CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 21008

STATISTICAL REVIEW(S)

STATISTICAL REVIEW AND EVALUATION

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NDA:	21-008
Priority Classification:	1P
Trade Name:	Sandostatin LAR®
Generic Name:	Octreotide acetate
Sponsor:	NOVARTIS
Indications:	Reduction of Growth hormone in Acromegaly, and control of Malignant Carcinoid syndrome.
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Submission Date:	5/29/1998

1.0 INTRODUCTION

1.1 Background

Sandostatin (octreotide acetate) Injection was approved in 1988 for the symptomatic treatment of patients with metastatic *carcinoid tumors* (for the suppression of severe diarrhea and flushing associated with carcinoid syndrome) and *acromegaly* (for the reduction of growth hormone and insulin-like growth factor associated with acromegaly). Sandostatin is given subcutaneously (s.c.) in 2 to 4 divided doses for a total of 60-120 injections per month, which is burdensome to patients.

Sandostatin LAR once a month injection, a long-acting preparation is intended for use in patients who have been found to be responsive to Sandostatin s.c.

In this application, the sponsors goal is to demonstrate that when patients are switched from Sandostatin s.c. to Sandostatin LAR preparation, it is as efficacious and safe as repetitive Sandostatin s.c. for both *acromegaly* and *carcinoid syndrome.*

1.2 Proposed Indication

The sponsor proposes the following as the indication for Sandostatin LAR (this is a direct quote taken from the sponsor's proposed draft package insert):

1.3 Organization of this Review

In reviewing this NDA, it appeared that the studies conducted in support of the claim were not designed appropriately in regard to formal hypothesis, the associated test statistic, and justification for adequate sample sizes needed to show desired effect size. Most of the evidence shown in support of the above indications was based on descriptive analyses, and statistical analysis were performed only for the carcinoid indication. Our evaluation in this report will focus on the agreement or disagreement with the sponsor's claim based on statistical tests performed using tabulated data since no data sets were provided at the time of this submission. This review will focus mostly on the efficacy results, its strengths and weaknesses in light of the study design. We will also briefly describe the safety profiles, specifically, any significant abnormalities or serious adverse events seen in these studies. Details of safety profiles will be included in the Medical Reviewer's review. PK/PD profiles of the two formulations will be evaluated elsewhere.

2.0 EVALUATION OF CARCINOID SYNDROME

Two studies were conducted to support the carcinoid syndrome indication: Study 351 and Study 451, an extension of study 351. In the following section, a brief description of each study will be followed by the study results.

2.1 Description of Study 351

This was a multicenter, 24-week period, randomized, parallel group, open-label study in which 93 subjects with a documented diagnosis (histologically confirmed) of carcinoid syndrome (clinically well-controlled on sandostatin s.c. therapy) have participated. After a two-week screening period and a mandatory 3-day washout period for the return of symptoms (stool frequency of at least two per day for two consecutive days and or three episodes of flushing per day) subjects were randomized to either 10, 20, or 30 mg doses of Sandostatin LAR or Sandostatin s.c.

Objectives

The primary and the secondary objectives of this study were:

- **Primary**: To determine over a 24-week period, the efficacy of 10, 20, and 30 mg doses of Sandostatin LAR administered at 4-week intervals in providing continuous symptomatic control of carcinoid syndrome compared to sandostatin s.c . TID.

- **Secondary:** To determine the safety and tolerability of sequential doses of Sandostatin LAR, to assess the dose proportionality of serum octreotide concentrations after sandostatin LAR at doses of 10, 20, and 30 mg, and to

monitor urinary 5-HIAA excretion as an indicator of serotonin release and metabolism.

Efficacy Measures

The efficacy criterion was degree and duration of suppression of carcinoid symptoms of flushing and stool frequency, as indicated by the need for s.c. rescue medication in patients randomized to one of the sandostatin LAR groups, or the need to for a 50% increase in dosage in patients randomized to the s.c group. As per protocol, the **primary efficacy endpoint** was defined as:

- **Treatment success:** no need for rescue medication (replacing s.c. in LAR dose groups or increased s.c. dosage in s.c. group) during weeks 17-20 and weeks 21-24.

- **Partial treatment success**: Need for rescue medication or increased dosage on no more than two occasions for a total of no more than 5-days during weeks 17-24.

- **Treatment failure**: Need for rescue medication or increased dosage on three occasions or for a total of more than 5-days during weeks 17-24.

The **secondary efficacy endpoints** were:

- time to rescue s.c. after day 11.
- proportion of patients experiencing increased stool frequency (>=2/day for two consecutive days compared to screening period) and flushing (>=3/day for at least one day) during a dosing interval.
- change from baseline and change from screening in urinary 5-HIAA levels (biological marker of carcinoid syndrome), stool frequency, and flushing frequency.

Safety variables

Safety analysis included evaluation of adverse events (at baseline and every 4-week interval), vital signs (at baseline and every 4-week interval), ECG (baseline and week 24), and special laboratory parameters (baseline and week 24).

Sample Size

In the protocol, the sponsor stated that carcinoid syndrome is rare, therefore, the number of patients available for study was limited in this study. Enrollment of 93 patients across 4 treatment groups was based on arbitrary clinical judgement rather than statistical grounds. The justification of sample size in regard to primary endpoint was not planned in the protocol. For rare disease, in general, a larger sample size is needed to support the intended claim. Based on

such a smaller number of patients any inferential testing performed and conclusions made based on the basis of the results of this study would be rather limited.

Sponsor's Statistical Analysis Method

Three populations were defined:

- **Safety analyzable**: All patients who had safety baseline and at least one follow-up evaluation.
- **Intent-to-treat**: all patients who had a baseline and at least one follow-up efficacy.
- **Efficacy Evaluable**: all patients who returned for at least the 20-week visit (dropouts prior to week 20 were classified as failures) .

The statistical analysis method included Fisher's Exact test to compare proportions of (pairwise between two dose groups) treatment success between treatment groups (the primary endpoint) , and Adverse event profile; ANOVA for change from baseline in 5-HIAA (the secondary endpoint) and vital signs.

2.1.1 **Results**

This section briefly describes the results of analyses performed based on the data compiled from the sponsor's submission. The primary and secondary efficacy analyses were based on both ITT and evaluable patient populations. Emphasis will be on both the treatment success (primary endpoint) and the secondary endpoints (supportive evidence) followed by comments on the overall results of the studies to support this indication.

Patient Disposition and Characteristics

A total of 93 patients were randomized to either LAR 10, 20, or 30 mg groups or Sandostatin s.c. group. Thirteen patients discontinued from the study for the following reasons: 3 due to deaths, 2 withdrawn, 2 treatment failure, 4 failed to return, 1 due to adverse event, and 1 for other reasons. The Majority (12/13) of the discontinued patients were in the LAR groups.

Sandostatin s.c. doses at screening were comparable between treatment groups (Table A). The mean age of patients among treatment groups differed significantly with 20 mg LAR group being younger than other groups. It appeared that patients randomized to LAR dose groups were diagnosed much earlier with carcinoid syndrome and were on s.c. for longer duration than patients randomized to receive s.c. sandostatin in this study.

Table A Patient Characteristics by Treatment groups, Study 351						
Characteristics	Measure	Treatment Groups (N=93)				
		Sandostatin s.c N=26	LAR 10 mg N=22	LAR 20 mg N=20	LAR 30 mg N=25	p-value
Sandostatin s.c. dose at screening	Mean	566	550	555	597	NS
Age (years)	Mean	59	61	54	63	0.03
Gender: Male Female		12(46%) 14(54%)	14(64%) 8(36%)	8(40%) 12(60%)	18(72%) 7(28%)	0.102
Weight(kg)	Mean	77	77	76	77	NS
Years since Dx.	Mean	4.8	4.7	6.0	5.8	NS
Years since start of s.c.	Mean	1.2	1.4	2.8	2.4	0.138

Overall Efficacy

The efficacy results for intent-to-treat (ITT), efficacy evaluable, and at endpoint populations are shown in Table B.

Treatment Success: After six months of therapy, the treatment success rate ranges from 60-63% for LAR doses compared to 54% for s.c. sandostatin in ITT analysis. Similar results were noted for evaluable patient analysis. There was no statistically significant (all p>.50) dose-response effect among LAR dose groups in either ITT or evaluable patient analysis indicating the treatment was equally effective at any dose of LAR. Overall, there were also no differences in response between S.C. and LAR dose groups, although the success rates in LAR dose groups were slightly higher than the S.C. group.

Use of Rescue S.C.: In approximately of patients in whom the treatment failed, the median time to rescue S.C. was lower in LAR groups than S.C. groups. LAR patients began to use rescue S.C. earlier (15 median days) compared to S.C. patients (46 median days) (not shown in Table B, Table 7 of Vol. 60; NDA 21-008). However, after 20 and 24 weeks of treatment, approximately of the patients began to use rescue S.C. and the use was similar in all treatment groups as shown in Table B.

Stool Frequency: The mean number of stool frequency ranged from per day during screening period, increased to per day during washout and then decreased to per day at week 20 and week 24 post-treatment in the ITT population (Table 9, p36, ISE, vol.60). The percent of patients experiencing increased stool frequency (at least 2/day for 2 consecutive days

above the average frequency during the screening period) at week 20 and week 24 were similar for all groups. There were no statistically significant differences between LAR groups or between s.c. and LAR doses.

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Flushing Episodes: Percent of patients experiencing flushing episodes, the symptoms of carcinoid syndrome, were higher for LAR dose groups compared to S.C. group which is consistent with the proportion using rescue s.c. except LAR 10 mg.

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Table B
Efficacy in Sandostatin S.C. and LAR dose groups at Visit, Intent-to-treat Population (Efficacy Evaluable), Study 351

Efficacy	Visit	N	Sand. S.C.	Sandostatin LAR Dose groups			P-values	
				10 mg	20 mg	30 mg	Overall[a]	Dose Effect[b]
Primary:								
Treatment Success(%)	Week 20	84(77)	61.5(66.7)	63.2(66.7)	62.5(71.4)	61.0(62.0)		
	Week 24	81(76)	53.8(58.3)	63.2(66.7)	60.0(64.3)	62.0(60.0)		
	Endpoint	93(77)	53.8(58.3)	54.5(66.7)	45.0(64.3)	52.0(57.1)		
Secondary:								
Use of Rescue S.C. (%)	Week 20	83(78)	38.5(33.3)	36.8(33.3)	33.3(28.6)	39.0(41.0)		
	Week 24	82(77)	50.0(45.8)	36.8(33.3)	40.0(35.7)	41.0(43.0)		
	Endpoint*	93(79)	50.0(45.8)	77.3(72.2)	70.0(66.7)	52.0(59.1)		
Increased Stool (%) (≥2/day)	Week 20	83(46)**	30.7(44.4)	26.3(41.6)	20.0(30.0)	13.0(13.3)		
	Week 24	82(45)	19.2(11.0)	22.7(33.3)	15.0(20.0)	20.0(21.4)		
	Endpoint	93(47)	19.2(11.0)	22.7(33.3)	15.0(18.0)	20.0(20.0)		
Flushing Episodes (%) (≥3/day)	Week 20	83(64)	23.0(25.0)	42.1(54.0)	13.3(18.0)	34.7(35.0)		
	Week 24	82(63)	23.0(25.0)	42.1(54.0)	26.6(36.3)	27.2(31.5)		
	Endpoint	93(65)	23.0(25.0)	45.4(54.0)	35.0(33.3)	28.0(30.0)		
Mean Urinary 5-HIAA (mg)	Baseline	68(61)	57(60)	213(203)	121(116)	96(96)	P=.009	
	Screening	77(65)	34(37)	86(87)	47(46)	96(91)		
	Week 20	57(55)	39(39)	100(99)	34(36)	123(112)	P=.041	
	Week 24	54(55)	40(40)	132(132)	38(41)	103(91)	P=.078	
	Endpoint	85(52)	48(52)	127(133)	61(58)	126(125)	P=.055	

+ Source: Table 5, 7.1, 9d, 9g, 10d, 12; Vol. 60, NDA 21-008.
a: P-values for the difference between all treatment groups using Fisher's exact test.
b: P-value for the differences in LAR dose groups.
* Last visit a patient took any rescue S.C.
** Baseline qualified: Patient had to exhibit a stool frequency increase during washout of >=2/day above the pre-washout period.

Urinary 5-HIAA: The 24-hour urinary 5-HIAA was the selected biological marker of carcinoid tumors assessed in this study. It has been suggested in the literature that elevated urinary 5-HIAA (>190 mg/d) is associated with bad prognosis. In this study, the assessment of urinary 5-HIAA was not considered if patients were using rescue s.c. 72 hours preceding the sample collection. Table B shows the number of patients for whom urinary 5-HIAA was available at baseline, screening and post-treatment periods.

At baseline, 33% of the patients in the LAR groups and 4% in the s.c. group had 5-HIAA excretion concentrations above >150 mg/d (Listing 4.6, Appendix 4.2, Vol.29). The mean at baseline was significantly (p=.009) higher in LAR patients compared to s.c. group indicating that patients randomized to LAR groups had more severe disease as indicated by higher urinary 5-HIAA. At week 20 and 24, there was a modest decrease in 5-HIAA in LAR groups but remained marginally higher than s.c. group with the exception of LAR 20 mg dose group.

Efficacy by Subgroups

Treatment success was also evaluated in two major subgroups: gender, and age (<60 years vs. >=60 years). Table C shows the distribution of treatment success rate by these two subgroups at post-treatment visits. Analysis by gender and age appears to suggest that s.c. sandostatin was more effective in females and older patients although similar results were not noted for patients in LAR dose groups. However, these difference between formulations were probably more due to chance and the small number of patients in each subgroup.

Table C
Treatment Success by Gender and Age groups, ITT population, Study 351

Visit	Subgroups N	Sandostatin S.C. n/N(%)	LAR 10 mg n/N(%)	LAR 20 mg n/N(%)	LAR 30 mg n/N(%)
Week 20	Male(N=49)	4/12(33.3)	9/13(69.2)	5/8(62.5)	11/16(68.8)
	Female(N=35)	12/14(85.7)	3/ 6(50.0)	5/8(62.5)	3/ 7(43.0)
	Age <60(N=36)	5/12(41.7)	3/ 5(60.0)	6/11(54.5)	5/ 9(55.6)
	Age≥60(N=47)	11/14(78.6)	9/14(64.3)	4/5(80.0)	9/14(64.3)
Week 24	Male(N=47)	3/12(25.0)	9/13(69.2)	5/7(71.4)	10/15(66.7)
	Female(N=34)	11/14(78.6)	3/ 6(50.0)	4/8(50.0)	3/ 6(50.0)
	Age <60(N=35)	3/12(25.0)	3/ 5(60.0)	5/10(50.0)	5/ 8(62.5)
	Age≥60(N=46)	11/14(78.6)	9/14(64.3)	4/ 5(80.0)	8/13(61.5)

Source: Compiled from sponsor's Table 5b, and 5c, Vol. 60, NDA 21-008.

Safety

The major safety goal in this study was to assess whether the safety profile of Sandostatin LAR was similar to that of Sandostatin s.c. Overall, almost 90% of the patients in s.c. or LAR groups experienced at least one adverse event during 6 months of therapy. The percentages of patients experiencing G.I. , Non-G.I., and serious AEs are summarized below.

Non-G.I. Adverse Events: The most common Non-G.I. events were fatigue, nausea, back pain, and respiratory disorders. In general, the LAR patients reported higher number of AEs than s.c. patients. There were no significant differences between LAR groups except the incidence of cardiovascular, musculoskeletal and vision disorders were higher in the 10 mg dose group compared to either the 20 or 30 mg groups.

G.I. Adverse Events: As expected approximately of the LAR and s.c. patients reported G.I. related events, most commonly nausea, abdominal pain, and flatulence but there appeared to be no statistically significant differences between LAR groups or between s.c. and LAR groups. Numbers of patients by body system were too small to make inferential analyses.

Serious Adverse Events: There were no differences in serious AE between s.c. and LAR groups and the sponsor noted that these events were mostly abdominal in nature.

Gallbladder: In study 351, approximately of the patients had gallstones at baseline but few normal patients developed new gallstone, sludge and bile duct dilation during therapy. Most of these patients were in LAR groups: 4(11%) vs. 1(6%) for gallstone, 2(13%) vs. 0% for sludge, and 4(11%) vs. 0% for bile duct dilation in LAR and s.c. groups, respectively.

Other Parameters: No differences between s.c. and LAR groups were noted in special laboratory parameters (Glycosylated Hemoglobin, Total Thyroxine, Free Thyroxene, TSH, Serum carotene) or routine laboratory tests

2.1.2 Comments on Efficacy and Safety Results

Study 351 enrolled patients who were clinically well-controlled (defined as control of stool frequency and flushing, the clinical symptoms of carcinoid syndrome) during the two weeks of screening on Sandostatin s.c. 100 to 300 μg t.i.d., were then randomized to either s.c. or LAR 10, 20, or 30 mg groups after the resumption of symptoms following a 3-day washout period.

The objective of this study was to assess whether control of carcinoid syndrome is similar in s.c. and LAR dose groups. The primary efficacy endpoint was the treatment success defined as no need to use rescue s.c. Sandostatin. The secondary endpoints were time to rescue s.c. sandostatin, stool frequency, flushing episodes, and urinary 5-HIAA (biological marker of carcinoid syndrome). The

sponsor's definition of time to rescue s.c. sandostatin was simply the complement of the primary endpoint, i.e., treatment failure.

After 6 months of therapy, the success rate in LAR groups was numerically similar: in LAR groups and s.c. group, respectively. Similar results were noted even after 5 months of therapy in both intent-to-treat and evaluable analyses. No dose-response effect was noted in any analysis.

The control of symptoms as indicated by increased stool frequency and flushing episodes were also similar across treatment groups. The use of rescue s.c. (a criteria of treatment success/failure) was similar across treatment groups after 6 months of therapy. At endpoint, the use was higher in LAR groups compared to s.c. group because patients in LAR groups dropped out earlier due to treatment failure.

The urinary 5-HIAA, a biological marker of carcionoid syndrome, was considerably higher for LAR groups at baseline and remained significantly higher for LAR groups after therapy indicating severity of the disease. Only patients in LAR 20 mg group have shown some post-treatment improvement similar to s.c patients, nevertheless in the majority of the patients in LAR groups this marker remained elevated. The sponsor indicates that not all patients who obtain control of carcinoid symptoms will experience a decrease in urinary 5-HIAA level.

The treatment success rate of in either ITT, evaluable or endpoint analysis in this study is similar to reported in the published literature despite the fact that patients randomized to LAR dose groups were more severe in carcinoid syndrome. Overall, the treatment success in controlling carcinoid syndrome was similar between s.c. and LAR dose groups. The adverse event rate was also not different between s.c. and LAR doses groups, although within dose groups there was higher incidence of some AE in the 10 mg group. No other abnormality was noted in laboratory parameters, except a few patients developed gallstones during therapy.

Inferential conclusion based on the results of this study is rather limited due to the fact that the study size was not powered to test any hypothesis with regard to treatment efficacy, and the use of differential types of rescue s.c. criterion could have influenced the study outcome since it was an open-label study.

2.2 Description of study 451

Study 451 is an open label extension of study 351 where patients who successfully completed study 351 were enrolled in this study, including those who had been on s.c. sandostatin. Patients received a dose of 20 mg LAR q.4 weeks for 4 injections followed by 30 mg LAR q.4 weeks for 9 injections. At the end of week 16 patients were switched from 20 mg to 30 mg dose. Patients were also permitted to use rescue sandostatin under the same criteria as for study 351.

The *primary* and *secondary* endpoints were same as in study 351. No formal statistical analyses were performed for this interim report.

2.2.1 Efficacy Results

A total of 78 patients entered in this study and 72 patients completed at least 6 months. Table D shows the efficacy results at weeks 20, 24, and at endpoint of therapy. At the end of six months of therapy, the success rate of across all dose groups in this study was more variable than the success rate of › seen in study 351. This variation may be due to switching patients from 10 to 20 and 30 mg dose groups. However, use of rescue s.c. sandostatin in this extension study was less than half in s.c. and 20 mg groups (19% and 15%) compared to what was seen in study 351 (50% and 36%). The use of rescue sandostatin by patients in the10 and 30 mg dose groups was similar between studies 351 and 451.

Mean urinary 5-HIAA showed little change after 6 months of therapy and was similar to study 351.

Safety

No safety data was collected in this open-label extension study.

2.2.2 Comments on Efficacy Results

In the submission, the sponsor neither clearly indicated the objective of this study nor described the study procedures. Patient enrollment to various dose groups was not clear. At one point, it was indicated that patients from the 20 mg dose were switched to 30 mg and at another point it was mentioned that the 10 mg dose group was also switched to 30 mg dose, yet the results shown in Table 16-27 included a10 mg dose group. Patients were not assigned to any dose group in any systemic manner, let alone in randomized fashion.

The effectiveness of LAR therapy shown in this interim report was similar to what was shown in study 351. The results of study 451 could not be considered supportive since the same patients were used in this study.

Table D Efficacy in Sandostatin S.C. and LAR dose groups at Visit, Intent-to-treat Population , Study 451							
Efficacy	Week	N	Sandostatin s.c.	LAR dose			
				10 mg	20 mg	30 mg	All Dose
Primary:							
Treatment Success(%)	Week 20	73	69.6	66.7	69.2	73.7	70.0
	Week 24	72	77.3	66.7	84.6	52.6	69.4
	Endpoint	78	72.0	68.4	84.6	52.4	68.0
Secondary:							
Use of Rescue s.c.	Week 20	74	29.2	33.3	30.8	26.3	29.7
	Week 24	71	19.0	33.3	15.4	47.4	29.6
Increased stool Freq/or Flushing Episodes (%)	Week 20	73	34.7	61.1	15.3	52.6	42.2
	Week 24	70	35.0	44.4	15.3	52.6	38.5
	Endpoint	78	40.0	42.1	15.3	47.6	38.4
Mean Urinary 5-HIAA (mg)	Baseline	61	56	217	75	98	61
	Screening	68	33	88	37	101	66
	Week 24	79	42	132	19	103	79
	Endpoint	88	72	106	41	117	72
Source: Table 16, 19, 25, and 27; vol. 60							

3.0 EVALUATION OF ACROMEGALY

The major studies in acromegalics were Study 201, 202 and 303, each of which had one or more extensions. The purposes of these studies were to (1) compare the degree of GH and IGF-I suppression and control of acromegalic symptoms by Sandostatin LAR with that of s.c. sandostatin, and (2) compare the safety of the two formulations.

The sponsor grouped these studies according to duration of exposure of LAR injections as shown in Table 3.1. Patients enrolled in these studies were (1) patients who have achieved GH <5 and >=50% decrease from pretreatment level while they were on s.c. sandostatin in another PK/PD study and (2) who had GH level rise to >=5 during the washout period prior to LAR injection. A few patients who did not meet this criterion were also allowed to enter these studies. In extension studies, the sponsor also titrated (up or down) depending on the GH level achieved in previous

studies. Prior to dosing LAR, a washout period was ensued to show GH level rise to >5 μg/L in order to continue in the trial.

It appears the sponsor started one PK/PD study (Study 201-E-00, not shown in Table E) with patients who were already good responders to s.c. sandostatin , and subsequently used the same patient pool in later studies with different doses and exposure. Therefore, these studies were not independent, well-controlled, and randomized. Table 3.1 shows briefly a summary of these studies.

Table E
Brief Summary of Acromegalic Studies

Study	Total Patients	Duration (months)	Doses	Study objective	Efficacy Measures
201-E-01 202-E-00	93	2	10, 20, and 30 mg	Comparison of LAR doses vs. S.C. sandostatin	• GH (μg/L) • IGF-I .
201-E-02 202-E-01	101	6	10, 20, 30, 40, and 60 mg		
201-E-04 202-E-03	97	9	10, 20, 30, and 40 mg		
201-E-03 202-E-02	103	12	10, 20, 30, 40, and 60 mg		
303-E-00 303-E-01	151	6	10, 20, and 30 mg		

In the following section, we will briefly describe the study procedures and then focus on the results of LAR therapy at various durations and doses.

3.1 Study Procedures

Patients enrolled in the first group, i.e., in Studies 201-E-01 and 202-E-00, were completers in the PK/PD study who underwent 4-8 weeks of screening during which they received sandostatin s.c.. If they achieved GH level of <5 μg/L and GH suppression of >=50% from pre-treatment level then they received a single injection of 20 mg or 30 mg LAR and were followed for 60 days. In study 202-E-00, patients included some "partial responders" who had GH level > 5 μg/L but with GH suppression >=50% who received either 10, 20 or 30 mg LAR and were followed for 60 days.

Patients enrolled in the second group were completers from the first group and who were again screened to meet the inclusion criteria for this 7 month open-label extension study. The majority of patients (78/101) received one 20 mg LAR injection at one month intervals.

Similarly, patients in the subsequent groups were enrolled in the same fashion. Most patients received LAR doses of 20 mg or 30 mg in the open-label extensions, although a few patients were titrated up or down to 10, 40, and rarely to 60 mg doses.

The only exception was study 303 in which patients with GH<10 ug/L on s.c. sandostatin were also enrolled although the majority of patients had levels <5 ug/L. In this study patients were switched directly from s.c. sandostatin to 20 mg LAR for three months and maintained at this dose or titrated dose for another 3 months depending upon GH level. After this 6 month period, an extension of another 6 months used doses of 10, 20, or 30 mg depending on GH level in the previous 6 months.

In all studies the ***primary endpoint*** was serum GH concentration level and the ***secondary endpoint*** was IGF-I level measured at every month for 12 months. Safety evaluations included local and systemic adverse events, vital signs, hematology, blood chemistry, and special laboratory parameters.

None of the studies was designed to test any hypothesis and therefore no justification for adequate sample sizes and statistical tests were performed.

3.1.1 Results

Efficacy: Serum GH and IGF-I Level

Table F shows the mean serum GH and IGF-I levels at screening, baseline and post-LAR months for all doses combined in each group of studies. During screening, patients were treated with s.c. sandostatin to achieve GH level of <5 ug/L and >=50% decrease from pretreatment levels to be eligible to receive sandostatin LAR. The purpose of these studies was to evaluate if patients could achieve and maintain this level, i.e., similar to s.c. after LAR therapy at various durations. In the first group of patients, the mean GH and IGF-I after one month of LAR therapy were similar to s.c. levels but by the second month these patients could not maintain the levels similar to s.c. In the second group of studies, the majority of the same patients appeared to achieve levels of GH and IGF-I similar to s.c. at the end of the six months of therapy. In all subsequent studies, LAR therapy appeared to be as effective as s.c. in controlling GH and IGF-I throughout the maintenance period.

Table F
Mean GH and IGF-I Serum Concentration During the 12 Months,
All Treated Patients

Group/ Studies	Endpoint(s)	Screening (s.c.)	Months since LAR Injection BL*	1	2	3	6	9	12
Group A									
201-E-01	GH	4.4	15.7	4.9	9.5	-	-	-	-
202-E-00	IGF-I	568	939	601	622	-	-	-	-
Total # of Patients(n)	-	**93**	**93**	**91**	**90**				
Group B									
201-E-02	GH	4.5	15.8	4.1	9.2	3.5	3.4	-	-
202-E-01	IGF-I	593	964	574	742	537	551	-	-
Total # of Patients	-	**101**	**100**	**98**	**78**	**100**	**99**		
Group C									
201-E03	GH	4.5	15.8	-	-	3.5	3.9	4.2	3.4
202-E-02	IGF-I	600	963	-	-	563	537	571	547
Total # of Patients	-	**103**	**103**			**103**	**101**	**101**	**99**
Group D									
201-E-04	GH	4.7	16.2	-	-	3.3	3.2	3.2	-
202-E-03	IGF-I	611	977	-	-	541	535	544	-
Total # of Patients	-	**97**	**97**		**91**	**96**	**90**		
Group E									
303-E-00	GH	2.6	-	2.8	2.5	2.3	2.1	2.0	2.2
303-E-01	IGF-I	438	-	458	406	406	425	417	413
Total # of Patients	-	**151**	-	**151**	**151**	**151**	**149**	**127**	**122**

Source: Table 11, 20, p27, p 42, vol.57 : Table 11, 20, p27, p 42, vol.57
* BL: Base line

GH and IGF-I level by Dose and Injection

Table G shows the mean GH and IGF-I levels by dose and monthly injections. Repeated monthly injections were administered to patients only in group B, C, and D studies. Results for dose 10 mg, and above 30 mg are not shown since the majority of patients received either 20 mg or 30 mg. In all three groups of studies, 20 mg LAR injection was more effective in controlling the GH and IGF-I levels at repeated injections than the 30 mg dose, although both doses maintained the levels similar to s.c. sandostatin. Note that patients who received 30 mg dose had higher levels of both GH and IGF-I at screening indicating greater severity of disease.

Table G

Mean serum GH and IGF-I by Dose and every 3rd Injection, Studies 201 and 202

Group	Efficacy Dose		Screening	Post-LAR Injections 3	6	9	12
B	GH	20 mg	2.6	1.5	1.7		
		30 mg	5.1	3.2	3.4		
	IGF-I	20 mg	891	441	448		
		30 mg	998	543	561		
C	GH	20 mg	2.0	1.9	1.8	1.9	1.6
		30 mg	4.0	4.1	5.6	6.2	4.7
	IGF-I	20 mg	544	448	426	442	419
		30 mg	578	623	610	689	660
D	GH	20 mg	1.8	1.5	1.4	1.4	
		30 mg	6.8	4.7	4.5	4.4	
	IGF-I	20 mg	514	375	381	387	
		30 mg	695	696	651	679	

Source: Vol. 57.

Normalization of GH and IGF-I Post-LAR Injections (FDA request)

The Medical Division requested an analysis by dose and time of normal GH (<=2.5 ug/L) and normal IGF-I (<=500 ug/L) levels for studies 201 and 202. Table H shows percent of patients who had normal GH and IGF-I only after every 3rd LAR Injections. This table excludes a few patients who received doses greater than 30 mg. See appendix Table I for details.

As seen in this table, approximately 60% of the patients in the 20 mg dose group maintained normal GH and IGF-I after post-LAR injections. Fewer patients who received 30 mg could maintain normal levels of GH and IGF-I post-LAR. Approximately 82% of the patients in this dose group failed to achieve normalization even after the 27th injection. This difference between 20 mg and 30 mg dose was also noted in mean GH and IGF-I concentration levels in studies 201 and 202.

Table H

Percent of patients with Normal (GH <2.5 μg/L and IGF-I <=500 μg/L) at Day 28 After every 3rd LAR Injection, Study 201 and 202 Patients.

Dose	Screening	Post-LAR Injections 3	6	9	12	15	18	21	27
10 mg	-								
20 mg	47%	63%	67%	57%	57%	56%	65%	69%	68%
30 mg	29%	29%	31%	26%	29%	29%	25%	15%	18%

Source: Table I, p54, vol. 57. See appendix

Safety

A total of 261 patients in studies 201, 202, and 301 were exposed to LAR injections at doses ranging from 10 mg to 40 mg.

The majority of patients (87%) in acromegalic studies 201 and 202 were exposed to LAR (cumulative duration of exposure) for more than 2 years and 70% of the patients in study 301 were exposed to LAR for more than a year.

Adverse Events: In all acromegalic studies, the majority of patients in LAR dose groups (65%, 75%, and 84% in 10 mg, 20 mg, and 30 mg respectively) experienced at least one adverse event, with the most common in the Gastrointestinal area, i.e., abdominal pain and diarrhea (20%, 36%, and 55% for 10 mg, 20 mg, and 30 mg dose) followed by flatulence and constipation. In general, there appeared to be a dose-related effect in adverse events, occurring more frequently in the 30 mg dose than in the lower doses. Injection site pain also appeared to be dose-related, occurring in 2%, 9%, and 11% of the patients in the 10 mg, 20 mg, and 30 mg dose groups.

The sponsor also compared the incidence of adverse events reported in NDA 19,667 (old formulation) in acromegaly patients on s.c. sandostatin vs. LAR patients in studies 201, 202, and 303. The incidence of G.I. events (abdominal pain, diarrhea) in LAR patients were lower (29% and 36% for abdominal pain and diarrhea) than s.c. patients (44% and 58%) except for flatulence, constipation, and nausea where the incidences for LAR patients were higher than s.c. patients. Note that patients in study 303 were not washed out from s.c. sandostatin before being placed on LAR, therefore, the higher incidence of some events may be attributable to the cumulative effect of s.c. sandostatin.

Serious adverse events: Eighteen percent (47/261) of patients reported a serious adverse event but only in 2 patients were these events considered drug related. Most of these events were due to underlying causes and the majority of these were reported by patients in the 20 mg and 30 mg dose groups.

Gallbladder: At the end of the study, incidence of new gallstones, sludge, and biliary duct dilation were reported in 5%, 9%, and 4% of the patients. Over the entire period of observation (>112 weeks), gallstone/or sludge occurred in 26% of the patients, all in the 20 mg and 30 mg dose groups.

Compared to data from NDA 19-667, the new incidence of gallstone in s.c. sandostatin patients was 21% compared to 5% in studies 201, 202, and 303. A higher incidence of sludge, bile duct dilation was also noted in s.c. patients than LAR patients.

3.1.2 Comments on Efficacy and Safety

Studies 201, 202, and 301 showed that Sandostatin LAR, in monthly doses of 20 mg, and 30 mg was similar to Sandostatin s.c. in controlling the GH and IGF-I levels, although 20 mg appeared to be more effective than 30 mg dose. Normalization of GH and IGF-I levels at monthly post-LAR injections was seen in of the patients who received 20 mg dose compared to only of the patients taking the 30 mg dose. The safety profiles in LAR patients were no different than s.c. patients except for an increased incidence of gallstones/sludge.

4.0 REVIEWER'S ASSESSMENT AND RECOMMENDATION

The sponsor's goal in this NDA was to demonstrate that Sandostatin LAR, a new formulation, is as efficacious and safe as the old formulation, sandostatin s.c., in treating patients with carcinoid tumors and acromegaly.

Carcinoid Tumor

To support the carcinoid tumor indication one randomized, parallel group open-label study for a duration of 6 months was conducted. Patients with documented diagnosis of carcinoid syndrome and clinically well-controlled on s.c. therapy, were randomized to receive either 10, 20, or 30 mg doses of Sandostatin LAR or Sandostatin s.c. after a 3-day washout period for the return of symptoms.

Patients were evaluated at baseline and every 4-week interval of post-therapy for efficacy and safety. The primary efficacy endpoint was treatment success defined as no need for s.c. sandostatin by a patient in LAR dose group or increased s.c. dosage by a patients in s.c. group for the control of symptoms as indicated by increased stool frequency or flushing episodes at 20 and 24 weeks of treatment. The secondary endpoints were stool frequency, flushing episodes, and urinary 5-HIAA (a biological marker of carcinoid tumor).

Although randomized, this study was not powered to test any hypothesis and the number of patients enrolled was rather arbitrary. The sponsor indicated that the incidence of carcinoid tumor is rare, therefore, number patient enrollment would be limited. Despite any formal hypothesis and the associated test statistic, the results between LAR dose group and s.c. groups were compared by Fisher's exact test.

A total of 93 patients were enrolled and 80 patients completed the study. Patients randomized to LAR therapy doses had severe disease as indicated by urinary 5-HIAA, years since diagnosis and prior length of s.c. treatment. An ITT and efficacy evaluable analysis revealed that:

(i) approximately of LAR sandostatin patients achieved complete success after 6 months of therapy compared to 54% of s.c. Sandostatin therapy in ITT

analysis population.

(ii) there was no statistically significant dose-related effect on treatment success, i.e., all three doses were equally effective in maintaining the symptoms similar to s.c. Sandostatin.

(iii) After day 11 of treatment, the LAR patients started to use the rescue s.c. much earlier (median of days) than s.c. sandostatin patients (median of 46 days) but at the end of 6 months of treatment, the number of patients using rescue s.c. was similar across all treatment groups.

Overall, LAR therapy to control carcinoid symptoms appeared to be similar to s.c. sandostatin in this study. The results from study 451, an extension of study 351, showed similar results in spite of the limitations.

Acromegaly

The sponsor conducted three acromegalic studies (201, 202, and 301) in support of the acromegaly indication. Patients enrolled in study 201 were entered subsequently in studies 202, and 301 for an extended duration. These studies were neither independent, not randomized or well-controlled. No formal hypothesis or statistical analysis method was planned to analyze the data.

The goal of these studies were to compare the degree of suppression of Growth Hormone (GH) and insulin-like growth factor (IGF-I) by LAR Sandostatin with that of s.c. Sandostatin. The results of these studies revealed that:

(i) Sandostatin LAR, in monthly doses of 20 mg, and 30 mg was similar to Sandostatin s.c. in controlling the GH and IGF-I levels, although 20 mg appeared to be more effective than 30 mg.

(ii) Normalization of GH and IGF-I levels at monthly post-LAR injections was seen in of the patients who received 20 mg dose compared to only of the patients taking 30 mg.

(iii) The safety profiles in LAR patients were no different than s.c. patients except for an increased incidence of gallstones/sludge.

From a statistical perspective, the results from these studies should be exercised with caution since the studies were not designed appropriately. Although LAR Sandostatin therapy appeared to control both acromegaly and cacinoid syndrome, the conclusion based on the results of these studies is rather limited due to the fact that studies sizes were not powered to test formal

hypothesis with regard to treatment efficacy, and in the case of carcinoid syndrome, the use of differential types of rescue medication between LAR and s.c. groups could have influenced the study outcome since it was an open-label study.

/S/ 11/12/98

APPEARS THIS WAY
ON ORIGINAL

Mahboob Sobhan, Ph.D.
Mathematical Statistician, HFD-715

concur: Todd Sahlroot, Ph.D. /S/ 11/12/98
Edward Nevius, Ph.D. /S/ 11/19/98

cc:
Archival NDA 21-008
HFD-510
HFD-510/Dr. Sobel/Dr. Temek/Dr. Orloff
HFD-715/Division File/Drs. Nevius/Welch/Sahlroot/Sobhan

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 21008

MICROBIOLOGY REVIEW(S)

REVIEW FOR HFD-510
OFFICE OF NEW DRUG CHEMISTRY
MICROBIOLOGY STAFF HFD-805

NOV 5 1998

Microbiologist's Review #1 of NDA 21-008
November 5, 1998

A. 1. **APPLICATION NUMBER:** 21-008

APPLICANT: Novartis Pharmaceutical Corporation
59 Route 10
East Hanover, NJ 07936-1080

2. **PRODUCT NAMES:** Sandostatin LAR Depot Injection

3. **DOSAGE FORM AND ROUTE OF ADMINISTRATION:** The drug product consists of 2 vials: a Sandostatin LAR vial (dosage: 10, 20 and 30 mg/vial, in 5 ml vial), and a Diluent vial (2 ml fill in a 2 ml vial). The drug product is to be administered by deep intra-muscular injection.

4. **METHOD(S) OF STERILIZATION:**

5. **PHARMACOLOGICAL CATEGORY:** 1P; acromegaly (over-production of growth hormone, somatotropin, typically caused by a tumor in the pituitary gland), malignant carcinoid tumors, VIPoma.

B. 1. **DATE OF INITIAL SUBMISSION:** May 29, 1998

2. **AMENDMENT:** none

3. **RELATED DOCUMENTS:** Response to FDA Request for Information

4. **ASSIGNED FOR REVIEW:** June 16, 1998

5. **DATE OF CONSULT REQUEST:** June 3, 1998

C. **REMARKS:**

Sandostatin LAR (Long Acting Repeatable) Depot Injection is a intra-muscular dosage form of Sandostatin intended to replace the current subcutaneous forms which

require a dosing regimen of 3 injections a day. Sandostatin LAR microsphere, administered once every four or more weeks, is intended for a slow release dosing.

D. CONCLUSIONS:

APPEARS THIS WAY
ON ORIGINAL

The submission contains adequate information for sterility assurance of the drug product. The NDA is recommended for approval on issues concerning Microbiology.

APPEARS THIS WAY
ON ORIGINAL

/S/ 11/5/98

Brenda Uratani, Ph.D.
Review Microbiologist

/S/ 11/5/98

APPEARS THIS WAY
ON ORIGINAL

cc:

NDA 21-008
HFD-510/ Div. File
HFD-805/ Uratani
HFD-510/Weber
drafted by: Brenda Uratani, 11/5/98
R/D initialed by P. Cooney, 11/5/98