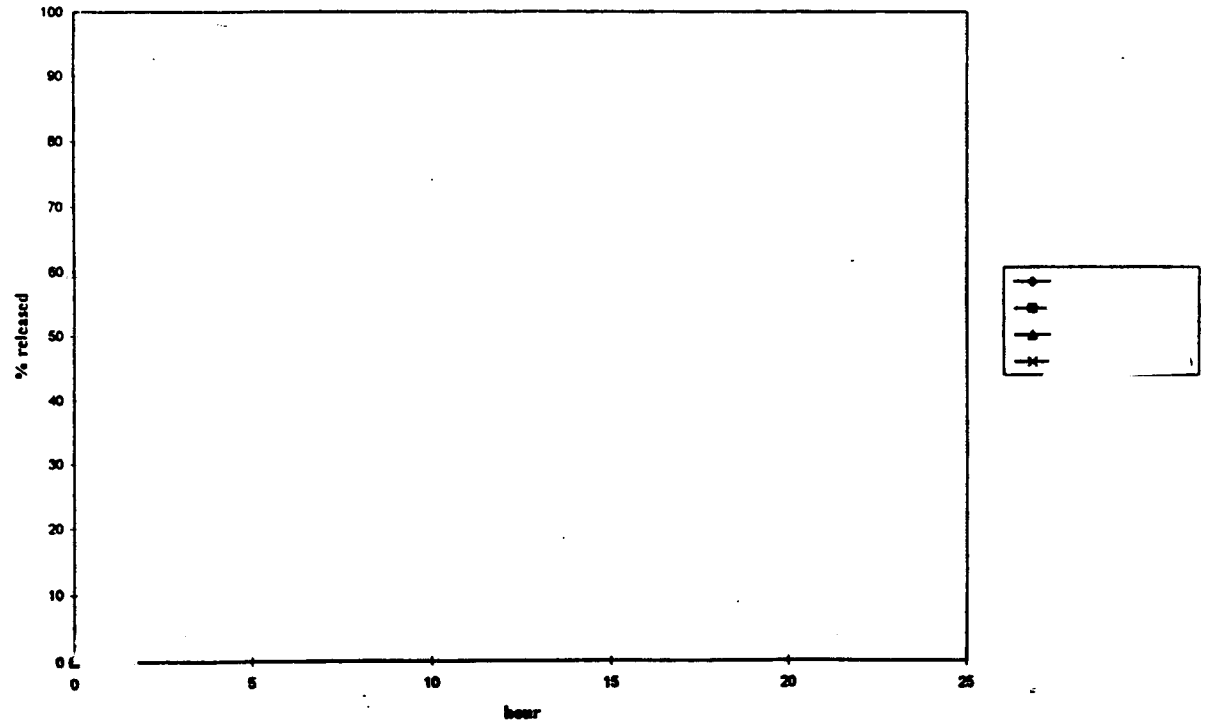
Drug product for clinical testing
Octreotide acetate, the pharmacologically active ingredient

DISSOLUTION:

Plot 1. Dissolution data

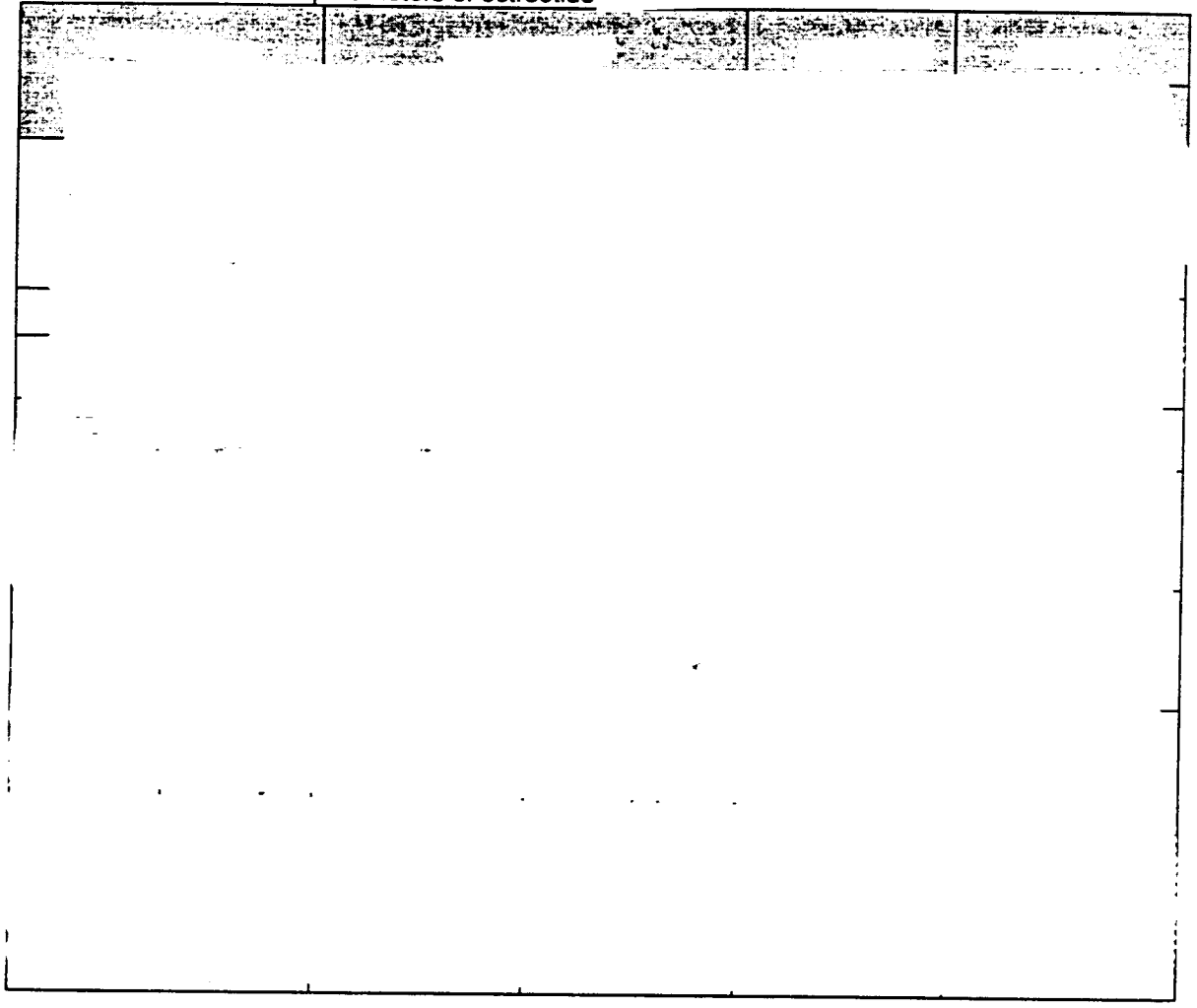


Plot 2. Dissolution data



ANALYTICAL METHODOLOGY:

Table 3: Performance parameters of octreotide



Reviewer's (Wei) comments:

The sponsor did adequate assessment on methods for determination of octreotide concentrations and adequate validation on kit for measurement of GH and for measurement of IGF-1.

Stability of Octreotide in Human Serum Samples:

Tables 4 and 5 show stability data for octreotide.

APPEARS THIS WAY
ON ORIGINAL

Table 4: Freeze/Thaw Stability Evaluation

Sample (n)	Freeze/Thaw cycles	%CV% (range)
7	4	3.83-42.3 [a]

[a] Only one sample had a CV of 42.3%. The CV 's of the 6 other samples fell between 3.83 to 18.3%.

Table 5: Long Term Stability Evaluation

Sample (n)	Time of measurement	Length of samples stored	CV% (range)
20	10 times	up to 23 months	4.96 to 38.6 [a]

[a] The samples with Octreotide concentrations below 200 pg/ml had relatively large CV (22.8 to 38.6%). The CV's of the rest of samples fell between 4.96 to 17.8%,

APPEARS THIS WAY
ON ORIGINAL

HUMAN PHARMACOKINETICS AND BIOAVAILABILITY STUDIES:

APPEARS THIS WAY
ON ORIGINAL

I. Bioavailability/Bioequivalence

APPEARS THIS WAY
ON ORIGINAL

A. Relative Bioavailability

Study E101 was a PK/BA analysis of Sandostatin® SC and single dose LAR in healthy subjects. Three subgroups of subjects received either a 3.0, 6.0, or 12.0 mg IM LAR (or matching placebo) injection. A bioavailability comparison of Sandostatin LAR to buffered acetate preparation was made 45 and 47 days after LAR injection. Each subject received TID SC (subcutaneous) injections of Sandostatin® solution (1/120th of LAR dose) or placebo on Day 45, and TID SC (1/60th of LAR dose) or placebo on Day 47. For formulations 20, and 30 mg LAR, subjects were divided into two dosing groups. Subjects in the first dosing group were given 50 and 100 μg TID SC (or matching placebo) on Day 1 and 3, respectively, and a 20.0 mg LAR (or matching placebo) injection on Day 5. Subjects in the second group were given 100 and 200

µg TID SC (or matching placebo) on Day 1 and 3, respectively, and a 30 mg IM LAR (or matching placebo) injection on Day 5. The LAR AUC for the lower doses (3 to 12 mg) was based on octreotide samples collected up to 44 days. For the 20 and 30 mg doses, LAR AUC was based on samples collected up to 107 days. For the SC AUC, an average AUC was calculated from 4 administrations of Sandostatin® SC. The 3 to 12 mg LAR doses were administered in the deltoid; 20 and 30 mg LAR were administered intragluteally. Relative bioavailability for each dose was calculated by comparing the AUC from the SC (reference) and LAR doses.

For higher dosage formulation (20 and 30 mg) the relative bioavailability was relatively consistent (Table 6). The low dosage formulations were administered as IM injections in the deltoid whereas the 20 and 30 mg formulations were administered as IM injections in the buttocks.

Table 6: Relative Octreotide Bioavailability (Study E101)

Dose Group	Dose-normalized LAR AUC $_{0\rightarrow 44D}$ (ng.hr/ml)/mg	Dose-normalized solution AUC (ng.hr/ml)/µg	Relative Bioavailability (%)
3 mg	18.16	115.27	15.5
6 mg	18.09	131.92	15.3
12 mg	32.14	179.85	18.7
20 mg	40.94; [68.88]^	115.44	35.5; [60.1]^
30 mg	47.48; [78.56]^	114.16	41.6; [63.4]^

^LAR AUC 0→107 Days.

APPEARS THIS WAY
ON ORIGINAL

Study L101 (n=6) was of similar design to E101 (SC then LAR doses) and demonstrated that the bioavailability of the 60 mg LAR was about 50% as compared to the SC formulation. There was also an indication that a 60 mg injection of LAR could lead to injection site adverse events (pain, swelling). The highest allowable dose, as per the proposed labeling, will be 40 mg.

Reviewer's (Shore) comments:
Since the 3 to 12 mg LAR doses were still releasing octreotide at day 44 and these doses were administered in the deltoid, the relative bioavailability estimates for the 3 to 12 mg LAR doses are not reliable. The 107 day estimates for the 20 and 30 mg doses are acceptable.

B. Bioequivalence

APPEARS THIS WAY
ON ORIGINAL

Study W352
Clinical development of LAR for acromegaly has been performed with LAR

Due to the long duration (> 90 days) of octreotide release from LAR, a single dose, parallel group design was agreed upon between the Agency and the sponsor for bioequivalence studies. Study W352 was such a study in healthy subjects using a single dose of the 30 mg formulation from each site.

Results are shown Table 7 and Figure 2.

APPEARS THIS WAY
ON ORIGINAL

Table 7: Mean Pharmacokinetic Parameters of Octreotide

Parameter	(N=30)	
	Non-dose normalized	Dose normalized
$C_{plateau}$ (ng/ml)	1.88 ± 0.79	0.105 ± 0.04
$AUC_{(0-63d)}$(h.ng/ml)	1651 ± 590.8	92.9 ± 34.9
$\Delta_{plateau}$ (h)	267 ± 195	NA
C_{max} (day 1) (ng/ml)	0.26 ± 0.09	0.015 ± 0.01
$C_{max,plateau}$ (day2-35) (ng/ml)	2.35 ± 0.98	0.13 ± 0.05

Reviewer's (Wei) comments:

1. *In Study W352, the sponsor did not use equal molar amount of products thus the design is not acceptable for a bioequivalence study.*
2. *The result from dose-normalized analysis demonstrated the dose proportionality up to 30 mg.*

Reviewer's (Shore) comments:

1. *PK data was collected for only 63 days thus not fully characterizing the concentration-time profile of the*

LAR product.

II. Pharmacokinetics

A. Healthy volunteers vs. patients

In a cross-study comparison of healthy subjects and acromegalic patients administered 0.1 mg SC as a single dose (Table 9) the mean Cmax and AUC were greater in the healthy subjects, as is already indicated in the current labeling for Sandostatin®.

APPEARS THIS WAY
ON ORIGINAL

Table 9. Single dose PK parameters (mean, CV%) pooled across studies for Sandostatin® Injection, 0.1 mg SC in acromegalic patients and healthy subjects

	Healthy subjects, n = 29 (studies E101, L101)	Acromegalic patients, n = 45 (studies C201-E-00/01, C202-E-00)
C_{max}/dose (pg/mL/mg)	65,833 (49)	41,676 (53)
t_{max} (h)	0.7 (42)	1.7 (84)
AUC (0-t) / dose (pgxh/mL/mg)	165,779 (46)	127,193 (42)

The cross-study pharmacokinetic parameters between healthy subjects and patients for LAR are summarized in Table 10.

Table 10. Single dose PK parameters (mean, CV%) pooled across studies for 30 mg LAR in acromegalic patients and healthy subjects

	healthy subjects, n = 64 (studies E101, L101, W352, W354)	acromegalic patients, n = 24 (studies C201-E-00/01, C202-E-00)
C_{max}/dose (pg/mL/mg)	119 (51)	81 (70)
t_{max} (d)	41 (54)	33 (47)
AUC (0-t) / dose (pgxh/mL/mg)	86,032 (37)	53,802 (46)
C_{max} day 1 / dose (pg/mL/mg)	53 (36)	42 (33)

Again, the LAR formulation has a greater Cmax and AUC in healthy subjects, consistent with the SC formulation.

Reviewer's (Shore) comments:

The LAR formulation shows similar trends in PK as the SC formulation in healthy subjects as well as patients with acromegaly indicating that the LAR formulation does not alter the inherent pharmacokinetics of octreotide.

B. Carcinoid tumors

Study SMSE 351 was a 24-week, multicenter, randomized study in which patients with carcinoid tumors received either Sandostatin® SC (daily injections) or 10, 20, or 30 mg LAR (monthly injections). Clinical symptoms were monitored. Trough octreotide serum concentrations were determined for the LAR groups at baseline, weeks 4, 8, 12, 16, 20, and end of study week 24. Table 11 shows the population analyzed in this study.

Serum octreotide concentrations reached steady-state after the second injection for the 20 and 30 mg doses, whereas steady-state was not attained until after three IM injections of the 10 mg dose.

Table 11. Demographics from study SMSE 351.

Background Demographics - Categorical Variables

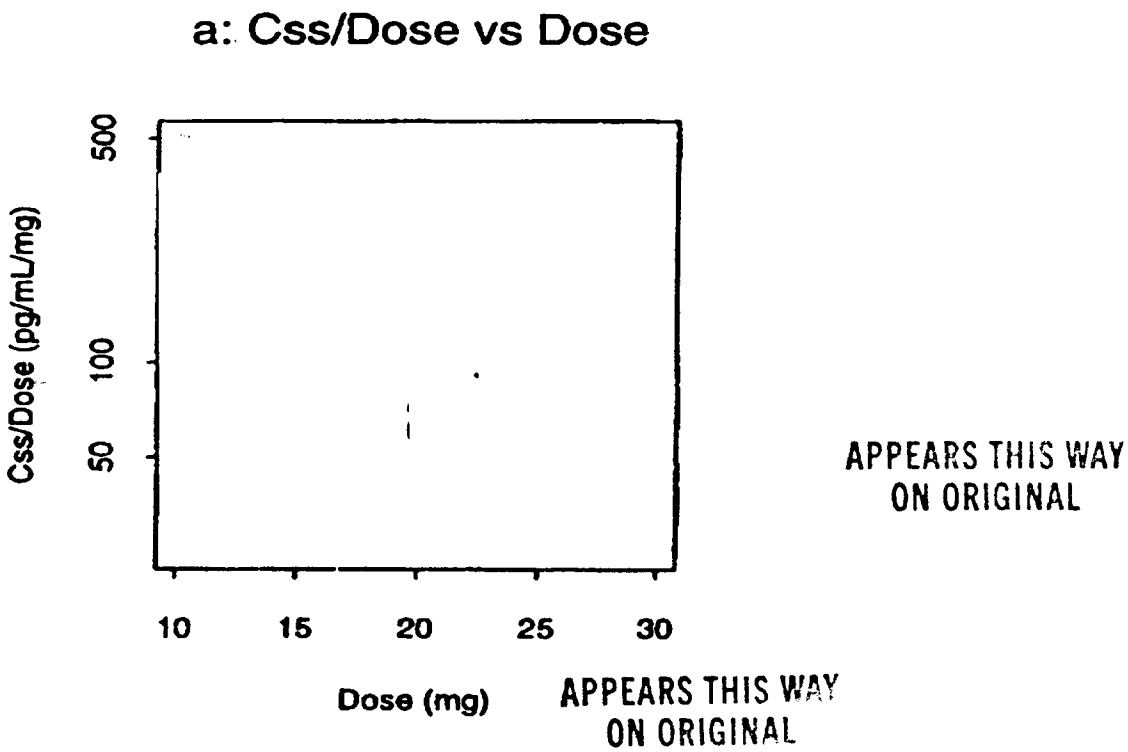
Variable	Group	Sandostatin S.C. n(%)	SMS LAR Dose Group 10 mg n(%)	20 mg n(%)	30 mg n(%)	p-Value*
Age	< 60 Years	12(46.2)	6(27.3)	13(65.0)	10(40.0)	
	>= 60 Years	14(53.8)	16(72.7)	7(35.0)	15(60.0)	0.098
	Total	26 (100)	22 (100)	20 (100)	25 (100)	
Sex	Male	12(46.2)	14(63.6)	8(40.0)	18(72.0)	
	Female	14(53.8)	8(36.4)	12(60.0)	7(28.0)	0.102
	Total	26 (100)	22 (100)	20 (100)	25 (100)	
Race	Caucasian	26 (100)	20(90.9)	19(95.0)	23(92.0)	
	Black	0	1 (4.5)	1 (5.0)	1 (4.0)	0.770
	Oriental	0	0	0	0	
	Other	0	1 (4.5)	0	1 (4.0)	
	Total	26 (100)	22 (100)	20 (100)	25 (100)	

* Overall p-Value from the Chi-square test.

APPEARS THIS WAY
ON ORIGINAL

The sponsor analyzed steady-state trough concentrations at weeks 16, 20, and 24 for dose proportionality. Figure 4 represents this data and the analysis indicated that there was proportionality between doses (p=0.3).

Figure 4. Dose proportionality analysis from study SMSE 351 (+ are females, o are males)



APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

Carcinoid patients who were female or over 60 years of age had median octreotide trough concentrations that were higher than the comparative group. However, there was no clinically relevant difference in the outcomes or side effects in these groups, the number of patients in any one of these subgroups was too small to result in dosage adjustment recommendations for the LAR product, and weight, age ,and gender

effects could not be fully separated.

III. Pharmacokinetic/Pharmacodynamic Relationships

Studies SMSC 201 and 202 (C201/202) were similar in study design, patient population, study drug and dosage. As such, the results were analyzed together in a PK-PD analysis. It should be noted that this PK-PD analysis only includes patients who were good responders on Sandostatin® SC and were antibody-free (antibodies could effect the assay results for octreotide but the presence of antibodies is not thought to effect octreotide activity). Both studies had the same design (Figures 5 and 6) which included a pre-study period with SC octreotide. Only patients who responded to octreotide treatment (growth hormone <5 ng/mL) were enrolled in the LAR phase where they received a first injection of LAR and were followed-up for 60 days. After the 60 days these patients were then enrolled in open-labeled extensions which were 6-, 12-, and 9-months long for a total of about 2 years of treatment. Patients in the extensions had their dose of LAR titrated based on GH response - doses of LAR were decreased if GH was < 1 ng/mL and increased if GH was > 5 ng/mL.

APPEARS THIS WAY
ON ORIGINAL

Figure 5. Schematic overview of study SMSC 201

Study timeline ⇨		⇨	⇨	⇨	⇨	⇨
Prestudy	Wash-out	Single Dose studies		Multiple Dose Studies		
Sandostatin® s.c. t.i.d.	1 - 3 days	Sandostatin LAR® Single i.m. injection		Sandostatin LAR® Monthly i.m. injections (10 - 40 mg / injection)		
				six-month extension	twelve-month extension	nine-month extension
standard protocol		SMSC201-E-00 n=14 pts.	3, 6, 9, 12 mg	Dose-adjustment	Dose-adjustment	Dose-adjustment
standard protocol		SMSC201-E-01 n=45 pts.	20 or 30 mg	SMSC201-E-02 n=43 pts.	SMSC201-E-03 n=41 pts.	SMSC201-E-04 n=36 pts.

APPEARS THIS WAY
ON ORIGINAL

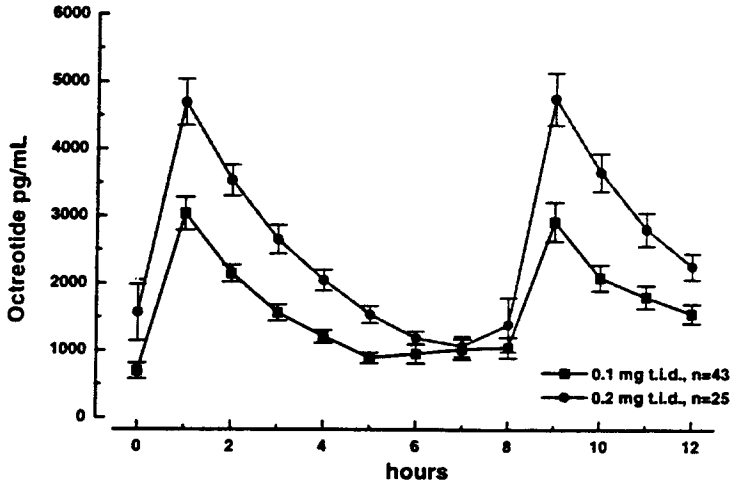
Figure 6: Schematic overview of study SMSC 202

Study timeline ⇨		⇨	⇨	⇨	⇨	⇨
Prestudy		Single Dose studies		Multiple Dose Studies		
Sandostatin® s.c. t.i.d.	Wash-out	Sandostatin LAR® Single i.m. injection		Sandostatin LAR® monthly i.m. injections (10 - 40 mg / injection)		
				Six-month extension Dose-adjustment	Twelve-month extension Dose-adjustment	Nine-month extension Dose-adjustment
standard protocol		SMSC202-E-00 n=56 pts.	20 or 30 mg	SMSC202-E-01 n=58 pts.	SMSC202-E-02 n=62 pts.	SMSC202-E-03 n=61 pts.

The pharmacokinetics of octreotide were investigated during the screening phases of the studies. Seventy-three out of 109 (67%) patients at screening were on 0.1 mg Sandostatin® SC t.i.d. (0.3 mg/day). Other dosages were 0.05 mg t.i.d. (2%), 0.2 mg t.i.d. (27%) and 0.3 mg t.i.d. (4%). Figure 7 shows the

mean octreotide concentrations, and parallel growth hormone concentrations, determined in the 0.1 and 0.2 mg t.i.d groups.

Figure 7: Mean,sd octreotide (upper panel) and growth hormone concentrations (lower panel) after SC t.i.d. (q 8 h) injections of Sandostatin® Injection



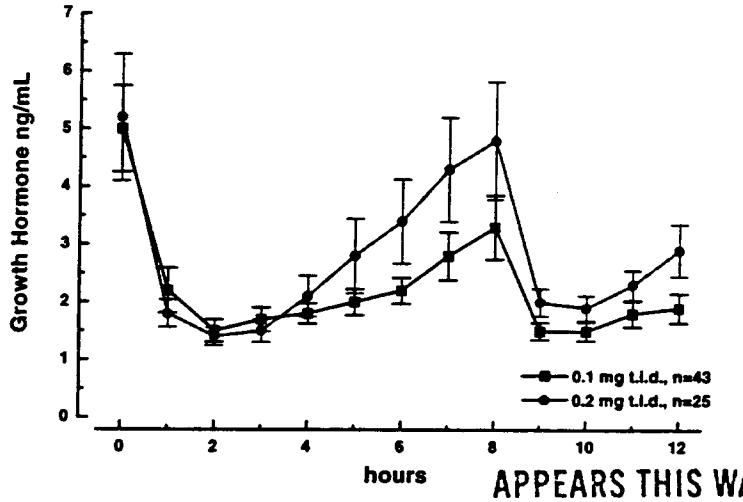


Figure 7 also demonstrates the direct effect of octreotide on growth hormone concentrations. The pharmacokinetic parameters for Sandostatin® SC appear in Table 12.

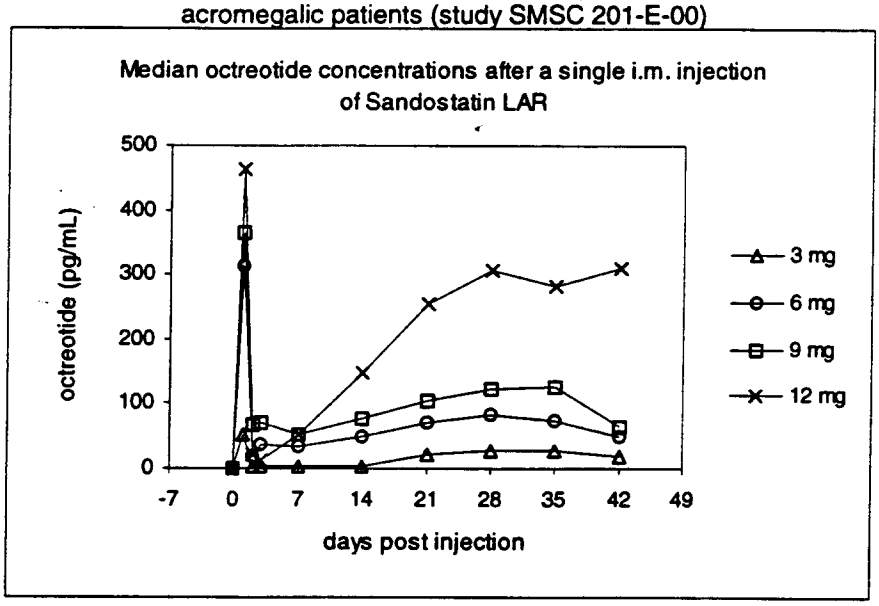
Table 12. Mean (CV%) pharmacokinetic parameters from studies C201 and C202.

PK Parameter	Sandostatin® Injection s.c.			
	0.05 mg t.i.d. (n=3)	0.1 mg t.i.d. (n=43)	0.2 mg t.i.d. (n=25)	0.3 mg t.i.d. (n=1)
C_{min} (pg/mL)	316 (72)	395 (78)	808 (64)	918
C_{max} (pg/mL)	2,354 (21)	3,821 (53)	5,381 (39)	6,472
$C_{average}$ (pg/mL)	1,115 (39)	1,653 (37)	2,650 (33)	3,413

A dose-finding study (C201-E-00) was undertaken which examined 3, 6, 9 and 12 mg LAR doses. The results of this study indicated that these doses were too low to suppress GH sufficiently (the study was stopped early). The median 12-hour concentrations of octreotide for each dose group during the study are shown in Figure 8.

APPEARS THIS WAY
ON ORIGINAL

Figure 8: Median concentrations of octreotide following a single IM injection of Sandostatin LAR® in acromegalic patients (study SMSC 201-E-00)



APPEARS THIS WAY
ON ORIGINAL

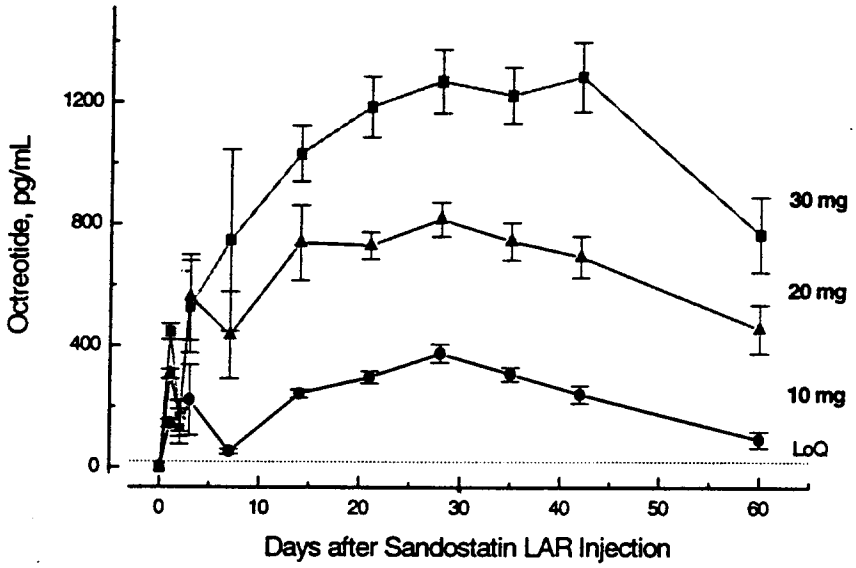
APPEARS THIS WAY
ON ORIGINAL

Octreotide concentrations of about 1 ng/mL are needed to adequately suppress GH – this data was available from the SC product studies as well as some literature. As such, the doses chosen for the clinical trials were 20 and 30 mg. A 10 mg dose was added because GH was suppressed to levels below 1 ng/mL in some patients and the 10 mg dose allowed down-titration for these patients.

The pharmacokinetics of single dose LAR were investigated during the double-blind phases of the studies. LAR dosages were 10 mg (n=11 patients), 20 mg (n=33) and 30 mg (n=23). The mean octreotide and corresponding growth hormone concentrations in these patients are shown in Figure 9.

APPEARS THIS WAY
ON ORIGINAL

Figure 9: Mean,sd octreotide (upper panel) and growth hormone concentrations (lower panel) after a single IM injection of LAR in acromegalic patients



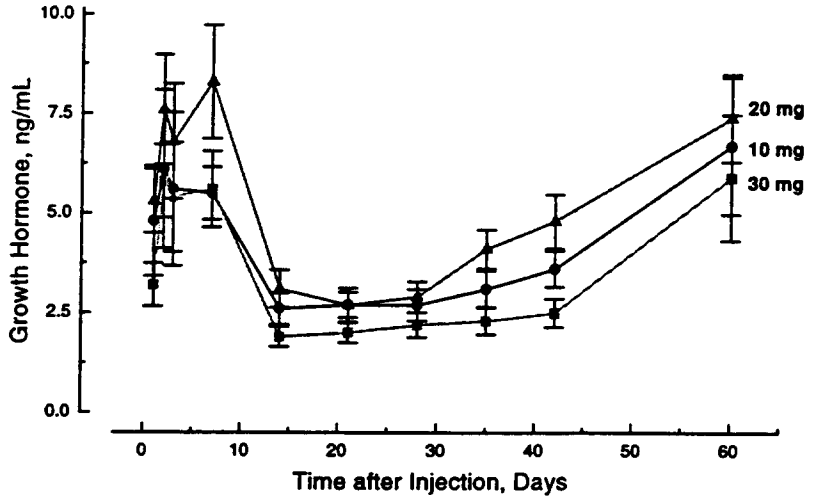


Table 13 summarizes the GH response to a single dose of LAR. For treatment of acgormegaly which is achieved for about 23 days with the 20 mg LAR dose.

APPEARS THIS WAY
ON ORIGINAL

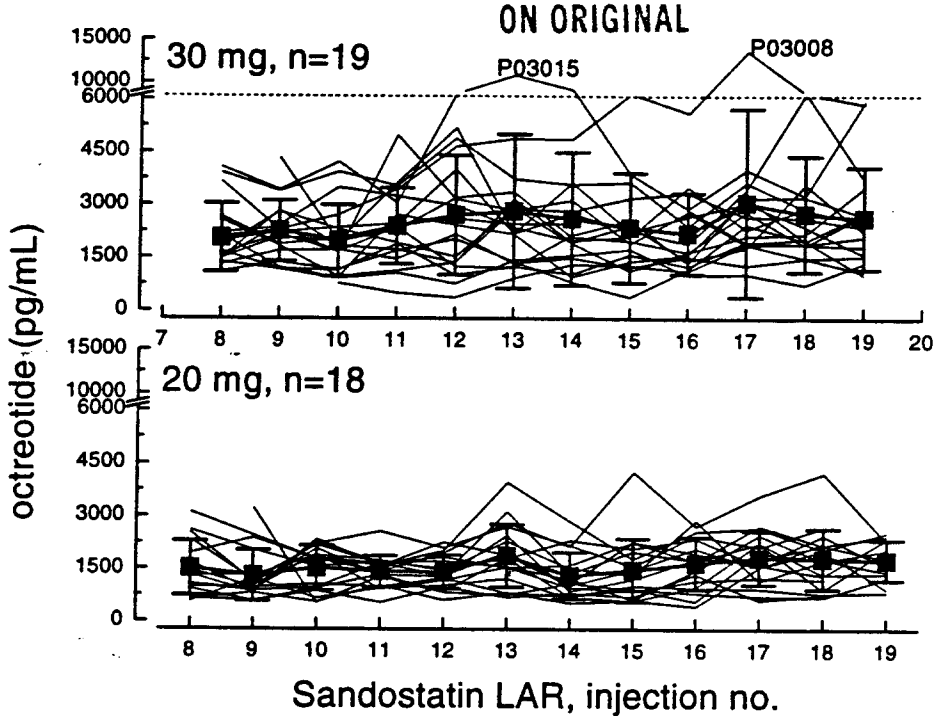
Table13. PD parameters of octreotide on GH in acromegalic patients after a single dose of IM LAR (mean±sd).

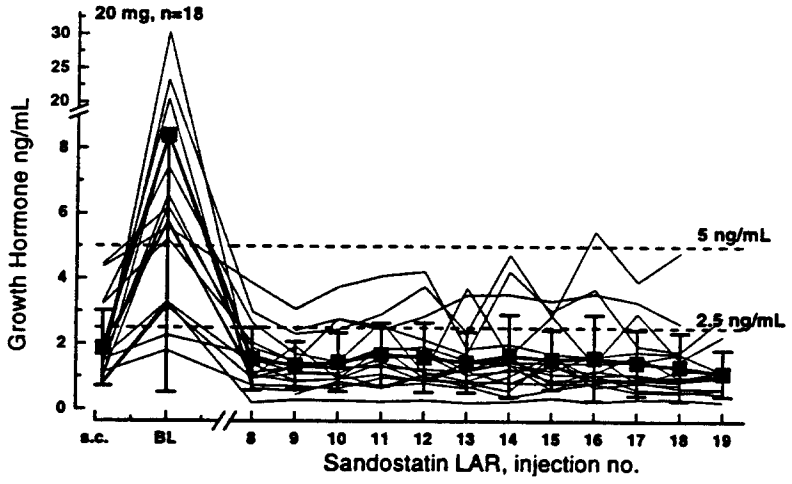
Parameters		Sandostatin LAR		
		10 mg n=11	20 mg n=33	30 mg n=23
$GH\text{-}t_{min}$	(d)	22.1 ± 17.6	17.9 ± 12.5	22.3 ± 17.7
GH_{min}	(ng/mL)	2.0 ± 1.3	2.0 ± 1.5	1.6 ± 1.1
GH-AUC	(ding/mL)	242 ± 129	295 ± 216	208 ± 145
$Dur_{<10\ ng/mL}$	(d)	57.6 ± 6.2	52.3 ± 12.1	57.0 ± 6.6
$Dur_{<5\ ng/mL}$	(d)	47.8 ± 14.6	41.0 ± 22.1	49.5 ± 12.2
$Dur_{<2.5\ ng/mL}$	(d)	20.9 ± 20.8	23.3 ± 23.7	29.8 ± 24.9
$Dur_{<1\ ng/mL}$	(d)	0.7 ± 1.9	4.1 ± 10.5	12.8 ± 20.7
$IGF\text{-}D_{sy\ 28}$	(ng/mL)	554 ± 187	602 ± 327	489 ± 268
$GH_{BL,\ avg.}$	(ng/mL)	9.1 ± 6.2	12.0 ± 9.1	12.0 ± 11.2
$IGF\text{-}1_{BL,avg}$	(ng/mL)	804 ± 151	952 ± 344	955 ± 370

The pharmacokinetics of multiple IM (q28 day) doses of LAR were determined in the long-term extension studies of SMSC 201 and SMSC 202 – 6-months, 12-months, and 9-months - for a total of 27 months. Assessment of accumulation was made by comparison of average octreotide concentrations on day 28 and only patients who were on continuous doses of LAR 20 or 30 mg were used for these calculations in order to ensure steady-state conditions. The individual and mean octreotide and growth hormone concentrations in the extension studies are shown in Figure 10.

APPEARS THIS WAY
ON ORIGINAL

Figure 10: Individual and mean (± S.D.) octreotide and growth hormone concentrations after multiple IM injections of Sandostatin LAR® in acromegalic patients in the extension studies of SMSC 201-E-03 and SMSC 202-E-02





The long-term stability of octreotide concentrations and durable suppression of GH are evident in Figure 10. Accumulation was assessed as the ratio of average octreotide concentrations at day 28 and ranged between 1.6 and 1.9.

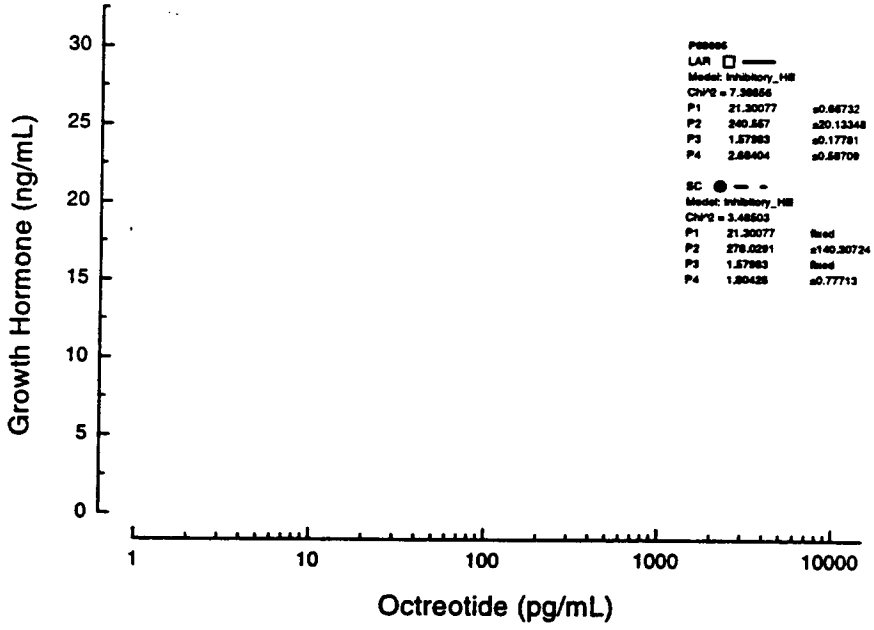
A PK-PD relationship was developed to compare the SC and LAR formulations. Seventy-two good responders and 13 partial/poor responders were included in this analysis; no patients had antibodies to octreotide because this would have made the octreotide concentration data suspect. The model used was as follows:

$$GH = (GH_{bl}-GH_{maxinh})*(1-C_{oct}^{H}/(C_{oct}-EC50^{H}+C_{oct}^{H}))+GH_{maxinh}$$

APPEARS THIS WAY
ON ORIGINAL

where:
-GH is the measured growth hormone level;
-GHbl is GH at baseline without octreotide;
-GHmaxinh is GH at maximal suppression with infinitely high octreotide concentrations;
-EC50 is the octreotide concentration that produces 50% of maximal GH suppression;
-H is the Hill coefficient (sigmoidicity parameter) describing the steepness/shape of the concentration-response curve.

This model describes an inverted sigmoid curve, starting at high baseline GH values (GHbl). The model takes into consideration that inhibition does not necessarily reach 100% and that a residual GH concentration (GHmaxinh) may remain, which is independent of octreotide. The model was fit to each patient's SC and LAR data using a non-linear regression package (Oracle) – all data from studies 201 and 202 which included paired octreotide concentration/GH levels were used. Mean overall parameters were then calculated. A 'typical' responder and non-responder patient's data are presented in Figures 11 and 12, respectively.



APPEARS THIS WAY
ON ORIGINAL

Figure 11. Responder patient's SC and LAR data used in modeling.

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

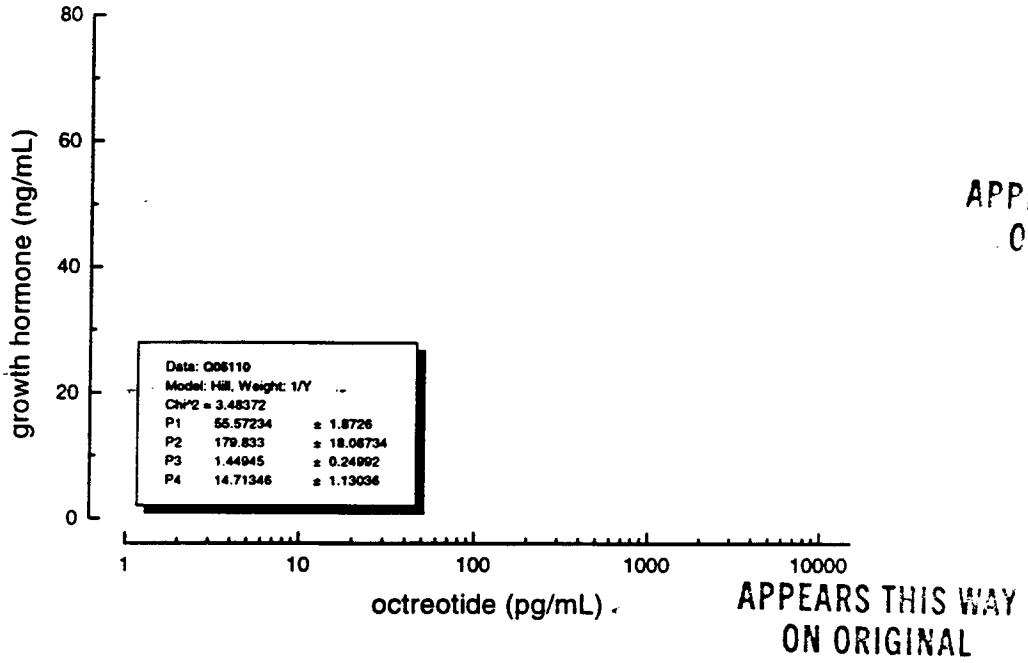


Figure 12. Non-responder patient's SC and LAR data used in modeling.

The mean (± S.D.) parameters defining the PK/PD relationship for Sandostatin® SC and LAR are summarized in Table 14 and Figure 13.

Table 14. Summary of model parameters from C201 and 202.

Acromegalic Patients	GH_{bl}	Sigmoidity parameter (H)	EC50 Sandostatin LAR®	EC50 Sandostatin® SC	GH_{maxinh} Sandostatin LAR®	GH_{maxinh} Sandostatin® SC
Partial Responders	54.1 ± 50.1	1.1 ± 0.4	1403.4 ± 2490.1	3814.3 ± 9747	3.6 ± 4.6	4.3 ± 6.0
Responders	13.6 ± 10.9	1.5 ± 0.8	167.9 ± 179.3	264.7 ± 390.1	1.6 ± 0.8	1.4 ± 0.7

As there were limited data from the SC administration, baseline GH as well as H were fixed for the SC model. To compare the SC and LAR parameters, a ratio of SC/LAR was generated for each individual. For EC50 and GH_{maxinh} the mean ratio for responders was 1.54 and 1.19, respectively. The parameter of interest is GH_{maxinh} since suppression of GH is a goal of therapy and the bioequivalence question is 'How does the LAR product suppress GH as compared with the SC product?'. EC50 is poorly fit with the SC due to scant data in the middle of the fitted curve; however, the precision of this parameter is less important than for GH_{maxinh}. When analyzed as a bioequivalence question, the point estimate (90%CI) on the Ln-transformed ratio of GH_{maxinh} (LAR/SC) was 1.10 which meets the bioequivalence criteria. Also, when examining the mean GH_{maxinh} for the two products, the difference between GH concentrations of 1.6 and 1.4 is not clinically relevant.

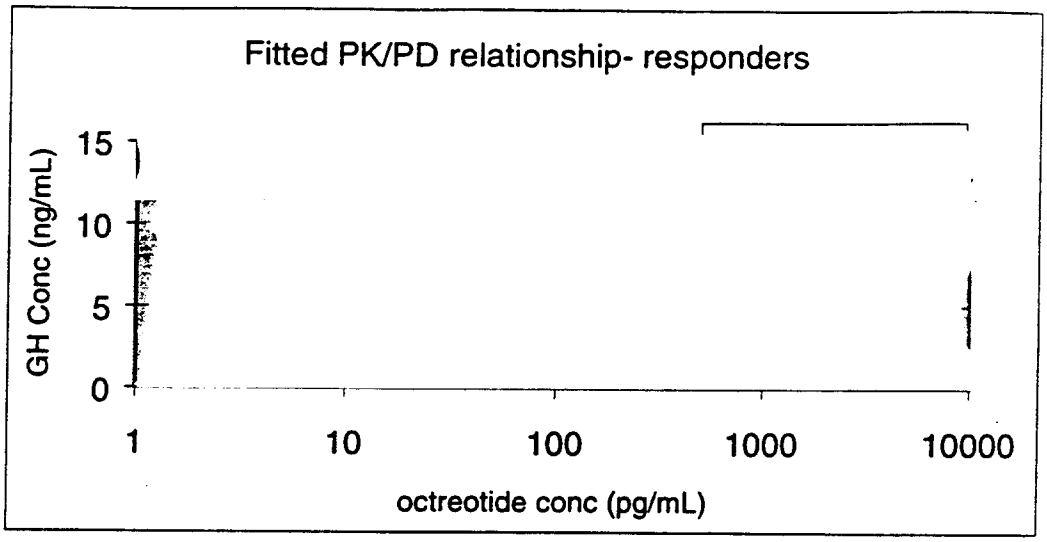


Figure 13. PK/PD relationship.

APPEARS THIS WAY
ON ORIGINAL

The analysis of the non-responders indicates that these patients are inherently less sensitive to octreotide - their EC50 parameters tend to be much greater than responders and the GH_{maxinh} remains high.

Dr Raymond Miller reviewed the model and found it to be adequate to assess the comparable effects of Sandostatin® SC and LAR on GH.

Reviewer's (Shore) comment:
The data indicate that the LAR and SC formulations are similar in their ability to decrease GH. There is no indication that the LAR formulation causes differences in the action of octreotide. Dose-finding studies justify the starting dose of 20 mg with titration, if needed, to either 10 or 30 mg based on response. Patient's who do not respond to the SC formulation initially would not receive the LAR formulation. The non-responder analysis indicates that there may be an inherent 'resistance' to the actions of octreotide in non-responders.

COMMENTS FROM THE MEDICAL OFFICER

APPEARS THIS WAY
ON ORIGINAL

1) The current standard of practice to evaluate therapy for acromegaly is monitoring IGF-1 as well as GH. Although some patients may have normalized GH with octreotide treatment, their IGF-1 may not respond adequately – the reverse is also true; the reasons are not fully understood. However, in conversation with Dr. Temeck it was conveyed to Dr. Shore that the response between Sandostatin® SC and LAR would be expected to be similar *within a given patient* with few exceptions. Therefore, for the purpose of comparing the two formulations, GH is an acceptable marker.

LABELING COMMENTS:

(~~Strikeout text~~ should be removed from labeling; Double underlined text should be added to labeling; ☞ indicates an explanation only and is not intended to be included in the labeling)

/S/ 04-NOV-98

Robert M. Shore, Pharm.D
Xiaoxiong Wei, Ph.D. /S/ 03-NOV-98
Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

APPEARS THIS WAY
ON ORIGINAL

RD initialed by Hae-Young Ahn, Ph.D., Team Leader 03-NOV-98

CPB Briefing 05-NOV-98
attendees: ShoreR, WeiX, MillerRa, ChenMe, AhnH, BawejaR, FosslerM, HuangS, HuntJ, KimSh

FT initialed by Hae-Young Ahn, Ph.D., Team Leader /S/ - 11/10/98

CC: NDA 21-008/N-000 (orig.,1 copy), HFD-510(Temeck, Weber, Niu), HFD-340 (Viswanathan), HFD-870(Wei, Ahn, ChenME), HFD-850(Lesko, Huang, MillerRA), CDR (Barbara Murphy).

Code: AE

APPEARS THIS WAY
ON ORIGINAL