CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-597

STATISTICAL REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF BIOSTATISTICS

Statistical Review and Evaluation

CLINICAL STUDIES

NDA:	21-597
Name of drug:	Serostim® [somatropin (rDNA origin) for injection]
Applicant:	Sereno Laboratories, Inc.
Indication:	Treatment of short bowel syndrome
Documents reviewed:	Vol. 1-8 dated 10/31/02
Project manager:	Alice Kacuba (HFD-180)
Clinical reviewer:	Hugo Gallo-Torres, M.D. (HFD-180)
Dates:	Received 10/31/02; user fee (10 months) 09/01/03
Statistical reviewer:	Dionne L. Price, Ph.D. (HFD-715)
Statistics team leader:	J. Todd Sahlroot, Ph.D. (HFD-715)
Biometrics division director:	S. Edward Nevius. Ph.D. (HFD-715)

Keywords: NDA review, clinical studies, analysis of covariance

1 EXECUTIVE SUMMARY OF STATISTICAL FINDINGS

1.1 CONCLUSIONS AND RECOMMENDATIONS

Sereno Laboratories, Incorporated has proposed Serostim®, a recombinant human growth hormone (rhGH), for the improvement of residual gut absorptive function in patients with short bowel syndrome (SBS). A primary claim of the sponsor is that rhGH, administered singly and as cotherapy with glutamine, reduces the total intravenous parenteral nutrition (IPN) volume requirements of SBS patients. The evidence taken from the reviewed study indicates statistical support favoring Serostim® for the treatment of short bowel syndrome. Additional claims are made regarding IPN calorie content and frequency of IPN administration. Evidence further suggests that Serostim® significantly reduces both IPN calorie content and frequency of administration among SBS patients.

Of note, all study participants received an oral diet individualized to meet nutritional needs. Moreover, modifications to the diet throughout the treatment period were necessary to maintain adequate nutritional status. Due to the daily changes to the diet after randomization and the potentially complex relationship between diet and total IPN volume, an unbiased statistical analysis of total IPN volume adjusting for the effect of diet is not possible. However, summary data on the diet and nutritional status of patients are included in the review to provide clinicians with a descriptive clarification of the nature and strength of the relationship between diet and IPN utilization over time.

1.2 OVERVIEW OF CLINICAL PROGRAM AND STUDIES REVIEWED

Background

Serostim®, as a drug product for the treatment of SBS, was introduced to the Food and Drug Administration via IND 48,570. The clinical development plan was discussed via several meetings, telephone conferences, and correspondences. Discussion topics included the appropriateness of a single study to establish efficacy, the appropriateness of various clinically defined outcomes, and the potential for confounding via the specialized oral diet individually formulated for each patient. The present submission contains a single, randomized, double-blind study designed to investigate the safety and efficacy of Serostim® for the proposed indication.

Study Design

Intravenous parenteral nutrition-dependent subjects diagnosed with SBS were entered into a two-week baseline period. During this period, each subject's IPN requirements were stabilized, and subjects began an oral diet specifically formulated for each subject, individually. Following baseline assessments, forty-one patients were randomized to

rhGH, rhGH and glutamine in cotherapy, or glutamine in a 2:2:1 ratio, respectively. During the four-week treatment duration, each subject's IPN was reduced according to a prespecified reduction scheme.

Statistical Analyses

In Study IMP20317, the primary measure of efficacy was the change in total volume of IPN from week 2 to week 6. "Total volume was defined as the sum of the volumes of IPN, supplemental lipid emulsion (SLE), and intravenous hydration fluid administered each week. " The primary outcome was analyzed utilizing an analysis of covariance model with baseline covariate. Pairwise comparisons between both rhGH treatment groups and glutamine were assessed utilizing Dunnett-Hsu test to control the Type I error rate at 5%.

The sponsor also identified two secondary measures of efficacy namely, the change in total IPN calories and the change in IPN frequency from baseline to the end of treatment. The two variables were analyzed similarly to the primary efficacy variable.

Sponsor's Results and Conclusions

In Study IMP20317, a statistically significant reduction in total IPN volume was achieved by patients receiving rhGH, singly or as cotherapy with glutamine, as compared to patients receiving only a specialized oral diet supplemented with glutamine. Moreover, patients in the rhGH groups achieved significant reductions in IPN caloric content and IPN administration frequency.

1.3 PRINCIPAL FINDINGS

Following my evaluation of the study, I conclude that Serostim®, administered singly or as cotherapy with glutamine, reduces the total IPN requirement of patients with short bowel syndrome. Specifically in the evaluated study, there exists a decrease in IPN utilization over the treatment duration of 3.8L, 7.7L, and 5.9L among the glutamine, rhGH and glutamine cotherapy, and the rhGH groups, respectively. Moreover, the drug product also produces significant reductions in weekly IPN calorie content and the frequency of IPN administration.

All patients in study IMP20317 received a specialized oral diet tailored to the individual nutritional needs of patients. As stated by the sponsor, " The objective of the diet is to ensure that each subject is able to maintain through oral feeding, adequate nutritional status, which can promote nutrient absorption and independence from IPN following discharge from the clinic." Summary data suggested an increase in the components of the oral diet from week 2 to week 6 across each treatment group. With the exception of the oral fluid component, larger increases in the intake of the quantified components of the oral diet were evident for the cotherapy group as compared to the glutamine group.

Thus, the greater reduction in total IPN requirements observed in the cotherapy group was accompanied by a greater increase in the specialized oral diet.

Additional issues deferred to the medical review of Dr. Hugo Gallo-Torres include the clinical significance of the rhGH effect, the appropriateness of the endpoints, and the appropriateness of a single study for the proposed indication.

2 STATISTICAL REVIEW AND EVALUATION OF EVIDENCE

2.1 INTRODUCTION AND BACKGROUND

Serostim® is a recombinant human growth hormone (rhGH) currently approved in the United States for the treatment of AIDS wasting or cachexia. Serostim® was originally evaluated for the aforementioned indication via adequate and well-controlled studies contained in NDA 20-604. Serono Laboratories, Inc. submitted the current application (NDA 21-597) on 31 October 2002. The present submission investigates the safety and efficacy of rhGH (singly and as cotherapy with glutamine) for the treatment of short bowel syndrome via a randomized, double-blind study.

The drug product for the proposed indication was initially introduced to the Food and Drug Administration via IND 48,750 submitted by Sereno Laboratories, Inc. on 31 August 1995. The IND protocol outlined Study GH-003. The study was also conducted under IND 58,284 submitted on 9 October 1997 by a second sponsor.

The clinical development plan was the subject of several meetings, telephone conferences, and correspondences between the Division of Metabolism and Endocrine Drug Products and the companies. Issues addressed included the appropriateness of one single center study to establish efficacy, the appropriateness of various clinically defined outcomes, and the potential for confounding via the proposed specialized oral diet individually formulated for each patient. Of note, the current NDA was transferred from the Division of Metabolism and Endocrine Drug Products to the Division of Gastrointestinal and Coagulant Drug Products shortly after submission.

2.2 DATA ANALYZED AND SOURCES

The sponsor provided Study IMP20317 (previously referenced as Study GH-003) in support of the proposed indication. I reviewed volumes 1-8 of NDA 21-597 dated 31 October 2002. The data were archived in the Food and Drug Administration internal document room under the network path location, \\CDESUB1\N20604\S_026\2002-10-31. Upon initial investigation of the data, I discovered that definitions of the variables were not provided. The division requested the data definition tables, and Sereno Laboratories, Inc. submitted the tables on 14 February 2003.

Study IMP20317 was a double-blind, phase 3, controlled study conducted in the United States. Forty-one patients were randomized to rhGH, glutamine, or a cotherapy of rhGH and glutamine in a 2:2:1 ratio, respectively.

2.3 STATISTICAL EVALUATION OF EVIDENCE ON EFFICACY /

Intravenous parenteral nutrition (IPN) dependent subjects diagnosed with short bowel syndrome (SBS) were entered into a two-week baseline period. During this period, each subject's IPN requirements were stabilized, and subjects began a specialized oral diet (SOD) specifically formulated for the individual subject. The specialized oral diet, as outlined in the protocol, is provided in the Appendix. Following baseline assessments, eligible subjects were randomized to treatment for a four-week duration. Patients received one of the three following treatment regimes: 0.10 mg/kg/d subcutaneous rhGH and a SOD supplemented with 27 g/d of oral glutamine placebo, 0.10 mg/kg/d subcutaneous rhGH and a SOD supplemented with 30 mg/d oral glutamine, or 0.10 mg/kg/d subcutaneous rhGH placebo and a SOD supplemented with 30 mg/d oral glutamine. Glutamine supplements were dispensed in packets, and patients mixed the packet contents with water or Crystal Light® beverage. During the treatment duration, each subject's IPN was reduced according to a prespecified reduction scheme (in Appendix).

The proposed objective of IMP20317 was to evaluate the change in total intravenous parenteral nutrition (IPN) requirements measured from baseline to the end of treatment.

2.3.1 SPONSOR'S RESULTS AND CONCLUSIONS

In Study IMP20317, a statistically significant reduction in total IPN volume was achieved by patients receiving rhGH, singly or as cotherapy with glutamine, as compared to patients receiving only a specialized oral diet supplemented with glutamine. Moreover, patients receiving rhGH, singly or as cotherapy with glutamine, achieved significant reductions in IPN caloric content and IPN administration frequency.

2.3.2 STATISTICAL METHODOLOGIES

The primary measure of efficacy was the change in total volume of IPN from Week 2 to Week 6. " Total volume was defined as the sum of the volumes of IPN, supplemental lipid emulsion (SLE), and intravenous hydration fluid administered each week. " The sponsor identified two secondary measures of efficacy, namely, the change in total IPN calories and the change in IPN frequency from baseline to the end of treatment. " Total calories were defined as the sum of kilocalories for carbohydrate, protein , and fat in the IPN and SLE administered each week and the kilocalories in the intravenous hydration fluid. " IPN frequency was calculated using the number of days per week of administration of IPN. If no intravenous parenteral nutrition was administered, IPN frequency was defined as the number of days per week of administration of SLE provided the amount of SLE was greater than 200 kilocalories.

The primary efficacy endpoint was analyzed via an analysis of covariance (ANCOVA) model with baseline measurement as a covariate. Primary analyses focused on assessing treatment group differences among rhGH (singly or as a cotherapy with glutamine) and

glutamine alone. The sponsor referenced the specialized oral diet supplemented with glutamine as SOD[GLN], and similarly referenced the specialized oral diet supplemented with placebo as SOD. Utilizing these references, the sponsor stated, "Since treatment with SOD[GLN] was not expected to alter IPN requirements, this study compared treatment with rhGH + SOD[GLN] to treatment with SOD[GLN] alone and treatment with rhGH+SOD to treatment with SOD[GLN] alone." The two pairwise comparisons of interest were examined via the Dunnett-Hsu test to control the type I error rate at 5%. The aforementioned analysis plan was also followed for the secondary variables of interest.

2.3.3 DETAILED REVIEW OF INDIVIDUAL STUDIES

The sponsor enrolled 41 patients across two sites in the United States. Of note, only three patients were enrolled at the second site, the University of Nebraska (Omaha). The primary site was the Nutritional Restart Center, a "referral center for patients with severe malabsorptive disorders." The sample size was based on a previous study by Byrne et al.[1] and was adequate to provide 80% power to detect a 6.6 L per week difference in IPN volume between each rhGH group and glutamine group (assuming a root mean square error of 5.5L per week). Primary analyses were performed on the intent to treat population consisting of all randomized patients. Additionally, the sponsor performed analyses on the efficacy evaluable population and a treatment responder population. The efficacy evaluable population included all patients who completed the study according to specified criteria. The treatment responder population included subjects who demonstrated a 100% reduction in total IPN volume. The latter two populations were not of focus in my review.

Approximately 71% of study participants were female, and the majority of study participants were Caucasian. The ages of subjects were between 20 and 75 with a mean age of 50 years (standard deviation of 15.6). Weight, number of years since most recent bowel resection, length of residual jejunum-ileum, percent of intact colon, and IPN history (frequency, volume, and calories) were evaluated as additional baseline characteristics. There were no statistically significant differences between treatment arms regarding demographic or the baseline characteristics. A summary of demographic variables and baseline characteristics is provided in the Appendix.

Of the 41 randomized study participants, 16 subjects were randomized to the rhGH arm, 16 subjects were randomized to the rhGH and glutamine cotherapy arm, and 9 subjects were randomized to the glutamine only arm. An individual in the rhGH treatment group did not complete the study due to an adverse event. Due to the small number of patients with missing efficacy data, concerns regarding the statistical methodology utilized to handle missing data are minimized. However, the sponsor did pre-specify methodology

[1] Byrne TA, Nompleggi DJ, Wilmore DW. Advances in the management of patients with intestinal failure. Transplant Proc 1996; 28(5):2683-2690.

to be utilized for missing data. According to the sponsor, missing baseline values were imputed via the mean observed baseline value for all subjects. Similarly, the mean observed change from baseline for a given week was calculated and added to the baseline value for a patient missing a post-baseline value. In addition, the data were analyzed using a last observation carried forward (LOCF) strategy as well as a mixed model repeated measures (MMRM) strategy.

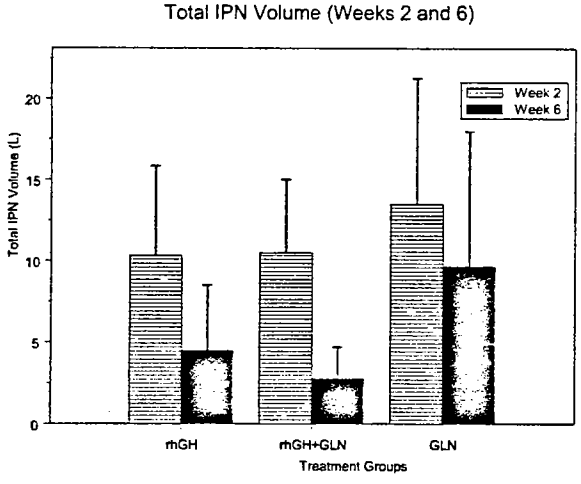
Table 1 depicts the results of the sponsor's analyses performed on the primary and secondary variables. Results for the efficacy variables are generated via methodology outlined in Section 2.3.2 with missing data handled via the sponsor's prespecified proposal. Models initially included a term for a baseline by treatment interaction. The interaction term was significant in the analysis of the primary efficacy variable; therefore, it was retained in the model. The interaction term was not significant in the analyses of the secondary variables; therefore, analysis models of secondary variables were run without the interaction term.

Table 1 Summary of change in Total IPN Volume. Calories, and Frequency from Week 2 to Week 6 for ITT Population by Treatment Group (as presented by sponsor)

Endpoints	rhGH (N=16)	p-value	rhGH + GLN (N=16)	p-value	GLN (N=9)
Mean change in total IPN volume [L/wk] (std deviation)	-5.9 (3.8)	0.043*	-7.7(3.2)	<0.001*	-3.8(2.4)
Mean Change in Total IPN Calories [kcal/wk] (Std. Dev)	-4338.3(1858.4)	0.005†	-5751.2(2081.9)	<0.001†	-2633.3(1340.5)
Mean Change in IPN or SLE Frequency [d/wk] (Std. Deviation)	-3.0(1.98)	0.025†	-4.2(1.4)	<0.001†	-2.0(0.9)

* P-values were determined from pairwise comparisons of treatment groups with the GLN treatment group by using Dunnett-Hsu t-test following ANCOVA with Week 2 as covariate including baseline by treatment interaction.
† P-values were determined from pairwise comparisons of treatment groups with the GLN treatment group by using Dunnett-Hsu t-test after ANCOVA with Week 2 as covariate.

Figure 1:



The results in Table 1 demonstrated significant differences in the mean changes in total IPN volume, calories, and frequency between groups. I additionally generated Figure 1 to further illustrate differences in the mean total IPN volume at week 2 and week 6 among the three treatment groups. A reduction in IPN utilization among patients receiving rhGH and the cotherapy composed of rhGH and glutamine was demonstrated in the study. The reduction in IPN utilization among patients receiving rhGH and glutamine in cotherapy was highly significant as compared to patients receiving glutamine alone suggesting a rhGH effect. A borderline significant reduction in IPN utilization was also noted in the rhGH (alone) group in comparison to the glutamine group. There existed a decrease in IPN utilization over the treatment duration (week 2 to week 6) of 3.8 L, 7.7 L and 5.9 L among the glutamine, rhGH and glutamine cotherapy, and rhGH alone groups, respectively. Additionally, highly significant reductions in IPN calories and frequency from week 2 to week 6 were evident from results displayed in Table 1. Of note, the observed differences between the rhGH groups and the glutamine group as well as the standard deviations were approximately 50 % smaller than expected for the primary efficacy outcome (as outlined in the sample size calculation). The notably smaller values may have possibly contributed to the statistically significant results.

With regards to the primary efficacy variable, I reanalyzed the data provided applying the same methodology and am in agreement with the sponsor's statistical results and conclusions as summarized in Section 2.3.1. Moreover, the results are very similar when utilizing LOCF and MMRM to handle missing data. Of note, a statistically significant baseline by interaction term was found in the analysis of the primary efficacy variable. The analysis is not invalidated by the apparent interaction; however, some caution is warranted in interpretation. Insight into the differential treatment effects across baseline IPN volume increases understanding thus aiding in an appropriate interpretation. The sponsor further reported results by using the estimated quartiles of the baseline as shown in Table 2. Based on Table 2, the sponsor concludes that subjects with higher baseline IPN requirements experience greater treatment effects as compared to subjects with lower IPN requirements at baseline.

Table 2: Baseline quartile results for mean change in total IPN

	rhGH +SOD	p-value*	rhGH + SOD[GLN]	p-value*	SOD[GLN]
First quartile (7.50)	-4.55 (0.64)	0.832	-5.77 (0.68)	0.229	-4.00 (0.97)
Second quartile (10.50)	-5.94 (0.57)	0.083	-7.75 (0.56)	0.001	-3.92 (0.81)
Third quartile (14.40)	-7.74 (0.71)	0.001	-10.32 (0.76)	0.001	-3.81 (0.76)

* P-values were determined from pairwise comparisons of treatment groups with the SOD[GLN] treatment group by using Dunnett Hsu t-test following ANCOVA. Means shown are LS-Means computed at the respective quartile values.

Analysis of the secondary variables, change in total IPN calories and change in IPN frequency, demonstrated further support of a statistically significant difference between rhGH (singly or as cotherapy) and a specialized oral diet supplemented with glutamine. Specifically, a statistical difference exists between the pairwise comparisons of interest, namely, rhGH as compared to glutamine alone and rhGH in cotherapy with glutamine as compared to glutamine alone.

Additional analyses outlined by the sponsor included an examination of the IPN requirements during the follow-up period (Week 6 to Week 18) and the effect of covariates. Pre-specified covariates that were individually assessed by the sponsor included age, sex, race, baseline weight, time since last resection, length of residual jejunum-ileum, presence of an intact colon, and IPN history. The protocol specified that continuous covariates would be examined via the Type I sums of squares. In consultation with the medical officer, Dr. Hugo Gallo-Torres, three covariates of particular interest were identified, namely weight, presence of an intact colon, and length of residual jejunum-ileum. Based on the results from the specified analysis, the sponsor concludes that the presence of an intact colon did not significantly influence the total IPN volume. However, the baseline weight and length of residual jejunum-ileum covariates were significant when added to the model. Moreover analyses with both covariates provided further support of the significant difference between the cotherapy of rhGH and glutamine as compared to glutamine alone.

I briefly evaluated the sponsor's analysis of the follow-up period. In particular, I investigated the analysis of the IPN volume utilizing an ANCOVA model with week 2 as a baseline covariate. Interest focused on observed differences in the change in IPN volume from baseline to week 18. Of note, the efficacy variable in the analysis was total IPN volume excluding the SLE and hydration components as those components were not measured during the follow-up period. Results indicate a significant reduction in IPN utilization among the cotherapy (rhGH and glutamine) group as compared to the glutamine only group. The results suggest that four weeks of treatment is sufficient to maintain the reduction in IPN utilization for a period of twelve weeks. The same significance was not achieved when comparing the rhGH group to the glutamine only group.

In addition to the review and verification of the sponsor's primary and secondary analyses, I also examined relationships of potential interest. The sponsor primarily focused on the total IPN volume defined as the sum of three components, namely, IPN, SLE, and hydration fluid. After an exploratory investigation, I determined that the IPN component had the greatest contribution to the total volume. Approximately 71 % of the total IPN volume calculations from week 2 and week 6 were equivalent to the IPN volume component. Moreover, I applied the same methodology as used in the analysis of the primary efficacy variable to the IPN component (excluding SLE and hydration fluids). The results also indicate a statistically significant difference between rhGH as compared to a diet supplemented with glutamine as well as a difference between rhGH in cotherapy with glutamine as compared to diet supplemented with glutamine.

The sponsor's analysis focused on two pairwise comparisons; however, an additional comparison may be obtained from the data. The relationship between rhGH alone versus rhGH in cotherapy with glutamine may be ascertained and provide some insight into the effect of glutamine. The sponsor applied the Dunnett-Hsu test which can appropriately be used to control the type I error rate when comparison of interest are between

treatments and a single control. In order to extend comparisons to include all pairwise comparisons, I applied multiple t-tests (unadjusted for multiplicity) as well as a Tukey-Kramer test (adjusted for multiplicity). The unadjusted analysis yielded a statistically significant result ($p = 0.0226$) in reduction in total volume when comparing rhGH and the cotherapy of rhGh and glutamine. The result suggested a glutamine effect. In contrast, a borderline statistically significant difference ($p = 0.0574$) in reduction in total IPN volume was achieved when applying an adjusted analysis to the comparison of interest. The result suggested a negligible glutamine effect. The primary efficacy variable in these analyses was the total IPN volume defined as the sum of IPN volume, SLE, and hydration fluids. Additionally, no statistically significant difference ($p = 0.1911$ and $p = 0.3868$, unadjusted and adjusted respectively) in reduction in IPN utilization was found to exist between rhGH and the rhGH and glutamine cotherapy when excluding the SLE and hydration fluid components.

All aforementioned analyses and results ignore data from the specialized oral diet. Due to the daily changes in the oral diet after randomization and the complex relationship between the diet and total IPN volume, an unbiased statistical analysis of total IPN volume adjusting for the effect of diet was not possible. However, summary data on the various components of the diet provide clinicians with a descriptive clarification of the oral diet intake during the study. The sponsor provided data and descriptive analyses for 5 of the 6 components of the oral diet, namely oral fluids, oral calories, protein, carbohydrates, and fat. An increase in intake from week 2 to week 6 was noted in all diet components across each treatment group. Specifically, there was a mean increase in oral fluids of 5.0 L, 4.9 L, and 4.7 L in the glutamine, rhGH and glutamine cotherapy, and the rhGH groups respectively. The mean change in oral calories was 566.2 kcal, 1504.0 kcal, and 1086.4 kcal in the glutamine, rhGH and glutamine cotherapy, and the rhGH groups respectively. The cotherapy group increased the protein consumption by 101.9 g while the rhGH alone and glutamine alone groups increased their protein consumption by 91.0 g and 36.6 g. The amount of carbohydrates consumed increased across groups (3.1 g, 62.5 g, and 74.8 g for the glutamine, rhGH, and cotherapy treatments). Lastly, an increase across groups was also noted in the amount of fat in the oral diet (17.1 g, 49.9 g, and 68.3 g respectively). Detailed descriptive tables of the components of the diet are in the Appendix. Of note, the resulting values produced by my analysis of the data were slightly varied from that of the sponsor. In that the variations were small, an attempt to explain the differences was neglected.

The sponsor additionally submitted (21 May 2003) analytical results pertaining to the specialized oral diet. The results were produced via ANCOVA models with effects for treatment and baseline components of the oral diet (separate model per component). Moreover, the change from baseline to week 6 in diet components was examined via ANCOVA models with effects for treatment and change in components. Since the relationship between diet and IPN volume was complex and the oral diet varied after randomization, the aforementioned analyses by the sponsor were not of focus in my review.

2.3.4 STATISTICAL REVIEWER'S FINDINGS

During the course of my review, some concern arose regarding the primary efficacy variable. The primary efficacy variable as stated in NDA 21-597 was " the change in total volume of IPN from Week 2 to Week 6. Total volume was defined as the sum of the volumes of IPN, supplemental lipid emulsion (SLE), and intravenous hydration fluid administered each week." Prior communications and correspondences suggested the primary endpoint was total IPN volume excluding the SLE and hydration fluid components. Specifically, I investigated the initial protocol submitted 31 August 1995 and the subsequent four amendments (dated 28 August 1998, 05 November 1999, 28 March 2000, and 19 October 2001, respectively). In the initial protocol, the primary efficacy variable was " the change from Control Period to the end of the Treatment Period in the total volume (ml/day or L/week) of IPN required by the patient(s) for nutritional support." In amendments 1-3, the primary efficacy variable remained unchanged from that defined in the original protocol. The definition of the primary efficacy variable in Amendment 4 corresponds to the submitted NDA. My analysis suggests that IPN volume is the primary contributor to the total IPN volume. Moreover, results regarding the two pairwise comparisons of primary interest to the sponsor are equivalent for the analysis of the total IPN volume including SLE and hydration fluids and the analysis of the volume excluding the SLE and hydration fluids. Thus, the initial concern has been diminished. However of note, results vary when the pairwise comparison between rhGH and the cotherapy are considered. A statistically significant difference in reduction in IPN utilization was not found to exist between rhGH and the rhGH and glutamine cotherapy when the SLE and hydration fluids were excluded from the definition of total IPN volume. Results varied when the efficacy variable was defined as the sum of three components (Section 2.3.3).

Background or historical documents indicate that the agency expressed concern regarding the use of a single study (and single center) to establish the safety and efficacy of Serostim® for the treatment of short bowel syndrome. The concern is compounded by the previous collaboration between Sereno Laboratories, Inc. and a second sponsor and subsequent dissolution of the collaboration. Thus, a degree of uncertainty exists regarding the dissemination of information before and after the dissolution of the collaboration. In as much in a meeting dated 6 September 2002, Sereno Laboratories, Inc. asked for confirmation that the safety and efficacy analysis plan would be adequate to support filing. As stated in the meeting minutes, " The Agency agreed that, with the caveat that additional information would be necessary, a review of the results could begin." I would defer such discussion regarding the scope of additional information as it pertains to the need for additional centers or an additional study to the review of the medical officer, Dr. Hugo Gallo-Torres.

At the aforementioned meeting, the agency expressed concern regarding the contribution of the specialized oral diet (SOD) to the efficacy. The SOD was standardized with regard to the relative composition of carbohydrates, fat, and protein; however, the diet was tailored to meet individualized needs of the patients. The meeting minutes reflect an

agreement that states, " The firm should quantify the intake in diet to determine whether there is an imbalance between treatment groups." The requested quantification of diet intake was provided to the agency on 21 May 2003 and was subsequently reviewed. Results indicated an increase in intake from week 2 to week 6 in all diet components across each treatment group. The clinical relevance of the increases is deferred to the medical review.

2.4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

Additional analyses examined the relationship between the primary efficacy variable and patients' age, gender, and race, respectively. The change in total IPN volume from baseline to week 4 was analyzed via ANCOVA models including the subgroup variable as a covariate. The age variable was categorized utilizing two subgroups, ages greater than or equal to 65 and ages less than 65. The variable denoting race was categorized utilizing two subgroups, Caucasian and non-Caucasian. Pairwise comparisons were assessed via the Dunnett-Hsu test. Due to the small sample sizes generated from analyses of subgroups, analyses are considered exploratory.

Thirty-three patients were younger than 65 with the remaining 12 patients being classified as greater than or equal to 65. Among younger patients (less than 65), the mean change in total volume from week 2 to week 6 was 6.44 L, 8.32 L, and 4.04 L in the rhGH only, rhGH and glutamine in cotherapy, and glutamine only groups respectively. Among older patients, the mean change was 5.41 L, 7.29 L, and 3.01 L in the three respective treatment groups (as presented by the sponsor). Of note, only one older patient received glutamine only. Adjusted analysis supported the efficacy of the rhGH and glutamine in cotherapy for the treatment of short bowel syndrome.

Seventy-one percent of patients were female. Among females, the mean change in total volume from week 2 to week 6 was 6.51 L, 8.24 L, and 2.85 L in the rhGH only, rhGH and glutamine in cotherapy, and glutamine only groups respectively (as presented by the sponsor). Among males, the mean change was 5.32 L, 7.89 L, and 6.07 L in the three respective treatment groups with 4, 5, and 3 persons per group. Analyses adjusted for gender supported the efficacy of the rhGH and glutamine in cotherapy for the treatment of short bowel syndrome.

Thirty-two patients were Caucasian. Among Caucasian subjects, the mean change in total volume from week 2 to week 6 was 6.26 L, 8.31 L, and 4.29 L in the rhGH only, rhGH and glutamine in cotherapy, and glutamine only groups respectively. Among non-Caucasians, the mean change was 5.41 L, 7.46 L, and 3.44 L in the three respective treatment groups (as presented by the sponsor). Analyses adjusted for race supported the efficacy of the rhGH and glutamine in cotherapy for the treatment of short bowel syndrome.

The sponsor did not propose any efficacy claims for any subgroup of patients. Overall, the results were consistent and lend support to the findings presented in the preceding section.

2.5 CONCLUSIONS AND RECOMMENDATIONS

Sereno Laboratories, Incorporated has proposed Serostim®, a recombinant human growth hormone (rhGH), for the improvement of residual gut absorptive function in patients with short bowel syndrome (SBS). A primary claim of the sponsor is that rhGH, administered singly and as cotherapy with glutamine, reduces the total intravenous parenteral nutrition (IPN) volume requirements of SAS patients. The evidence taken from the reviewed study indicates statistical support favoring Serostim® for the treatment of short bowel syndrome. Additional claims are made regarding IPN calorie content and frequency of IPN administration. Evidence further suggests that Serostim® significantly reduces both IPN calorie content and frequency of administration among SBS patients.

Of note, all study participants received an oral diet individualized to meet nutritional needs. Moreover, modifications to the diet throughout the treatment period were necessary to maintain adequate nutritional status. Due to the daily changes to the diet after randomization and the potentially complex relationship between diet and total IPN volume, an unbiased statistical analysis of total IPN adjusting for the effect of diet is not possible. However, data on the diet and nutritional status of patients may provide clinicians with a descriptive clarification of the nature and strength of the relationship between diet and IPN utilization over time. Summary data suggest an increase in the components of the oral diet from week 2 to week 6 across each treatment group.

Furthermore, issues including the clinical significance of the rhGH effect, the appropriateness of the endpoints, and the appropriateness of a single study for the proposed indication are deferred to the medical review of Dr. Hugo Gallo-Torres.

2.6 LABELLING

A portion of the sponsor's proposed label reads as follows:

> A randomized, double-blind, controlled, parallel-group multi-center Phase 3 clinical study evaluated the efficacy and safety of the administration of Serostim® in subjects with Short Bowel Syndrome (SBS) who are dependent on intravenous parenteral nutrition (IPN) for nutritional support. The primary endpoint was the change in weekly total IPN volume. The secondary endpoints were the change in weekly IPN caloric content and the change in the frequency of IPN administration per week. Subjects received either Serostim® with a specialized diet supplemented with glutamine (Group 1), Serostim® with a specialized diet not supplemented with glutamine (Group 2) or

claim of duration or persistence would require a more in-depth investigation and possible adjustments for multiplicity in the analyses.

2.7 APPENDIX

Summary of Demographic and Baseline Characteristics by Treatment Group

Characteristic	rhGH + SOD N=16 n (%)	rhGH + SOD[GLN] N=16 n (%)	SOD[GLN] N=9 n (%)	p-value*
Age (years)				
Mean	50.5	52.5	45.0	0.521
St. Dev.	17.1	14.4	15.5	
Median	53	53	42	
Min. Max	26, 74	20,73	24, 75	
<65	12 (75)	13 (81)	8 (89)	
• 65	4 (25)	3 (19)	1 (11)	
Sex				0.913
Male	4 (25)	5 (31)	3 (33)	
Female	12 (75)	11 (69)	6 (67)	
Race				0.064
Caucasian	15 (94)	12 (75)	5 (56)	
Non-Caucasian	1 (6)	4 (25)	4 (44)	
Weight(kg) †				0.977
Mean	61.4	62.1	61.3	
St. Dev.	10.4	11.4	8.5	
Number of yrs since resection				
Mean	5.1	4.6	3.9	0.855
St. Dev.	5.9	4.6	3.9	
Length of residual jejunum-ileum				
Mean	84.2	68.4	62.3	0.584
St. Dev.	49.8	32.7	30.8	
Colon Intact				
Percent	67.1	52.6	61.8	0.442
St. Dev.	28.1	33.5	36.3	
Number of days per week of IPN administration				
Mean	5.2	5.5	5.9	0.680
St. Dev.	1.9	1.9	1.5	
IPN Volume per week (mL/wk)				
Mean	13.8	13.0	13.1	0.880
St. Dev.	5.3	4.3	4.6	
IPN calories per week (kcal/wk)				
Mean	11620.8	10403.8	10224.9	0.814
St. Dev.	4167.3	2496.3	4037.9	

* Categorical variables were compared by using Fisher's exact test. Continuous variables were compared by using ANOVA with main effect term of treatment. Treatment differences were compared via a Kruskal-Wallis test for length of residual jejunum-ileum.

† Weight is the average of each patient's weight at 1 month and 2 months before screening.

Descriptive Statistics for Components of the Oral Diet

		GLN (n=9)	rhGH (n=15)	rhGH + GLN (n=16)
Oral Fluid (L/week)				
Week 2	Mean	15.1(5.8)	16.5(5.6)	15.5 (4.0)
	Median	14.1	15.7	14.6
	Range	(5.3, 24.2)	(6.5, 29.5)	(7.8, 23.5)
Week 6	Mean	20.1(8.9)	21.3(4.2)	20.4(2.5)
	Median	19.4	20.3	19.7
	Range	(8.6, 40.3)	(14.6, 32.1)	(15.4,25.1)
Change	Mean	5.0(6.5)	4.7(3.7)	4.9(3.7)
	Median	3.9	5.1	4.5
	Range	(-4.3,20.0)	(-2.6,12.9)	(-2.4,11.2)
Oral Calories (kcal/Week)				
Week 2	Mean	15791.2(5270)	15966.5(4935.3)	15420.1(2875.6)
	Median	17199.0	16212.0	14752.0
	Range	(8442.0, 2358.3)	(5635.0,22743.0)	(9926.0,21168.0)
Week 6	Mean	16357.4(4632.5)	17052.9(3395.0)	16924.0(3615.9)
	Median	15183.0	16800.0	16761
	Range	(8911.0,25228.0)	(10192.0,22729.0)	(11466.0,23114.0)
Change	Mean	566.2(3548.2)	1086.4(4013.1)	1504.6(1963.1)
	Median	763.0	308.0	1386.0
	Range	(-4522.0,6741.0)	(-6426.0,9814.0)	(-2835.0,4361.0)
Protein(g/wk)				
Week 2	Mean	899.1(319.6)	826.5(274.9)	817.3(137.5)
	Median	854.0	882.0	798.0
	Range	(469.0,1484.0)	(287.0,1232.0)	(574.0,1204.0)
Week 6	Mean	935.7(235.6)	917.5(195.6)	919.2(185.7)
	Median	861.0	924.0	924.0
	Range	(567.0,1379.0)	(518.0, 1246.0)	(616.0,1302.0)
Change	Mean	36.6(208.1)	91.0 (176.7)	101.9(140.3)
	Median	21.0	105.0	101.5
	Range	(-259.0,378.0)	(-175.0,490.0)	(-189.0, 336.0)
Carbohydrates(g/wk)				
Week 2	Mean	1810.7(640.7)	1968.4(560.4)	1911.9(477.4)
	Median	2107.0	1960.0	1781.5
	Range	(791.0,2604.0)	(770.0,2849.0)	(1239.0,3038.0)
Week 6	Mean	1813.8(604.0)	2030.9(489.4)	1986.7(497.5)
	Median	1694.0	1981.0	1911.0
	Range	(847.0,2989.0)	(1127.0,2828.0)	(1302.0,3283.0)
Change	Mean	3.11(549.0)	62.5(541.3)	74.8(226.5)
	Median	-28.0	21.0	101.5
	Range	(-665.0, 714.0)	(-847.0, 1190.0)	(-280.0,602.0)

		GLN (n=9)	rhGH (n=15)	rhGH + GLN (n=16)
Fat(g/wk)				
Week 2	Mean	550.7(195.2)	531.5(199.3)	497.9(125.9)
	Median	567.0	525.0	514.5
	Range	(315.0,931.0)	(154.0,791.0)	(294.0,749.0)
Week 6	Mean	567.8(154.5)	581.5(133.6)	566.1(158.5)
	Median	581.0	574.0	535.5
	Range	(315.0,861.0)	(350.0,756.0)	(336.0,903.0)
Change	Mean	17.1(137.8)	50.0(145.9)	68.3(108.3)
	Median	49.0	35.0	80.5
	Range	(-203.0,266.0)	(-273.0,315.0)	(-119.0,252.0)

STUDY DIET (as presented by the sponsor)

The diet employed for SBS patients consists entirely of foods that patients can purchase from local sources. The diet provides approximately 50% to 55% of total daily calories from carbohydrates, 20% from protein, and 25% to 30% from fat. Rehydration fluids and dietary supplements (e.g., multivitamins, minerals, calcium, and zinc) are also provided. The objective of the diet is to ensure that each patient is able to maintain, through oral feeding, adequate nutritional status that can promote nutrient absorption and independence from IPN following discharge from the clinic.
The diet varies among patients according to their individual requirements. In general, the diet used in conjunction with the rhGH treatment of SBS patients includes the following:

1.0 Calories

The daily caloric requirements are determined by multiplying the following variables: resting energy expenditure (REE), calculated from standard equations or indirect calorimetry; an activity factor (AF), based on the patient's level of physical activity; and a malabsorption factor (MF), based on the patient's degree of malabsorption and diarrhea.

Daily Calories: REE x AF (1.2 to 1.5) x MF (1.2 to 1.7).

Nutrient-dense foods are provided to maximize caloric intake and limit food volume.

Serving of food to the patients is distributed throughout the day (6 to 8 meals per day).

2.0 Carbohydrates

Carbohydrates are provided to equal 50% to 55% of total daily caloric intake.

Complex carbohydrates are emphasized (e.g., rice, potato, pasta, cereal and grain products).

Intake of simple sugars is limited (e.g., lactose, sucrose, and fructose).

3.0 Proteins

Protein is provided to equal 20% of total daily caloric intake.

A significant source of protein is provided at each meal (6 to 8 times per day). Protein sources rich in essential amino acids (chicken, fish, and turkey) are emphasized.

4.0 **Fat**

Fat is provided to equal 25% to 30% percent of total caloric intake.

Fats (oils and margarine) rich in linolenic and linoleic acid (soybean oil and safflower oil) are provided to prevent essential fatty-acid deficiency.

5.0 **Fluids**

Oral rehydration solutions (carbohydrate and sodium-containing beverages) are provided as the primary source of hydration. Oral rehydration solutions are initiated at 1.5 liters per day and are increased as needed, based on stool volumes and urine output.

Intake of hypo-osmolar and hyperosmolar beverages such as water, regular soda, and most fruit juices is limited.

Fluid intake is distributed throughout the day.

6.0 **Specific Oral Nutrients**

Specific oral nutrients are included, or excluded, to maintain appropriate serum electrolyte concentrations, prevent nutrient deficiencies, and avoid the long-term complications associated with altered bowel function.

Included Components (commercially available in grocery, drug, and health-food stores).

— Multivitamin/mineral supplements (1 to 2 tablets every day)

— Vitamin B12 (100 to 300 JLg every month -given intramuscularly if the terminal ileum is missing)

— Fat-soluble vitamins (A, E, D, K) (These vitamins may be provided if indicated in increased doses to treat or prevent deficiencies.)

— Calcium (1500 to 3000 mg daily)

— Zinc (15 mg daily if stool volumes are greater than 1 Ud)

— Other electrolytes (including potassium, magnesium, and phosphorus) as required to maintain serum concentrations

Excluded Components

Oxalate (Food and beverages rich in oxalate are restricted to decrease the likelihood of calcium-oxalate renal stone formation).

7.0 **Diet Individualization**

The diet is tailored to meet the individual nutritional needs of each patient. Upon admission to the in-patient facility, each patient's nutritional and hydration status is assessed. In addition, all patients undergo extensive diet education, both in the classroom setting and via individualized counseling sessions. The patient's oral intake is assessed for adequacy and compliance to the prescribed diet. Food sensitivities are identified by reviewing the recorded intake and the volume of stool output over a given time period within a given day. The diet is then adjusted to eliminate or restrict a nutrient (e.g., lactose) that appears to be contributing to increased stool output. Specific supplements are added to correct nutrient deficiencies identified during the Baseline assessment and during serum evaluations.

IPN WEANING (as presented by the sponsor)

IPN requirements will be reduced when the patient demonstrates all 3 of the following:

1.0 Ability to hydrate, demonstrated by the following:

- A positive enteral balance (defined as enteral fluid intake [mL] minus volume of stool output [mL]) greater than or equal to approximately 500 cc per day or the patient's calculated insensible fluid losses greater than or equal to approximately 12 mUkg/d, and/or

- A urine volume, demonstrated by the following:

— Greater than or equal to 0.5 cc/kg for 24 hours on the nights that the patient does not infuse IPN, or

— Approximately 75% of the patient's calculated minimum urine volume prior to nighttime infusion

2.0 Ability to maintain serum electrolytes within the limits of normal range with or without the use of enteral electrolyte supplement(s)

3.0 Ability to sustain an appropriate body weight demonstrated by the following:

- An ability to maintain body weight while maintaining total body water (reflected by a relatively stable measurement of whole body resistance as measured by bioelectrical impedance analysis), or an ability to gain body weight while maintaining total body water (reflected by a relatively stable or decreasing measurement of whole body resistance measured by bioelectrical impedance analysis), and/or

- An ability to consistently consume 80% to 100% of estimated total caloric requirements (as calculated from standard equations)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Dionne Price
7/25/03 10:58:11 AM
BIOMETRICS

Todd Sahlroot
7/25/03 02:57:14 PM
BIOMETRICS

S. Edward Nevius
7/25/03 03:28:07 PM
BIOMETRICS
Concur with review.